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(54) Title: METHODS AND COMPOSITIONS FOR DETECTING CANCER USING COMPONENTS OF THE U2 SPLICEOSOMAL PARTICLE

(57) Abstract: The present invention relates to cancer-associated proteins and nucleic acids that encode or bind specifically to cancer-associated proteins, which represent markers for cancer detection. Specifically, the invention provides a family of methods and compositions for detecting cancer, for example, breast cancer, in an individual using components of the U2 spliceosomal particle. A target cancer-associated protein may be detected, for example, by reacting the sample with a labeled binding moiety, for example, a labeled antibody capable of binding specifically to the protein. The invention also provides kits useful in the detection of cancer in an individual.



WO 2006/034278 A2

**METHODS AND COMPOSITIONS FOR DETECTING CANCER USING COMPONENTS
OF THE U2 SPLICEOSOMAL PARTICLE**

Reference to Related Applications

[0001] This application claims the benefit of U.S. Patent Application Serial No. 60/612,310, filed September 21, 2004, the disclosure of which is incorporated by reference herein.

Field of the Invention

- 5 [0002] The present invention relates generally to methods and compositions for the detection and/or treatment of cancer. More specifically, the present invention relates to cancer-associated proteins and nucleic acids that encode or bind specifically to such cancer-associated proteins, which represent markers for cancer detection.

Background of the Invention

- 10 [0003] Breast cancer is one of the leading causes of death in women. While the pathogenesis of breast cancer is unclear, transformation of normal breast epithelium to a malignant phenotype may be the result of genetic factors, especially in women under 30 years of age (Miki *et al.* (1994) *Science* 266: 66-71). However, it is likely that other, non-genetic and epigenetic factors also have a significant effect on the etiology of the disease and its natural history. Regardless of
15 the cancer's origin, cancer morbidity increases significantly if it is not detected early in its progression. Because of the premium placed on early detection in the management of cancer, great medical and commercial effort has been focused in the last three decades on meeting this goal. For example, research has linked alleles of the BRCA1 and BRCA2 genes to hereditary and early-onset breast cancer (Wooster *et al.* (1994) *Science* 265: 2088-2090). However, it is
20 understood that BRCA mutations fail to account for the majority of breast cancers (Ford *et al.* (1995) *British J. Cancer* 72: 805-812).

- [0004] There is, therefore, a need in the art for specific, reliable markers that are differentially expressed in normal and cancerous tissue and that may be useful in the diagnosis of cancer, in the prediction of its onset, or the treatment of cancer. Such markers and methods for
25 their use are provided herein.

- 2 -

Summary of the Invention

[0005] The invention provides a variety of methods and compositions for detecting the presence of cancer, for example, breast cancer, in a human or other mammal. The invention is based, in part, upon the discovery that components of spliceosomal particle U2, also referred to
5 herein as the U2 particle, are detectable at a higher concentration in a sample (for example, a body fluid) harvested from a mammal with cancer relative to a corresponding sample from a normal mammal, that is, a mammal without the cancer. The invention also is based, in part, upon the discovery that these components can be observed in an intact complex present in a sample, for example, a body fluid sample, from a mammal with cancer. Accordingly, the
10 complex and its components can be used as cancer markers useful in diagnosing or monitoring the status of a cancer.

[0006] The components of the U2 particle include a small nuclear RNA called "U2 snRNA" and a plurality of different proteins. The protein components include, for example, U2 snRNP B", SAP155, SAP145, SPF31, SAP130, SAP114, SAP62, SAP61, SAP49, U2 snRNP A', p14,
15 U2AF35, U2AF65, U2AF1-RS2, hPrp5p, hPrp19, HuR, ALY, SR140, CHERP, hPrp43, HSP75, PUF60, Hsp60, SPF45, BRAF35, SF2/ASF, SF3b14b, SF3b10, SF3a120, SF3a66, SF3a60, and SPF30. The protein components also include Sm proteins, such as, SmB/B', SmD3, SmD2, SmD1, SmE, SmF, and SmG. It is understood that certain of the Sm proteins are also found in spliceosomal particles other than the U2 particle.

[0007] The invention provides methods for detecting or monitoring a cancer in a mammal by detecting the presence, absence, or amount (which can be an absolute amount or a relative amount) of one or more components of the U2 particle. The methods of the invention may be performed on any relevant tissue or body fluid sample. For example, methods of the invention may be performed on breast tissue, such as breast biopsy tissue. Alternatively, the methods of
25 the invention may be performed on a human body fluid sample such as blood, serum, plasma, nipple aspirate, ductal lavage fluid, fine needle aspirate, sweat, tears, urine, peritoneal fluid, lymph, vaginal secretions, semen, spinal fluid, ascitic fluid, saliva or sputum. It is contemplated, however, that the methods of the invention also may be useful in detecting cancer in other tissue or body fluid samples.

- 3 -

[0008] Detection of cancer can be accomplished using any one of a number of assay methods well known and used in the art. For example, a protein or nucleic acid can be detected by a spectroscopic approach such as mass spectrometry or fluorescence spectroscopy, or through the use of a binding moiety that specifically binds the protein or nucleic acid, as in an immunoassay, a nucleic acid hybridization method, or a method such as RT-PCR involving amplification of a nucleic acid.

[0009] Certain methods for detecting breast cancer by detecting U2 snRNP B'' are known in the art. See, for example, U.S. Patent No. 6,936,424. The present invention, however, provides improved methods of detecting U2 snRNP B'' and other components of the U2 particle, based in part upon the discovery that these components are present as an intact complex in a body fluid in mammals with cancer. Accordingly, in one aspect, the invention relates to a method of diagnosing cancer in a mammal by disrupting a complex comprising one or more components of the U2 particle prior to detecting and/or measuring the amount of one or more of the components. The component can be U2 snRNP B'', U2 snRNA, or another component of the U2 particle, such as SAP155, SAP145, SPF31, SAP130, SAP114, SAP62, SAP61, SAP49, U2 snRNP A', p14, U2AF35, U2AF65, U2AF1-RS2, hPrp5p, hPrp19, HuR, ALY, SR140, CHERP, hPrp43, HSP75, PUF60, Hsp60, SPF45, BRAF35, SF2/ASF, SF3b14b, SF3b10, SF3a120, SF3a66, SF3a60, and SPF30.

[0010] In certain embodiments, disruption of the complex, which can be achieved by providing a chemical denaturant, heat, an acid, a base, a salt, or another factor known to affect protein-protein or protein-nucleic acid interactions, facilitates the subsequent detection and/or measurement of the U2 particle component. For example, if a U2 particle component is subsequently detected using a binding moiety that specifically binds the component, disruption of the complex can increase the accessibility of the component to a binding moiety. Alternatively, if a U2 particle component is subsequently detected by mass spectrometry, disrupting the complex in advance can simplify the mass spectrometry analysis.

[0011] In one embodiment, the presence of the component is indicative of the presence of cancer, for example, breast cancer, in a mammal. In another embodiment, an amount of the component is indicative of the presence of cancer, for example, breast cancer, in a mammal.

- 4 -

[0012] In another aspect, the invention provides methods that relate to combining a tissue or body fluid sample isolated from a mammal with a purified binding moiety with an affinity for a component of the U2 particle other than U2 snRNP B'' to form a complex. The methods further involve detecting and/or measuring the amount of the complex of the component. It is important to note that these methods using one or more non-B'' components of the U2 particle may advantageously be combined with detection of U2 snRNP B'' or with use of a binding moiety with an affinity for U2 snRNP B''. For example, an anti-U2 snRNP B'' antibody can be used to purify a U2 particle prior to detection of U2 snRNA or of another protein component of the particle. As another example, an antibody that binds specifically to the 2,2,7-trimethylguanosine cap of the U2 snRNA molecule can be used to purify the U2 particle prior to detection of U2 snRNP B'', for example, by immunoassay or mass spectrometry.

[0013] In one embodiment, the method of detecting or monitoring a cancer, for example, breast cancer, includes exposing a sample isolated from the mammal to a purified binding moiety capable of binding specifically to a component of spliceosomal particle U2. The binding moiety forms a complex with the component; the presence, absence or amount of the complex is then detected or determined, providing information indicative of the presence or absence of the cancer in the mammal.

[0014] The binding moiety can be a protein with an affinity for the snRNA, such as a snuportin protein, or for a protein component of the spliceosomal particle other than U2 snRNP B'', such as SAP155, SAP145, SPF31, SAP130, SAP114, SAP62, SAP61, SAP49, U2 snRNP A', p14, U2AF35, U2AF65, U2AF1-RS2, hPrp5p, hPrp19, HuR, ALY, SR140, CHERP, hPrp43, HSP75, PUF60, Hsp60, SPF45, BRAF35, SF2/ASF, SF3b14b, SF3b10, SF3a120, SF3a66, SF3a60, and SPF30. For example, the binding moiety can be an antibody or an antigen-binding fragment thereof. Exemplary antibodies include, for example, an anti-2,2,7-trimethylguanosine antibody, an anti-Sm antibody, an anti-SMN antibody, an anti-Importin B antibody, an anti-snuportin antibody, an anti-Ran antibody, or an anti-Ran-GTP antibody. The binding moiety alternatively can be a nucleic acid or a nucleic acid analog (such as a peptide nucleic acid, a locked nucleic acid, or other nucleic acid analog, for example, a morpholino containing oligonucleotide) having an affinity for the U2 snRNA or for a protein component of the spliceosomal particle.

- 5 -

[0015] After complex formation, the presence, absence, or amount of the complex can be determined by mass spectrometry, RT-PCR, immunoassay or use of another labeled or unlabeled binding moiety, or another assay technique known in the art. The detecting and/or measuring step can involve detection of a second, different component of the U2 particle, which could be any component, including U2 snRNA, U2 snRNP B", or another protein component.

[0016] The invention also is based, in part, upon the discovery that a binding moiety that specifically binds 2,2,7-trimethylguanosine can be used to purify a naturally-occurring, circulating snRNA bearing a 2,2,7-trimethylguanosine cap, even in the complex environment of a mammalian body fluid. Accordingly, in one aspect, the invention provides a method of detecting one or more snRNAs bearing a 2,2,7-trimethylguanosine moiety by contacting the sample with a binding moiety, such as a snuportin protein, an antibody, or an antigen-binding fragment thereof, that specifically binds 2,2,7-trimethylguanosine to permit complex formation between the binding moiety and the one or more snRNAs and detecting the presence or absence of the complex. The presence or amount of complex formation can be indicative of the presence or extent of cancer in the mammal.

[0017] In another aspect, the invention provides kits for purifying or detecting a U2 snRNA. In one embodiment, the kit includes (i) a purified binding moiety that specifically binds 2,2,7-trimethylguanosine and (ii) one or more molecules (nucleic acids or nucleic acid analogs) complementary to at least a portion of a U2 snRNA. Generally, the molecules are complementary to a portion at least three nucleotides in length, and preferably at least five, at least eight, or at least ten nucleotides in length. The purified binding moiety can be a snuportin protein or an antibody or antigen-binding fragment thereof.

[0018] In another embodiment, the kit includes a purified binding moiety that specifically binds a U2 snRNA and one or more reference samples having amounts of U2 snRNA indicative of the presence of a cancer such as breast cancer. Thus, for example, a tissue or body fluid sample from a mammal with the cancer can be provided as a positive control. Alternatively, a synthetic U2 snRNA sequence or a fragment thereof can be provided as a positive control. The binding moiety can be, for example, a nucleic acid or nucleic acid analog complementary to at least a portion of the U2 snRNA; an antibody or antigen-binding fragment thereof; or a snuportin protein. The kit also optionally includes a receptacle for receiving a sample from a patient.

- 6 -

[0019] Thus, the invention provides a family of methods and compositions for detecting and monitoring the status of a cancer in a mammal, such as a human. Specifically, the invention provides improved methods for detecting and/or measuring cancer marker U2 snRNP B". The invention also provides methods for detecting and/or measuring other cancer markers present in the U2 particle. The invention provides methods for breast cancer-associated proteins, which permit specific and early, preferably before metastases occur, detection of breast cancer in an individual. In addition, the invention provides kits useful in the detection of breast cancer in an individual. In addition, the invention provides methods utilizing the breast cancer-associated proteins as targets and indicators, for treating breast cancers and for monitoring of the efficacy of such a treatment. These and other numerous additional aspects and advantages of the invention will become apparent upon consideration of the following figures, detailed description, and claims which follow.

Description of the Drawings

[0020] The invention can be more completely understood with reference to the following drawings, in which:

[0021] Figure 1 is a schematic representation showing the involvement of the U2 spliceosomal particle in the removal of an intron during mRNA maturation;

[0022] Figure 2 is a schematic representation showing the relative positioning of several components of the U2 particle;

[0023] Figure 3 is a schematic representation showing the structure of mature U2 snRNA as described in Lührmann et al. (1990) *Biochim. Biophys Acta* 1087: 265-292;

[0024] Figure 4A is a schematic representation of a morpholine residue and figure 4B is schematic representation of a short segment of a morpholino containing oligonucleotide comprising two subunits joined by an intersubunit linkage; and

[0025] Figure 5 is a picture of a gel showing the presence of U2 snRNA amplified in greater amounts from five serum samples from women diagnosed with breast cancer (denoted "C") than the amounts from three serum samples from healthy women (denoted "N").

- 7 -

Detailed Description of the Invention

[0026] The present invention provides methods and compositions for the detection of snRNAs, spliceosomal particle U2 and components thereof, and cancer. The invention is based, in part, upon the discovery that components of the U2 particle are present in a complex in a tissue or body fluid from mammals with cancer and that the components are detectable at a higher concentration in samples from mammals with a cancer than in samples from healthy mammals. It is understood that the term cancer embraces both cancerous lesions and pre-cancerous lesions. Although U2 snRNA and components of the U2 particle are known in the art, it was not previously appreciated that levels of U2 snRNA or, indeed, of circulating complexes containing known components of the U2 particle, can differentiate a tissue or body fluid of a healthy individual from a tissue or body fluid of an individual with cancer.

[0027] The U2 particle is involved in the maturation of messenger RNA as depicted in Figure 1. The top line of Figure 1 shows a portion of an immature or heterologous RNA. Two exons (exon 1 and exon 2), which ultimately are united in the mature message, are separated by an intervening intron. The intron contains within it a "branch point" sequence, which is used to guide the maturation process. Without wishing to be bound by theory, it is understood that the U1 particle binds to the upstream consensus sequence (GU), while at the same time, the U2 particle binds to the branch point. The U2 particle remains bound to the branch point, while the U1 is displaced by the U4/5/6 complex at the GU site. The U2 particle then mediates the connection of U5 between the exon units, while at the same time liberating U4 and U6 in turn. U2 and U6 form a meta-stable "lariat" structure with the intronic RNA. Ultimately, all the U particles involved in this splicing event are released and recycled in the cell.

[0028] It has been found that components of the U2 particle are detectable in a circulating body fluid in individuals with cancer and that one or more of the components are present in a complex in the body fluid. Without wishing to be bound by theory, it is contemplated that snRNPs normally buried within the nucleus may be externalized by apoptosis or oxidative stress associated with cancer. These externalized snRNPs find their way into the serum where they remain largely intact for a period of time. The present invention takes advantage of the relative stability of the complex in body fluids and the tissues contacted by those fluids to permit detection of the cancer even using a sample taken at a location potentially remote from the site of the cancer.

- 8 -

[0029] The U2 particle includes the U2 snRNA and a plurality of different proteins. The sequence of a human gene encoding U2 snRNA is set forth in SEQ ID NO. 1. The RNA of U2 snRNA sequence appearing in Figure 3 corresponds substantially to residues 259-446 in SEQ ID NO. 1. It appears that the thymidine residue appearing as residue "299" of SEQ ID NO. 1 is replaced by a bond in Figure 3. It is contemplated that this and other differences may result from naturally occurring variants of mammalian U2 snRNA. Accordingly, the term U2 snRNA includes RNA molecules having at least 80%, optionally at least 85%, and, optionally at least 90% identity to residues 259-446 of SEQ ID NO. 1 or fragments thereof containing 40 contiguous bases.

[0030] In order to determine the percentage identity of a test sequence relative to a reference nucleotide sequence, the candidate sequence and the reference sequence can be compared using the BLAST 2 SEQUENCE program (which produces the alignment of two given sequences using the BLAST engine for local alignment) using all the default parameters. This software is available from the National Center for Biotechnology Information ("NCBI").

[0031] The proteins in the U2 particle include, for example, U2 snRNP B", SAP155, SAP145, SPF31, SAP130, SAP114, SAP62, SAP61, SAP49, U2 snRNP A', p14, U2AF35, U2AF65, U2AF1-RS2, hPrp5p, hPrp19, HuR, ALY, SR140, CHERP, hPrp43, HSP75, PUF60, Hsp60, SPF45, BRAF35, SF2/ASF, SF3b14b, SF3b10, SF3a120, SF3a66, SF3a60, and SPF30. The protein components also include Sm proteins, such as, SmB/B', SmD3, SmD2, SmD1, SmE, SmF, and SmG. It is understood that certain of the Sm proteins are also found in spliceosomal particles other than the U2 particle. Of these, at least the thirteen proteins, SAP155, SAP145, SAP130, SAP114, SAP62, SAP61, SAP49, U2 snRNP A', U2 snRNP B", p14, U2AF35, U2AF65, and U2AF1-RS2, are specific to the U2 particle. The U2 particle can be isolated in a 12S and a 17S form (Behrens, S. E. *et al.* (1993) *Proc. Natl. Acad. Sci. USA* 90:8229-33; Behrens, S. E. *et al.* (1993) *Mol. Cell Biol.* 13:307-19; and Hartmuth, K. *et al.* (2002) *Proc. Natl. Acad. Sci. USA* 99:16719-16724). The B" protein is a stable component of both forms (Behrens, S. E. *et al.* (1993) *Proc. Natl. Acad. Sci. USA* 90:8229-33). In contrast, the two essential multimeric splicing factors, SF3a and SF3b, are present only in the 17S form (Behrens, S. E. *et al.* (1993) *Proc. Natl. Acad. Sci. USA* 90:8229-33); Behrens, S. E. *et al.* (1993) *Mol. Cell Biol.* 13:307-19; Brosi, R. *et al.* (1993) *Science* 262:102-05; Kramer, A. *et al.* (1999) *J. Cell Biol.* 145:1355-68; Staknis, D. *et al.* (1994) *Mol. Cell Biol.* 14). SF3a consists of three subunits

- 9 -

(spliceosome-associated proteins (SAPs) 61, 62 and 114), and SF3b consists of four subunits (SAPs 49, 130, 145 and 155) (Brosi, R. *et al.* (1993) *J. Biol. Chem.* 268:17640-46; Das, B. K. *et al.* (1999) *Mol. Cell Biol.* 19:6796-802; Kramer, A. *et al.* (1999) *J. Cell Biol.* 145:1355-68).

[0032] U2 snRNP B'' includes a protein having the amino acid sequence set forth in SEQ ID NO. 3 and variants thereof. Variants include (a) a protein having at least 85% sequence identity, more preferably at least 90% sequence identity to the amino acid sequence set forth in SEQ ID NO. 3, (b) a protein having an amino acid sequence comprising the consensus sequence set forth in SEQ ID NO. 4, wherein Xaa represents any amino acid, or (c) a protein fragment comprising at least 25 consecutive amino acids set forth in SEQ ID NO. 3 or SEQ ID NO. 4. The fragments optionally have at least 75%, optionally at least 85%, and optionally at least 90% of the biological activity of the full length protein set forth in SEQ ID NO. 3. It is understood that the variants include allelic variants of U2 snRNP B''. Furthermore it is understood that U2 snRNP B'' includes a protein that binds specifically to an antibody that binds specifically to the protein of SEQ ID NO. 3. A gene encoding the U2 snRNP B'' protein of SEQ ID NO. 3 is set forth in SEQ ID NO. 2.

[0033] SAP155 includes a protein having the amino acid sequence set forth in SEQ ID NO. 6 and variants thereof. Variants include (a) a protein having at least 85% sequence identity, more preferably at least 90% sequence identity to the amino acid sequence set forth in SEQ ID NO. 6, (b) a protein having an amino acid sequence comprising the consensus sequence set forth in SEQ ID NO. 7, wherein Xaa represents any amino acid, or (c) a protein fragment comprising at least 25 consecutive amino acids set forth in SEQ ID NO. 6 or SEQ ID NO. 7. The fragments optionally have at least 75%, optionally at least 85%, and optionally at least 90% of the biological activity of the full length protein set forth in SEQ ID NO. 6. It is understood that the variants include allelic variants of SAP155. Furthermore it is understood that SAP155 includes a protein that binds specifically to an antibody that binds specifically to the protein of SEQ ID NO. 6. A gene encoding the SAP155 protein of SEQ ID NO. 6 is set forth in SEQ ID NO. 5.

[0034] SAP145 includes a protein having the amino acid sequence set forth in SEQ ID NO. 9 and variants thereof. Variants include (a) a protein having at least 85% sequence identity, more preferably at least 90% sequence identity to the amino acid sequence set forth in SEQ ID NO. 9, (b) a protein having an amino acid sequence comprising the consensus sequence set forth in SEQ ID NO. 10, wherein Xaa represents any amino acid, or (c) a protein fragment comprising at least

- 10 -

15 consecutive amino acids set forth in SEQ ID NO. 9 or SEQ ID NO. 10. The fragments optionally have at least 75%, optionally at least 85%, and optionally at least 90% of the biological activity of the full length protein set forth in SEQ ID NO. 9. It is understood that the variants include allelic variants of SAP145. Furthermore it is understood that SAP145 includes a protein that binds specifically to an antibody that binds specifically to the protein of SEQ ID NO. 9. A gene encoding the SAP145 protein of SEQ ID NO.9 is set forth in SEQ ID NO. 8.

[0035] SPF31 includes a protein having the amino acid sequence set forth in SEQ ID NO. 12 and variants thereof. Variants include (a) a protein having at least 85% sequence identity, more preferably at least 90% sequence identity to the amino acid sequence set forth in SEQ ID NO. 12, (b) a protein having an amino acid sequence comprising the consensus sequence set forth in SEQ ID NO. 13, wherein Xaa represents any amino acid, or (c) a protein fragment comprising at least 25 consecutive amino acids set forth in SEQ ID NO. 12 or SEQ ID NO. 13. The fragments optionally have at least 75%, optionally at least 85%, and optionally at least 90% of the biological activity of the full length protein set forth in SEQ ID NO. 12. It is understood that the variants include allelic variants of SPF31. Furthermore it is understood that SPF31 includes a protein that binds specifically to an antibody that binds specifically to the protein of SEQ ID NO. 12. A gene encoding the SPF31 protein of SEQ ID NO. 12 is set forth in SEQ ID NO. 11.

[0036] Sequence similarity searches using the BLAST algorithm were conducted in the NCBI's *GenBank* database using SAP155 (SEQ ID NO. 6), SAP145 (SEQ ID NO. 9), U2 snRNP B" (SEQ ID NO. 3), and SPF31 (SEQ ID NO. 12) proteins as queries. The BLAST results were filtered to identify sequences for mammalian proteins that had an average identity greater than 85% and that had a total length of all BLAST HSP greater than 90% of the query length. Multiple sequence alignments were produced using CLUSTAL W (1.82). All parameters were set as the default. Consensus sequences were constructed based on manual analysis of multiple alignments. In the consensus sequences, "Xaa" represents an alternate amino acid residue or a peptide bond.

[0037] SAP130 includes a protein having the amino acid sequence set forth in SEQ ID NO. 15 and variants thereof. Variants include (a) a protein having at least 85% sequence identity, more preferably at least 90% sequence identity to the amino acid sequence set forth in SEQ ID NO. 15, or (b) a protein fragment comprising at least 25 consecutive amino acids set forth in SEQ ID NO. 15. The fragments optionally have at least 75%, optionally at least 85%, and

- 11 -

optionally at least 90% of the biological activity of the full length protein set forth in SEQ ID NO. 15. It is understood that the variants include allelic variants of SAP130. Furthermore it is understood that SAP130 includes a protein that binds specifically to an antibody that binds specifically to the protein of SEQ ID NO. 15. A gene encoding the SAP130 protein of SEQ ID NO. of SEQ ID NO. 15 is set forth in SEQ ID NO. 14.

[0038] SAP114 includes a protein having the amino acid sequence set forth in SEQ ID NO. 17 and variants thereof. Variants include (a) a protein having at least 85% sequence identity, more preferably at least 90% sequence identity to the amino acid sequence set forth in SEQ ID NO. 17, or (b) a protein fragment comprising at least 25 consecutive amino acids set forth in SEQ ID NO. 17. The fragments optionally have at least 75%, optionally at least 85%, and optionally at least 90% of the biological activity of the full length protein set forth in SEQ ID NO. 17. It is understood that the variants include allelic variants of SAP114. Furthermore it is understood that SAP114 includes a protein that binds specifically to an antibody that binds specifically to the protein of SEQ ID NO. 17. A gene encoding the SAP114 protein of SEQ ID NO. 17 is set forth in SEQ ID NO. 16.

[0039] SAP62 includes a protein having the amino acid sequence set forth in SEQ ID NO. 19 and variants thereof. Variants include (a) a protein having at least 85% sequence identity, more preferably at least 90% sequence identity to the amino acid sequence set forth in SEQ ID NO. 19, or (b) a protein fragment comprising at least 25 consecutive amino acids set forth in SEQ ID NO. 19. The fragments optionally have at least 75%, optionally at least 85%, and optionally at least 90% of the biological activity of the full length protein set forth in SEQ ID NO. 19. It is understood that the variants include allelic variants of SAP62. Furthermore it is understood that SAP62 includes a protein that binds specifically to an antibody that binds specifically to the protein of SEQ ID NO. 19. A gene encoding the SAP62 protein of SEQ ID NO. 19 is set forth in SEQ ID NO. 18.

[0040] SAP61 includes a protein having the amino acid sequence set forth in SEQ ID NO. 21 and variants thereof. Variants include (a) a protein having at least 85% sequence identity, more preferably at least 90% sequence identity to the amino acid sequence set forth in SEQ ID NO. 21, or (b) a protein fragment comprising at least 25 consecutive amino acids set forth in SEQ ID NO. 21. The fragments optionally have at least 75%, optionally at least 85%, and optionally at least 90% of the biological activity of the full length protein set forth in SEQ ID NO. 21. It is

- 12 -

understood that the variants include allelic variants of SAP61. Furthermore it is understood that SAP61 includes a protein that binds specifically to an antibody that binds specifically to the protein of SEQ ID NO. 21. A gene encoding the SAP61 protein of SEQ ID NO. 21 is set forth in SEQ ID NO. 20.

5 **[0041]** SAP49 includes a protein having the amino acid sequence set forth in SEQ ID NO. 23 and variants thereof. Variants include (a) a protein having at least 85% sequence identity, more preferably at least 90% sequence identity to the amino acid sequence set forth in SEQ ID NO. 23, or (b) a protein fragment comprising at least 25 consecutive amino acids set forth in SEQ ID NO. 23. The fragments optionally have at least 75%, optionally at least 85%, and optionally at least
10 90% of the biological activity of the full length protein set forth in SEQ ID NO. 23. It is understood that the variants include allelic variants of SAP49. Furthermore it is understood that SAP49 includes a protein that binds specifically to an antibody that binds specifically to the protein of SEQ ID NO. 23. A gene encoding the SAP49 protein of SEQ ID NO. 23 is set forth in SEQ ID NO. 22.

15 **[0042]** U2 snRNP A' includes a protein having the amino acid sequence set forth in SEQ ID NO. 25 and variants thereof. Variants include (a) a protein having at least 85% sequence identity, more preferably at least 90% sequence identity to the amino acid sequence set forth in SEQ ID NO. 25, or (b) a protein fragment comprising at least 25 consecutive amino acids set forth in SEQ ID NO. 25. The fragments optionally have at least 75%, optionally at least 85%,
20 and optionally at least 90% of the biological activity of the full length protein set forth in SEQ ID NO. 25. It is understood that the variants include allelic variants of U2 snRNP A'. Furthermore it is understood that U2 snRNP A' includes a protein that binds specifically to an antibody that binds specifically to the protein of SEQ ID NO. 25. A gene encoding the U2 snRNP A' protein of SEQ ID NO. 25 is set forth in SEQ ID NO. 24.

25 **[0043]** p14 includes a protein having the amino acid sequence set forth in SEQ ID NO. 27 and variants thereof. Variants include (a) a protein having at least 85% sequence identity, more preferably at least 90% sequence identity to the amino acid sequence set forth in SEQ ID NO. 27, or (b) a protein fragment comprising at least 25 consecutive amino acids set forth in SEQ ID NO. 27. The fragments optionally have at least 75%, optionally at least 85%, and optionally at least
30 90% of the biological activity of the full length protein set forth in SEQ ID NO. 27. It is understood that the variants include allelic variants of p14. Furthermore it is understood that p14

- 13 -

includes a protein that binds specifically to an antibody that binds specifically to the protein of SEQ ID NO. 27. A gene encoding the p14 protein of SEQ ID NO. 27 is set forth in SEQ ID NO. 26.

[0044] U2AF35 includes a protein having the amino acid sequence set forth in SEQ ID NO. 29 and variants thereof. Variants include (a) a protein having at least 85% sequence identity, more preferably at least 90% sequence identity to the amino acid sequence set forth in SEQ ID NO. 29, or (b) a protein fragment comprising at least 25 consecutive amino acids set forth in SEQ ID NO. 29. The fragments optionally have at least 75%, optionally at least 85%, and optionally at least 90% of the biological activity of the full length protein set forth in SEQ ID NO. 29. It is understood that the variants include allelic variants of U2AF35. Furthermore it is understood that U2AF35 includes a protein that binds specifically to an antibody that binds specifically to the protein of SEQ ID NO. 29. A gene encoding the U2AF35 protein of SEQ ID NO. 29 is set forth in SEQ ID NO. 28.

[0045] U2AF65 includes a protein having the amino acid sequence set forth in SEQ ID NO. 31 and variants thereof. Variants include (a) a protein having at least 85% sequence identity, more preferably at least 90% sequence identity to the amino acid sequence set forth in SEQ ID NO. 31, or (b) a protein fragment comprising at least 25 consecutive amino acids set forth in SEQ ID NO. 31. The fragments optionally have at least 75%, optionally at least 85%, and optionally at least 90% of the biological activity of the full length protein set forth in SEQ ID NO. 31. It is understood that the variants include allelic variants of U2AF65. Furthermore it is understood that U2AF65 includes a protein that binds specifically to an antibody that binds specifically to the protein of SEQ ID NO. 31. A gene encoding the U2AF65 protein of SEQ ID NO. 31 is set forth in SEQ ID NO. 30.

[0046] U2AF1-RS2 includes a protein having the amino acid sequence set forth in SEQ ID NO. 33 and variants thereof. Variants include (a) a protein having at least 85% sequence identity, more preferably at least 90% sequence identity to the amino acid sequence set forth in SEQ ID NO. 33, or (b) a protein fragment comprising at least 25 consecutive amino acids set forth in SEQ ID NO. 33. The fragments optionally have at least 75%, optionally at least 85%, and optionally at least 90% of the biological activity of the full length protein set forth in SEQ ID NO. 33. It is understood that the variants include allelic variants of U2AF1-RS2. Furthermore it is understood that U2AF1-RS2 includes a protein that binds specifically to an antibody that binds

- 14 -

specifically to the protein of SEQ ID NO. 33. A gene encoding the U2AF1-RS2 protein of SEQ ID NO. 33 is set forth in SEQ ID NO. 32.

[0047] hPrp5p includes a protein having the amino acid sequence set forth in SEQ ID NO. 35 and variants thereof. Variants include (a) a protein having at least 85% sequence identity, more preferably at least 90% sequence identity to the amino acid sequence set forth in SEQ ID NO. 35, or (b) a protein fragment comprising at least 25 consecutive amino acids set forth in SEQ ID NO. 35. The fragments optionally have at least 75%, optionally at least 85%, and optionally at least 90% of the biological activity of the full length protein set forth in SEQ ID NO. 35. It is understood that the variants include allelic variants of hPrp5p. Furthermore it is understood that hPrp5p includes a protein that binds specifically to an antibody that binds specifically to the protein of SEQ ID NO. 35. A gene encoding the hPrp5p protein of SEQ ID NO. 35 is set forth in SEQ ID NO. 34.

[0048] hPrp19 includes a protein having the amino acid sequence set forth in SEQ ID NO. 37 and variants thereof. Variants include (a) a protein having at least 85% sequence identity, more preferably at least 90% sequence identity to the amino acid sequence set forth in SEQ ID NO. 37, or (b) a protein fragment comprising at least 25 consecutive amino acids set forth in SEQ ID NO. 37. The fragments optionally have at least 75%, optionally at least 85%, and optionally at least 90% of the biological activity of the full length protein set forth in SEQ ID NO. 37. It is understood that the variants include allelic variants of hPrp19. Furthermore it is understood that hPrp19 includes a protein that binds specifically to an antibody that binds specifically to the protein of SEQ ID NO. 37. A gene encoding the hPrp19 protein of SEQ ID NO. 37 is set forth in SEQ ID NO. 36.

[0049] HuR includes a protein having the amino acid sequence set forth in SEQ ID NO. 39 and variants thereof. Variants include (a) a protein having at least 85% sequence identity, more preferably at least 90% sequence identity to the amino acid sequence set forth in SEQ ID NO. 39, or (b) a protein fragment comprising at least 25 consecutive amino acids set forth in SEQ ID NO. 39. The fragments optionally have at least 75%, optionally at least 85%, and optionally at least 90% of the biological activity of the full length protein set forth in SEQ ID NO. 39. It is understood that the variants include allelic variants of HuR. Furthermore it is understood that HuR includes a protein that binds specifically to an antibody that binds specifically to the protein

- 15 -

of SEQ ID NO. 39. A gene encoding the HuR protein of SEQ ID NO. 39 is set forth in SEQ ID NO. 38.

[0050] ALY includes a protein having the amino acid sequence set forth in SEQ ID NO. 41 and variants thereof. Variants include (a) a protein having at least 85% sequence identity, more preferably at least 90% sequence identity to the amino acid sequence set forth in SEQ ID NO. 41, or (b) a protein fragment comprising at least 25 consecutive amino acids set forth in SEQ ID NO. 41. The fragments optionally have at least 75%, optionally at least 85%, and optionally at least 90% of the biological activity of the full length protein set forth in SEQ ID NO. 41. It is understood that the variants include allelic variants of ALY. Furthermore it is understood that ALY includes a protein that binds specifically to an antibody that binds specifically to the protein of SEQ ID NO. 41. A gene encoding the ALY protein of SEQ ID NO. 41 is set forth in SEQ ID NO. 40.

[0051] SR140 includes a protein having the amino acid sequence set forth in SEQ ID NO. 43 and variants thereof. Variants include (a) a protein having at least 85% sequence identity, more preferably at least 90% sequence identity to the amino acid sequence set forth in SEQ ID NO. 43, or (b) a protein fragment comprising at least 25 consecutive amino acids set forth in SEQ ID NO. 43. The fragments optionally have at least 75%, optionally at least 85%, and optionally at least 90% of the biological activity of the full length protein set forth in SEQ ID NO. 43. It is understood that the variants include allelic variants of SR140. Furthermore it is understood that SR140 includes a protein that binds specifically to an antibody that binds specifically to the protein of SEQ ID NO. 43. A gene encoding the SR140 protein of SEQ ID NO. 43 is set forth in SEQ ID NO. 42.

[0052] CHERP includes a protein having the amino acid sequence set forth in SEQ ID NO. 45 and variants thereof. Variants include (a) a protein having at least 85% sequence identity, more preferably at least 90% sequence identity to the amino acid sequence set forth in SEQ ID NO. 45, or (b) a protein fragment comprising at least 25 consecutive amino acids set forth in SEQ ID NO. 45. The fragments optionally have at least 75%, optionally at least 85%, and optionally at least 90% of the biological activity of the full length protein set forth in SEQ ID NO. 45. It is understood that the variants include allelic variants of CHERP. Furthermore it is understood that CHERP includes a protein that binds specifically to an antibody that binds

- 16 -

specifically to the protein of SEQ ID NO. 45. A gene encoding the CHERP protein of SEQ ID NO. 45 is set forth in SEQ ID NO. 44.

[0053] hPrp43 includes a protein having the amino acid sequence set forth in SEQ ID NO. 47 and variants thereof. Variants include (a) a protein having at least 85% sequence identity, more preferably at least 90% sequence identity to the amino acid sequence set forth in SEQ ID NO. 47, or (b) a protein fragment comprising at least 25 consecutive amino acids set forth in SEQ ID NO. 47. The fragments optionally have at least 75%, optionally at least 85%, and optionally at least 90% of the biological activity of the full length protein set forth in SEQ ID NO. 47. It is understood that the variants include allelic variants of hPrp43. Furthermore it is understood that hPrp43 includes a protein that binds specifically to an antibody that binds specifically to the protein of SEQ ID NO. 47. A gene encoding the hPrp43 protein is of SEQ ID NO. 47 set forth in SEQ ID NO. 46.

[0054] HSP75 includes a protein having the amino acid sequence set forth in SEQ ID NO. 49 and variants thereof. Variants include (a) a protein having at least 85% sequence identity, more preferably at least 90% sequence identity to the amino acid sequence set forth in SEQ ID NO. 49, or (b) a protein fragment comprising at least 25 consecutive amino acids set forth in SEQ ID NO. 49. The fragments optionally have at least 75%, optionally at least 85%, and optionally at least 90% of the biological activity of the full length protein set forth in SEQ ID NO. 49. It is understood that the variants include allelic variants of HSP75. Furthermore it is understood that HSP75 includes a protein that binds specifically to an antibody that binds specifically to the protein of SEQ ID NO. 49. A gene encoding the HSP75 protein of SEQ ID NO. 49 is set forth in SEQ ID NO. 48.

[0055] PUF60 includes a protein having the amino acid sequence set forth in SEQ ID NO. 51 and variants thereof. Variants include (a) a protein having at least 85% sequence identity, more preferably at least 90% sequence identity to the amino acid sequence set forth in SEQ ID NO. 51, or (b) a protein fragment comprising at least 25 consecutive amino acids set forth in SEQ ID NO. 51. The fragments optionally have at least 75%, optionally at least 85%, and optionally at least 90% of the biological activity of the full length protein set forth in SEQ ID NO. 51. It is understood that the variants include allelic variants of PUF60. Furthermore it is understood that PUF60 includes a protein that binds specifically to an antibody that binds specifically to the

- 17 -

protein of SEQ ID NO. 51. A gene encoding the PUF60 protein is of SEQ ID NO. 51 set forth in SEQ ID NO. 50.

[0056] Hsp60 includes a protein having the amino acid sequence set forth in SEQ ID NO. 53 and variants thereof. Variants include (a) a protein having at least 85% sequence identity, more preferably at least 90% sequence identity to the amino acid sequence set forth in SEQ ID NO. 53, or (b) a protein fragment comprising at least 25 consecutive amino acids set forth in SEQ ID NO. 53. The fragments optionally have at least 75%, optionally at least 85%, and optionally at least 90% of the biological activity of the full length protein set forth in SEQ ID NO. 53. It is understood that the variants include allelic variants of Hsp60. Furthermore it is understood that Hsp60 includes a protein that binds specifically to an antibody that binds specifically to the protein of SEQ ID NO. 53. A gene encoding the Hsp60 protein of SEQ ID NO. 53 is set forth in SEQ ID NO. 52.

[0057] SPF45 includes a protein having the amino acid sequence set forth in SEQ ID NO. 55 and variants thereof. Variants include (a) a protein having at least 85% sequence identity, more preferably at least 90% sequence identity to the amino acid sequence set forth in SEQ ID NO. 55, or (b) a protein fragment comprising at least 25 consecutive amino acids set forth in SEQ ID NO. 55. The fragments optionally have at least 75%, optionally at least 85%, and optionally at least 90% of the biological activity of the full length protein set forth in SEQ ID NO. 55. It is understood that the variants include allelic variants of SPF45. Furthermore it is understood that SPF45 includes a protein that binds specifically to an antibody that binds specifically to the protein of SEQ ID NO. 55. A gene encoding the SPF45 protein of SEQ ID NO. 55 is set forth in SEQ ID NO. 54.

[0058] BRAF35 includes a protein having the amino acid sequence set forth in SEQ ID NO. 57 and variants thereof. Variants include (a) a protein having at least 85% sequence identity, more preferably at least 90% sequence identity to the amino acid sequence set forth in SEQ ID NO. 57, or (b) a protein fragment comprising at least 25 consecutive amino acids set forth in SEQ ID NO. 57. The fragments optionally have at least 75%, optionally at least 85%, and optionally at least 90% of the biological activity of the full length protein set forth in SEQ ID NO. 57. It is understood that the variants include allelic variants of BRAF35. Furthermore it is understood that BRAF35 includes a protein that binds specifically to an antibody that binds

- 18 -

specifically to the protein of SEQ ID NO. 57. A gene encoding the BRAF35 protein of SEQ ID NO. 57 is set forth in SEQ ID NO. 56.

[0059] SF2/ASF includes a protein having the amino acid sequence set forth in SEQ ID NO. 59 and variants thereof. Variants include (a) a protein having at least 85% sequence identity, more preferably at least 90% sequence identity to the amino acid sequence set forth in SEQ ID NO. 59, or (b) a protein fragment comprising at least 25 consecutive amino acids set forth in SEQ ID NO. 59. The fragments optionally have at least 75%, optionally at least 85%, and optionally at least 90% of the biological activity of the full length protein set forth in SEQ ID NO. 59. It is understood that the variants include allelic variants of SF2/ASF. Furthermore it is understood that SF2/ASF includes a protein that binds specifically to an antibody that binds specifically to the protein of SEQ ID NO. 59. A gene encoding the SF2/ASF protein of SEQ ID NO. 59 is set forth in SEQ ID NO. 58.

[0060] SF3b14b includes a protein having the amino acid sequence set forth in SEQ ID NO. 61 and variants thereof. Variants include (a) a protein having at least 85% sequence identity, more preferably at least 90% sequence identity to the amino acid sequence set forth in SEQ ID NO. 61, or (b) a protein fragment comprising at least 25 consecutive amino acids set forth in SEQ ID NO. 61. The fragments optionally have at least 75%, optionally at least 85%, and optionally at least 90% of the biological activity of the full length protein set forth in SEQ ID NO. 61. It is understood that the variants include allelic variants of SF3b14b. Furthermore it is understood that SF3b14b includes a protein that binds specifically to an antibody that binds specifically to the protein of SEQ ID NO. 61. A gene encoding the SF3b14b protein of SEQ ID NO. 61 is set forth in SEQ ID NO. 60.

[0061] SF3b10 includes a protein having the amino acid sequence set forth in SEQ ID NO. 63 and variants thereof. Variants include (a) a protein having at least 85% sequence identity, more preferably at least 90% sequence identity to the amino acid sequence set forth in SEQ ID NO. 63, or (b) a protein fragment comprising at least 25 consecutive amino acids set forth in SEQ ID NO. 63. The fragments optionally have at least 75%, optionally at least 85%, and optionally at least 90% of the biological activity of the full length protein set forth in SEQ ID NO. 63. It is understood that the variants include allelic variants of SF3b10. Furthermore it is understood that SF3b10 includes a protein that binds specifically to an antibody that binds

- 19 -

specifically to the protein of SEQ ID NO. 63. A gene encoding the SF3b10 protein of SEQ ID NO. 63 is set forth in SEQ ID NO. 62.

[0062] SF3a120 includes a protein having the amino acid sequence set forth in SEQ ID NO. 65 and variants thereof. Variants include (a) a protein having at least 85% sequence identity, more preferably at least 90% sequence identity to the amino acid sequence set forth in SEQ ID NO. 65, or (b) a protein fragment comprising at least 25 consecutive amino acids set forth in SEQ ID NO. 65. The fragments optionally have at least 75%, optionally at least 85%, and optionally at least 90% of the biological activity of the full length protein set forth in SEQ ID NO. 65. It is understood that the variants include allelic variants of SF3a120. Furthermore it is understood that SF3a120 includes a protein that binds specifically to an antibody that binds specifically to the protein of SEQ ID NO. 65. A gene encoding the SF3a120 protein of SEQ ID NO. 65 is set forth in SEQ ID NO. 64.

[0063] SF3a66 includes a protein having the amino acid sequence set forth in SEQ ID NO. 67 and variants thereof. Variants include (a) a protein having at least 85% sequence identity, more preferably at least 90% sequence identity to the amino acid sequence set forth in SEQ ID NO. 67, or (b) a protein fragment comprising at least 25 consecutive amino acids set forth in SEQ ID NO. 67. The fragments optionally have at least 75%, optionally at least 85%, and optionally at least 90% of the biological activity of the full length protein set forth in SEQ ID NO. 67. It is understood that the variants include allelic variants of SF3a66. Furthermore it is understood that SF3a66 includes a protein that binds specifically to an antibody that binds specifically to the protein of SEQ ID NO. 67. A gene encoding the SF3a66 protein of SEQ ID NO. 67 is set forth in SEQ ID NO. 66.

[0064] SF3a60 includes a protein having the amino acid sequence set forth in SEQ ID NO. 69 and variants thereof. Variants include (a) a protein having at least 85% sequence identity, more preferably at least 90% sequence identity to the amino acid sequence set forth in SEQ ID NO. 69, or (b) a protein fragment comprising at least 25 consecutive amino acids set forth in SEQ ID NO. 69. The fragments optionally have at least 75%, optionally at least 85%, and optionally at least 90% of the biological activity of the full length protein set forth in SEQ ID NO. 69. It is understood that the variants include allelic variants of SF3a60. Furthermore it is understood that SF3a60 includes a protein that binds specifically to an antibody that binds

- 20 -

specifically to the protein of SEQ ID NO. 69. A gene encoding the SF3a60 protein of SEQ ID NO. 69 is set forth in SEQ ID NO. 68.

[0065] SPF30 includes a protein having the amino acid sequence set forth in SEQ ID NO. 71 and variants thereof. Variants include (a) a protein having at least 85% sequence identity, more preferably at least 90% sequence identity to the amino acid sequence set forth in SEQ ID NO. 71, or (b) a protein fragment comprising at least 25 consecutive amino acids set forth in SEQ ID NO. 71. The fragments optionally have at least 75%, optionally at least 85%, and optionally at least 90% of the biological activity of the full length protein set forth in SEQ ID NO. 71. It is understood that the variants include allelic variants of SPF30. Furthermore it is understood that SPF30 includes a protein that binds specifically to an antibody that binds specifically to the protein of SEQ ID NO. 71. A gene encoding the SPF30 protein of SEQ ID NO. 71 is set forth in SEQ ID NO. 70.

[0066] SmB/B' includes a protein having the amino acid sequence set forth in SEQ ID NO. 73 and variants thereof. Variants include (a) a protein having at least 85% sequence identity, more preferably at least 90% sequence identity to the amino acid sequence set forth in SEQ ID NO. 73, or (b) a protein fragment comprising at least 25 consecutive amino acids set forth in SEQ ID NO. 73. The fragments optionally have at least 75%, optionally at least 85%, and optionally at least 90% of the biological activity of the full length protein set forth in SEQ ID NO. 73. It is understood that the variants include allelic variants of SmB/B'. Furthermore it is understood that SmB/B' includes a protein that binds specifically to an antibody that binds specifically to the protein of SEQ ID NO. 73. A gene encoding the SmB/B' protein of SEQ ID NO. 73 is set forth in SEQ ID NO. 72.

[0067] SmD3 includes a protein having the amino acid sequence set forth in SEQ ID NO. 75 and variants thereof. Variants include (a) a protein having at least 85% sequence identity, more preferably at least 90% sequence identity to the amino acid sequence set forth in SEQ ID NO. 75, or (b) a protein fragment comprising at least 25 consecutive amino acids set forth in SEQ ID NO. 75. The fragments optionally have at least 75%, optionally at least 85%, and optionally at least 90% of the biological activity of the full length protein set forth in SEQ ID NO. 75. It is understood that the variants include allelic variants of SmD3. Furthermore it is understood that SmD3 includes a protein that binds specifically to an antibody that binds specifically to the

- 21 -

protein of SEQ ID NO. 75. A gene encoding the SmD3 protein of SEQ ID NO. 75 is set forth in SEQ ID NO. 74.

[0068] SmD2 includes a protein having the amino acid sequence set forth in SEQ ID NO. 77 and variants thereof. Variants include (a) a protein having at least 85% sequence identity, more preferably at least 90% sequence identity to the amino acid sequence set forth in SEQ ID NO. 77, or (b) a protein fragment comprising at least 25 consecutive amino acids set forth in SEQ ID NO. 77. The fragments optionally have at least 75%, optionally at least 85%, and optionally at least 90% of the biological activity of the full length protein set forth in SEQ ID NO. 77. It is understood that the variants include allelic variants of SmD2. Furthermore it is understood that SmD2 includes a protein that binds specifically to an antibody that binds specifically to the protein of SEQ ID NO. 77. A gene encoding the SmD2 protein of SEQ ID NO. 77 is set forth in SEQ ID NO. 76.

[0069] SmD1 includes a protein having the amino acid sequence set forth in SEQ ID NO. 79 and variants thereof. Variants include (a) a protein having at least 85% sequence identity, more preferably at least 90% sequence identity to the amino acid sequence set forth in SEQ ID NO. 79, or (b) a protein fragment comprising at least 25 consecutive amino acids set forth in SEQ ID NO. 79. The fragments optionally have at least 75%, optionally at least 85%, and optionally at least 90% of the biological activity of the full length protein set forth in SEQ ID NO. 79. It is understood that the variants include allelic variants of SmD1. Furthermore it is understood that SmD1 includes a protein that binds specifically to an antibody that binds specifically to the protein of SEQ ID NO. 79. A gene encoding the SmD1 protein of SEQ ID NO. 79 is set forth in SEQ ID NO. 78.

[0070] SmE includes a protein having the amino acid sequence set forth in SEQ ID NO. 81 and variants thereof. Variants include (a) a protein having at least 85% sequence identity, more preferably at least 90% sequence identity to the amino acid sequence set forth in SEQ ID NO. 81, or (b) a protein fragment comprising at least 25 consecutive amino acids set forth in SEQ ID NO. 81. The fragments optionally have at least 75%, optionally at least 85%, and optionally at least 90% of the biological activity of the full length protein set forth in SEQ ID NO. 81. It is understood that the variants include allelic variants of SmE. Furthermore it is understood that SmE includes a protein that binds specifically to an antibody that binds specifically to the protein

- 22 -

of SEQ ID NO. 81. A gene encoding the SmE protein of SEQ ID NO. 81 is set forth in SEQ ID NO. 80.

[0071] SmF includes a protein having the amino acid sequence set forth in SEQ ID NO. 83 and variants thereof. Variants include (a) a protein having at least 85% sequence identity, more preferably at least 90% sequence identity to the amino acid sequence set forth in SEQ ID NO. 83, or (b) a protein fragment comprising at least 25 consecutive amino acids set forth in SEQ ID NO. 83. The fragments optionally have at least 75%, optionally at least 85%, and optionally at least 90% of the biological activity of the full length protein set forth in SEQ ID NO. 83. It is understood that the variants include allelic variants of SmF. Furthermore it is understood that SmF includes a protein that binds specifically to an antibody that binds specifically to the protein of SEQ ID NO. 83. A gene encoding the SmF protein of SEQ ID NO. 83 is set forth in SEQ ID NO. 82.

[0072] SmG includes a protein having the amino acid sequence set forth in SEQ ID NO. 85 and variants thereof. Variants include (a) a protein having at least 85% sequence identity, more preferably at least 90% sequence identity to the amino acid sequence set forth in SEQ ID NO. 85, or (b) a protein fragment comprising at least 25 consecutive amino acids set forth in SEQ ID NO. 85. The fragments optionally have at least 75%, optionally at least 85%, and optionally at least 90% of the biological activity of the full length protein set forth in SEQ ID NO. 85. It is understood that the variants include allelic variants of SmG. Furthermore it is understood that SmG includes a protein that binds specifically to an antibody that binds specifically to the protein of SEQ ID NO. 85. A gene encoding the SmG protein of SEQ ID NO. 85 is set forth in SEQ ID NO. 84.

[0073] In order to produce variants of the disclosed proteins or other proteins present in the U2 spliceosomal particles that may also serve as identifiers for the U2 particle, any one or more of the naturally-occurring protein sequences may be used as a reference sequence to determine whether a candidate sequence possesses sufficient amino acid similarity to have a reasonable expectation of success in the methods of the present invention.

[0074] To determine whether a candidate peptide region has the requisite percentage identity to a reference polypeptide or peptide oligomer, the candidate amino acid sequence and the reference amino acid sequence are first aligned using the dynamic programming algorithm

- 23 -

described in Smith and Waterman (1981), *J. Mol. Biol.* 147:195-197, in combination with the BLOSUM62 substitution matrix described in Figure 2 of Henikoff and Henikoff (1992), "Amino acid substitution matrices from protein blocks", *Proc. Natl. Acad. Sci. USA* (1992), 89:10915-10919. For the present invention, an appropriate value for the gap insertion penalty is -12, and an appropriate value for the gap extension penalty is -4. Computer programs performing alignments using the algorithm of Smith-Waterman and the BLOSUM62 matrix, such as the GCG program suite (Oxford Molecular Group, Oxford, England), are commercially available and widely used by those skilled in the art.

[0075] Once the alignment between the candidate and reference sequence is made, a percent identity score may be calculated. To calculate a percent identity, the aligned amino acids of each sequence are compared sequentially. If the amino acids are non-identical, the pairwise identity score is zero; otherwise the pairwise identity score is 1.0. The raw identity score is the sum of the identical aligned amino acids. The raw score is then normalized by dividing it by the number of amino acids in the smaller of the candidate or reference sequences. The normalized raw score is the percent identity. Insertions and deletions are ignored for the purposes of calculating percent similarity and identity. Accordingly, gap penalties are not used in this calculation, although they are used in the initial alignment.

[0076] Figure 2 shows a schematic illustration of the U2 particle structure. The U2 snRNA gene is a reiterated sequence occurring on several chromosomes and having known pseudogenes. This reiteration feature gives assays an inherent sensitivity. Several of the known RNA binding components are shown. Figure 3 shows a drawing of a mature U2 snRNA, aligned as it is predicted to appear at physiologic temperature and tonicity. The stem-loop IV, which binds the B" protein, appears on the right hand side of the drawing. Also illustrated in Figures 2 and 3 is the 2,2,7-trimethylguanosine "CAP" structure of the U2 snRNA. The CAP structure is unique to U RNAs, and consists of a 5' to 5' phosphotriester link between the leading guanidine residue and the adenosine that follows it. The leading guanidine is methylated twice at position 2 and once at position 7. This CAP structure is antigenic. Anti-CAP antibodies are available commercially from a variety of sources. The CAP ligand and commercially available anti-CAP antibodies permit capture of U2 snRNA-containing complexes from human serum.

[0077] Sequences for exemplary primers useful in reverse transcription and PCR amplification of the human U2 snRNA sequence are set forth in SEQ ID NO. 86 and SEQ ID

- 24 -

NO. 87. In combination with commercially-available RT-PCR kits, the RT-PCR primers can be used to amplify U2 snRNA from a human body fluid, such as serum. The RT-PCR primers are unsubstituted, but could be adapted for use in a quantitative real-time RT-PCR system. This adaptation would allow a direct and quantitative comparison of the test and control populations in the study of breast cancer and other diseases.

[0078] The U2 snRNA or other U2 particle component to be detected preferably is purified prior to the detection step. For example, one component of the U2 particle can be used as a target for the purification. Thereafter, a second different component of the U2 particle can be analyzed to determine whether an individual has or is at risk of developing cancer, for example, breast cancer. It is understood that the cancer includes both cancerous and pre-cancerous lesions.

[0079] Purification can involve a binding moiety that recognizes the 2,2,7 trimethylguanosine CAP, such as a natural or recombinant snurportin (SPN-1) protein or a polyclonal or monoclonal antibody. Alternatively, purification can involve a binding moiety that recognizes the sequence of the snRNA or a protein directly or indirectly associated with the snRNA, such as U2 snRNP B' or another component of the U2 particle. Streptavidin, avidin, or a similar compound can be used to capture a biotinylated form of the U2 complex that may circulate. Additionally, morpholino antisense oligos can be used to capture components of the U2 particle. Antibodies raised against the general U particle family, including anti-Sm, anti-SMN, anti-ImportinB, anti-snurportin, anti-Ran, or anti Ran-GTP antibodies can also be used.

[0080] Elution of U2 particle components from a binding moiety used for purification is not generally required prior to detection. For example, an RT-PCR reaction to amplify U2 snRNA or a fragment thereof can be performed without separating a U2 snRNA from an antibody to the 2,2,7-trimethylguanosine moiety prior to commencing the reaction. Elution, however, often is preferred. Elution from a binding moiety recognizing 2,2,7-trimethylguanosine can be achieved, for example, by administering a competing ligand, such as free 7-methylguanosine. Elution from antibodies to other components can be achieved by disrupting the antigen-antibody interaction, for example, by reducing the pH.

[0081] One embodiment of the purification detection process involves capturing a U2 particle via one or more antibodies immobilized on a solid support, for example, beads packed within a column. After binding, components of the U2 particle are eluted and submitted for

- 25 -

analysis. Briefly, the samples can be analyzed by amplification of U2 SnRNA by RT-PCR. Following amplification, the amplification products can be fractionated by polyacrylamide gel electrophoresis and the bands visualized by ethidium bromide staining (see Figure 5). As shown in Figure 5, higher levels of amplicon were observed in samples from women with breast cancer relative to samples from healthy women. In that experiment, the sensitivity and specificity were 100%.

[0082] Exemplary protocols for detecting target proteins and nucleic acids present in the U2 particle are described in the following sections.

I. Exemplary Protocols for Detecting a Target Nucleic Acid

[0083] A target nucleic acid molecule, for example, U2 snRNA may be detected using a labeled binding moiety capable of specifically binding the target nucleic acid. The binding moiety may comprise, for example, a protein, a nucleic acid or a peptide nucleic acid. Additionally, a target nucleic acid may be detected by conducting, for example, a Northern blot analysis using labeled oligonucleotides, for example, nucleic acid fragments complementary to and capable of hybridizing specifically with at least a portion of a target nucleic acid. The probes hybridize with complementary nucleic acid sequences presented in the test specimen, and can provide exquisite specificity. A short, well-defined probe for a single unique sequence is most precise and preferred. Larger probes are generally less specific. While an oligonucleotide of any length may hybridize to a target such as U2 snRNA, oligonucleotides typically within the range of 8-100 nucleotides, preferably within the range of 15-50 nucleotides, are envisioned to be most useful in standard hybridization assays. Choices of probe length and sequence allow one to choose the degree of specificity desired. Hybridization preferably is carried out at a temperature from 50° to 65°C in a high salt buffer solution, formamide or other agents to set the degree of complementarity required. Furthermore, the state of the art is such that probes can be manufactured to recognize essentially any DNA or RNA sequence. For additional particulars, see, for example, Guide to Molecular Techniques, Berger et al., Methods of Enzymology, Vol. 152, 1987.

[0084] Because the complete nucleotide sequence encoding the U2 snRNA is known and/or can be determined readily using techniques well known in the art, complementary oligonucleotides or peptide nucleic acids which hybridize specifically with any portion of the U2

- 26 -

snRNA transcript or non-coding sequences can be prepared using conventional oligonucleotide and peptide nucleic acid synthesis methodologies. A variety of sequence lengths of oligonucleotide or peptide nucleic acid may be used to hybridize to U2 snRNA transcripts. However, very short sequences (e.g., sequences containing less than 8-15 nucleobases) may bind the target nucleic acid with less specificity.

[0085] Certain oligonucleotides suffer from such limitations as poor specificity, instability, unpredictable targeting and undesirable non-antisense effects. Nucleic acid analogs containing, for example, morpholino groups, can overcome some of these limitations. Morpholino containing oligonucleotides are assembled from four different morpholino subunits, each of which contains one of the four genetic bases (adenosine, thymidine, guanosine or cytosine) linked to a 6-membered morpholine ring (see Figure 4A). Eighteen to 25 subunits of the four subunit types are joined in a specific order by non-ionic phosphorodiamidate intersubunit linkages to give a morpholino oligonucleotide. Figure 4B shows a short segment of a morpholino oligonucleotide, comprising two subunits joined by an intersubunit linkage. The morpholino oligonucleotides with their 6-membered morpholine backbone moieties joined by non-ionic linkages afford beneficial properties relative to RNA, DNA, and their analogs having 5-membered ribose or deoxyribose backbone moieties joined by ionic linkages. Morpholinos have desirable qualities in terms of serum stability and hybridization stringency.

[0086] A wide variety of different labels coupled to probes or antibodies may be employed in the assays described in this section and in the following section. The labeled reagents may be provided in solution or coupled to an insoluble support, depending on the design of the assay. The various conjugates may be joined covalently or noncovalently, directly or indirectly. When bonded covalently, the particular linkage group will depend upon the nature of the two moieties to be bonded. A large number of linking groups and methods for linking are taught in the literature. Broadly, the labels may be divided into the following categories: chromogens; catalyzed reactions; chemiluminescence; radioactive labels; and colloidal-sized colored particles. The chromogens include compounds which absorb light in a distinctive range so that a color may be observed, or emit light when irradiated with light of a particular wavelength or wavelength range, e.g., fluorescers. Both enzymatic and nonenzymatic catalysts may be employed. In choosing an enzyme, there will be many considerations including the stability of the enzyme, whether it is normally present in samples of the type for which the assay is designed, the nature

- 27 -

of the substrate, and the effect if any of conjugation on the enzyme's properties. Potentially useful enzyme labels include oxidoreductases, transferases, hydrolases, lyases, isomerases, ligases, or synthetases. Interrelated enzyme systems may also be used. A chemiluminescent label involves a compound that becomes electronically excited by a chemical reaction and may then emit light that serves as a detectable signal or donates energy to a fluorescent acceptor. Radioactive labels include various radioisotopes found in common use such as the unstable forms of hydrogen, iodine, phosphorus or the like. Colloidal-sized colored particles involve material such as colloidal gold that, in aggregate, form a visually detectable distinctive spot corresponding to the site of a substance to be detected. Additional information on labeling technology is disclosed, for example, in U.S. Patent No. 4,366,241.

[0087] A common method of *in vitro* labeling of nucleotide probes involves nick translation wherein the unlabeled DNA probe is nicked with an endonuclease to produce free 3'hydroxyl termini within either strand of the double-stranded fragment. Simultaneously, an exonuclease removes the nucleotide residue from the 5'phosphoryl side of the nick. The sequence of replacement nucleotides is determined by the sequence of the opposite strand of the duplex. Thus, if labeled nucleotides are supplied, DNA polymerase will fill in the nick with the labeled nucleotides. Alternatively, nucleotide probes can be labeled by 3'end labeling. Furthermore, there are currently commercially available methods of labeling DNA with fluorescent molecules, catalysts, enzymes, or chemiluminescent materials. Biotin labeling kits are commercially available (Enzo Biochem, Inc.) under the Bio-Probe trade name. This type of system permits the probe to be coupled to avidin which in turn is labeled with, for example, a fluorescent molecule, enzyme, antibody, etc. For further disclosure regarding probe construction and technology, see, for example, Sambrook *et al.*, *Molecular Cloning, A Laboratory Manual* (Cold Spring Harbor, N.Y., 1982).

[0088] The oligonucleotide selected for hybridizing to the target nucleic acid, whether synthesized chemically or by recombinant DNA methodologies, is isolated and purified using standard techniques and then preferably labeled (e.g., with ^{35}S or ^{32}P) using standard labeling protocols. A sample containing the target nucleic acid then is run on an electrophoresis gel, the dispersed nucleic acids transferred to a nitrocellulose filter and the labeled oligonucleotide exposed to the filter under stringent hybridizing conditions, e.g., 50% formamide, 5 X SSPE, 2 X Denhardt's solution, 0.1% SDS at 42°C, as described in Sambrook *et al.* (1989) *supra*. The filter

- 28 -

may then be washed using 2 X SSPE, 0.1% SDS at 68°C, and more preferably using 0.1 X SSPE, 0.1% SDS at 68°C. Other useful procedures known in the art include solution hybridization, and dot and slot RNA hybridization. Optionally, the amount of the target nucleic acid present in a sample then is quantitated by measuring the radioactivity of hybridized fragments, using standard procedures known in the art.

[0089] In addition, using a combination of appropriate oligonucleotide primers, the skilled artisan can determine the level of the target nucleic acid by standard polymerase chain reaction (PCR) procedures as described elsewhere herein, for example, by quantitative PCR.

Conventional PCR based assays are discussed, for example, in Innes et al (1990) "PCR

Protocols; A guide to methods and Applications", Academic Press and Innes et al. (1995) "PCR Strategies" Academic Press, San Diego, CA. For example, U2 snRNA is detectable using a fewer number of PCR cycles in the serum of women with breast cancer than in the serum of healthy women. Additionally, the nucleic acids encoding marker proteins may be detected using nucleic acid probes having a sequence complementary to at least a portion of the sequence encoding the marker protein.

II. Exemplary Protocols for Detecting a Target Protein

[0090] A cancer marker, such as a component of a U2 particle, may be detected, for example, by combining the marker with a binding moiety capable of specifically binding the marker. The binding moiety may comprise, for example, a member of a ligand-receptor pair, i.e., a pair of molecules capable of having a specific binding interaction. The binding moiety may comprise, for example, a member of a specific binding pair, such as antibody-antigen, enzyme-substrate, protein-nucleic acid, protein-protein, or other specific binding pair known in the art. Binding proteins may be designed which have enhanced affinity for a target. Optionally, the binding moiety may be linked with a detectable label, such as an enzymatic, fluorescent, radioactive, phosphorescent or colored particle label. The labeled complex may be detected, e.g., visually or with the aid of a spectrophotometer or other detector.

[0091] A cancer marker may also be detected using any of a wide range of immunoassay techniques available in the art. For example, the skilled artisan may employ a sandwich immunoassay format to detect a cancer marker in a body fluid sample. Alternatively, the skilled

- 29 -

artisan may use conventional immuno-histochemical procedures for detecting the presence of the cancer marker in a tissue sample using one or more labeled binding proteins.

[0092] In a sandwich immunoassay, two antibodies capable of binding the marker generally are used, e.g., one immobilized onto a solid support, and one free in solution and labeled with a detectable chemical compound. Examples of chemical labels that may be used for the second antibody include radioisotopes, fluorescent compounds, and enzymes or other molecules that generate colored or electrochemically active products when exposed to a reactant or enzyme substrate. When a sample containing the marker is placed in this system, the marker binds to both the immobilized antibody and the labeled antibody, to form a "sandwich" immune complex on the support's surface. The complexed protein is detected by washing away non-bound sample components and excess labeled antibody, and measuring the amount of labeled antibody complexed to protein on the support's surface. Alternatively, the antibody free in solution, which can be labeled with a chemical moiety, for example, a hapten, may be detected by a third antibody labeled with a detectable moiety which binds the free antibody or, for example, the hapten coupled thereto.

[0093] Both the sandwich immunoassay and tissue immunohistochemical procedures are highly specific and very sensitive, provided that labels with good limits of detection are used. A detailed review of immunological assay design, theory and protocols can be found in numerous texts in the art, including "Practical Immunology", Butt, W.R., ed., (1984) Marcel Dekker, New York and "Antibodies, A Laboratory Approach", Harlow *et al.* eds., (1988) Cold Spring Harbor Laboratory.

[0094] In general, immunoassay design considerations include the preparation of antibodies (e.g., monoclonal or polyclonal antibodies) having sufficiently high binding specificity for the target to form a complex that can be distinguished reliably from products of nonspecific interactions. As used herein, the term "antibody" is understood to mean binding proteins, for example, antibodies or other proteins comprising an immunoglobulin variable region-like binding domain, having the appropriate binding affinities and specificities for the target protein. The higher the antibody binding specificity, the lower the target protein concentration that can be detected. As used herein, the terms "specific binding" or "binding specifically" are understood to mean that the binding moiety, for example, a binding protein has a binding affinity for the target protein of greater than about 10^5 M^{-1} , more preferably greater than about 10^7 M^{-1} .

- 30 -

[0095] Antibodies to an isolated target may be generated using standard immunological procedures well known and described in the art. See, for example, "Practical Immunology" (1984) *supra*. Briefly, an isolated target is used to raise antibodies in a host, such as a mouse, goat or other suitable mammal. The marker protein is combined with a suitable adjuvant capable of enhancing antibody production in the host, and is injected into the host, for example, by intraperitoneal administration. Any adjuvant suitable for stimulating the host's immune response may be used. A commonly used adjuvant is Freund's complete adjuvant (an emulsion comprising killed and dried microbial cells and available from, for example, Calbiochem Corp., San Diego, or Gibco, Grand Island, NY). Where multiple antigen injections are desired, the subsequent injections may comprise the antigen in combination with an incomplete adjuvant (e.g., cell-free emulsion). Polyclonal antibodies may be isolated from the antibody-producing host by extracting serum containing antibodies to the protein of interest. Monoclonal antibodies may be produced by isolating host cells that produce the desired antibody, fusing these cells with myeloma cells using standard procedures known in the immunology art, and screening for hybrid cells (hybridomas) that react specifically with the target and have the desired binding affinity.

[0096] Antibody binding domains also may be produced biosynthetically and the amino acid sequence of the binding domain manipulated to enhance binding affinity with a preferred epitope on the target. Specific antibody methodologies are well understood and described in the literature. A more detailed description of their preparation can be found, for example, in "Practical Immunology" (1984) *supra*.

[0097] In addition, genetically engineered biosynthetic antibody binding sites, also known in the art as BABS or sFv's, may be used in the practice of the instant invention. Methods for making and using BABS comprising (i) non-covalently associated or disulfide bonded synthetic V_H and V_L dimers, (ii) covalently linked V_H - V_L single chain binding sites, (iii) individual V_H or V_L domains, or (iv) single chain antibody binding sites are disclosed, for example, in U.S. Patent Nos.: 5,091,513; 5,132,405; 4,704,692; and 4,946,778. Furthermore, BABS having requisite specificity for a cancer marker can be derived by phage antibody cloning from combinatorial gene libraries (see, for example, Clackson *et al.* (1991) *Nature* 352: 624-628). Briefly, phage each expressing on their coat surfaces BABS having immunoglobulin variable regions encoded by variable region gene sequences derived from mice pre-immunized with an isolated cancer marker, or a fragment thereof, are screened for binding activity against the

- 31 -

immobilized marker. Phage which bind to the immobilized marker are harvested and the gene encoding the BABS is sequenced. The resulting nucleic acid sequences encoding the BABS of interest then may be expressed in conventional expression systems to produce the BABS protein.

[0098] Cancer markers may also be detected using gel electrophoresis techniques available in the art. In two-dimensional gel electrophoresis, proteins are separated first in a pH gradient gel according to their isoelectric point. The resulting gel then is placed on a second polyacrylamide gel, and the proteins separated according to molecular weight (see, for example, O'Farrell (1975) *J. Biol. Chem.* 250: 4007-4021).

[0099] One or more marker proteins may be detected by first isolating proteins from a sample obtained from an individual suspected of having cancer, and then separating the proteins by two-dimensional gel electrophoresis to produce a characteristic two-dimensional gel electrophoresis pattern. The pattern may then be compared with a standard gel pattern produced by separating, under the same or similar conditions, proteins isolated from normal or cancer cells. The standard gel pattern may be stored in, and retrieved from an electronic database of electrophoresis patterns. The presence of a cancer-associated protein in the two-dimensional gel provides an indication that the sample being tested was taken from a person with cancer. As with the other detection assays described herein, the detection of two or more proteins, for example, in the two-dimensional gel electrophoresis pattern further enhances the accuracy of the assay. The presence of a plurality, e.g., two to five, cancer-associated proteins on the two-dimensional gel provides an even stronger indication of the presence of a cancer in the individual. The assay thus permits the early detection and treatment of cancer.

[0100] Mass spectrometry may also be used to detect a marker protein. Preferred mass spectrometry methods include MALDI-TOF mass spectrometry and MALDI-TOF using derivatized chip surfaces (SELDI). Useful mass spectrometry methods for detecting a marker protein are described, for example, in U.S. Patent Nos. 5,719,060; 5,894,063; 6,124,137; 6,207,370; 6,225,047; 6,281,493; 6,322,970; and 6,936,424. In these methods, the presence and/or amount of a particular marker protein in a separation profile can be monitored.

Alternatively, the presence and/or amount of a plurality of marker proteins in a separation profile can be monitored. In such approaches, the separation profile of a marker protein or proteins derived from a test patient of unknown disposition may be compared against the separation profile of the marker protein or proteins derived from a control sample (for example, a negative

- 32 -

control where an individual is confirmed not to have breast cancer or a positive control where individual(s) is or are have been having breast cancer). The amounts of one or more of the marker proteins in the test sample relative to the amount of the same or similar proteins in the control sample can be a diagnostic or prognostic indicator of whether the individual providing the test sample may have breast cancer and/or the severity of the breast cancer. For example, a result in which the amount of a particular marker protein in the separation protein from a test individual is less than or equal to the amount of marker protein in a negative control sample is indicative that the test individual does not have breast cancer. In contrast, a result in which the amount of a particular marker protein in the separation profile from a test individual is greater than the amount of the marker protein in a positive control sample is indicative that the test individual may have breast cancer.

[0101] The invention may be more completely understood by reference to the following non-limiting examples.

EXAMPLES

Example 1 Detection of Free U2 SnRNP B" in Serum

[0102] This Example describes the development of a sandwich immunoassay for detecting free U2 snRNP B" protein in a sample that has been externalized from a nucleus, for example, by apoptosis or oxidative stress associated with cancer. Paired monoclonal antibodies were selected that recognize distinct epitopes on the U2 snRNP B" protein.

[0103] ELISA microtiter plates were coated with a 1D5 capture antibody. The 1D5 capture antibody is a monoclonal antibody that was created using recombinant U2 snRNP B" (see, SEQ ID NO. 3) as an antigen and binds to an epitope on U2 snRNP B" that is different from the epitope bound by the 4G3 monoclonal antibody (available from, for example, Eurodiagnostika, The Netherlands). These plates then were blocked by incubation with bovine serum albumin (BSA) at a concentration of 2 µg/mL for 4 hours at room temperature. Then, 400 µL of serum sample was diluted in a mixture of normal human serum (NHS): phosphate-buffered saline (PBS) 1:1, at ratios of 1:1, 1:2, 1:4, and 1:8 of sample to diluent. The diluted sample was added to the plate and incubated for 1 hour at 37°C, after which the plate was washed 3 times with PBS. Subsequently, 400 µL of a biotinylated detection antibody, biotinylated 4G3 (obtained from Eurodiagnostika, The Netherlands) at a concentration of 0.2 µg/mL was added to the plate and

- 33 -

incubated for 1 hour at 37°C. After incubation, the plate was washed 3 times with PBS.

Following incubation, Streptavidin-horse radish peroxidase fusion protein (SA-HRP)(obtained from Jackson ImmunoResearch, Inc.) was added to plate and incubated for 15 minutes at room temperature.

- 5 [0104] 100 µL of DAKO TMB Blue 1-Step Component Microwell Peroxidase (DAKO Corporation, Carpinteria California) was added to the plate to generate a signal, which was measured colorimetrically using a Spectramax Plus (Molecular Devices) spectrophotometer. The signals were scored for optical density at a wavelength of 450 nm and the concentration of U2 snRNP B'' was determined using a standard curve generated using known amounts of U2 snRNP
- 10 B''. The standard curves were generated using 5 levels of recombinant U2 snRNP B''.

[0105] It is contemplated that concentrations of U2 snRNP B'' greater than a predetermined threshold value can be indicative of the presence of breast cancer in the donor.

Example 2 Detection of Complexed U2 snRNP B'' in Serum

- [0106] This Example describes the development of a second sandwich immunoassay that
- 15 recognizes U2 snRNP B'' when it was complexed to other proteins in a sample.

[0107] Paired monoclonal antibodies were selected that recognized distinct epitopes on the U2 snRNP B'' protein. ELISA microtiter plates were coated with a 1D5 capture antibody and blocked by incubation with bovine serum albumin (BSA) at a concentration of 2 µg/mL for 4 hours at room temperature.

- 20 [0108] The samples were first denatured with 2M urea to disrupt the U2 complex. Then, 400 µL of the denatured sample was diluted in mixture of normal human serum (NHS): phosphate-buffered saline (PBS) 1:1, at ratios of 1:1, 1:2, 1:4, and 1:8 of sample to diluent. The diluted sample was added to the plate and incubated with the plate for 1 hour at 37°C, after which the plate was washed 3 times with PBS. Subsequently, 400 µL of a biotinylated detection antibody,
- 25 biotinylated 4G3 (Eurodiagnostika, The Netherlands) at a concentration of 0.2 µg/mL was added to the plate and incubated for 1 hour at 37°C. After incubation, the plate was washed 3 times with PBS. Following incubation, Streptavidin-horse radish peroxidase fusion protein (SA-HRP)(Jackson ImmunoResearch, Inc.) was added to plate and incubated for 15 minutes at room temperature.

- 34 -

- [0109] 100 μ L of DAKO TMB Blue 1-Step Component Microwell Peroxidase (DAKO Corporation, Carpinteria California) was added to the plate to generate a signal, which was measured colorimetrically using a Spectramax Plus (Molecular Devices) spectrophotometer. The signals were scored for optical density at a wavelength of 450 nm. The resulting values were used to calculate the concentration of U2 snRNP B'' by interpolation from a calibration curve created using different concentrations of U2 snRNP B''. A level of U2 snRNP B'' higher than a determined threshold was indicative of cancer in the sample. The standard curves were generated using 5 levels of isolated U2 snRNP B''-associated complex. The minimum analytical detection limit was set at the signal level 3 SD above the mean signal of zero analyte.
- 10 [0110] Fifty patient samples comprising 14 from patients with cancer and 36 with benign disease or no detectable disease were tested. The results are shown in Table 1. Seven samples from the fourteen patients with cancer were positive by the complexed U2 snRNP B'' immunoassay, and 9 of thirty-six samples from patients free of cancer were positive.

- 35 -

TABLE 1

Truth Table Complexed U2 snRNP B ⁺ Immunoassay Test			
	CANCER (+)	CANCER (-)	
Immunoassay Test (+)	True Positive (TP) 7	False Positive (FP) 9	Total Immunoassay (+) 16
Immunoassay Test (-)	False Negative (FN) 7	True Negative (TN) 27	Total Immunoassay (-) 34
	Total Cancer 14	Total Non-Cancer 36	Total Population 50

[0111] The sensitivity of the assay was calculated as $TP/(TP+FN)$: $7/14 = 50\%$; the specificity was calculated as $TN/(TN+FP)$: $27/36 = 75\%$; the positive predictive value was calculated as $TP/(TP+FP)$: $7/16 = 44\%$; the negative predictive value was calculated as $TN/(TN+FN)$: $27/34 = 79\%$; and the diagnostic accuracy was calculated as $TP+TN/(TP+TN+FP+FN)$: $34/50 = 68\%$.

Example 3 Purification and Screening Method for U2 snRNA

[0112] This Example shows that it is possible to detect U2 snRNA in a sample using an antibody that binds specifically to the 2,2,7, trimethylguanosine CAP.

10 [0113] The serum samples used in this Example required no extensive pretreatment, but were diluted in a mild salt and detergent solution (1:10 "CSK" buffer: 10 mM NaCl, 30 mM sucrose, 1 mM PIPES pH 6.8, 500 μ M $MgCl_2$, 0.05% Triton X-100) at a mixture of not less than 1:1 with the 1:10 CSK buffer. In addition, 10 μ L of RNase inhibitor (Ambion Inc., Austin, TX, Catalog number 2682) was added to each sample.

15 [0114] A separate capture column was prepared for each sample. The resin used to prepare each capture column contained 2,2,7-trimethylguanosine agarose-linked conjugate from Oncogene Science (Catalog number NA02A). The resin was placed in a polypropylene centrifuge filter apparatus (for example, Pierce EZ Kit catalog number 4051742). The amount of resin was 50 μ g, but other amounts are contemplated. The resin column was washed three
20 times with 400 μ L of coupling buffer before use (200 mM ammonium acetate with 16 μ L of RNASecure™ (Ambion catalog number 7005)). A 1/25 volume of RNASecure™ was added to all column washes. The washes consisted of direct addition of the wash solution to the column

- 36 -

bed followed by centrifugation for 1 minute on a tabletop micro-centrifuge (for example the National Labnet Company model C-1200) at 1000 revolutions per minute. The wash was discarded from the collection tube of the column apparatus. The collection tube was reused until the product was eluted.

5 [0115] 400 μ L of diluted sera was added to each of the prepared columns. Each column was allowed to tumble 1 hour at room temperature on a benchtop test tube rotary rocker (Barnstead/Thermolyne model 400110) at a rotation frequency of 8 revolutions per minute. The void volume of liquid was removed by repeating the centrifugation step into the collection tube. This volume, referred to as the "flow through," was used for analysis of the protocol. The
10 column was washed as indicated above three times using 400 μ L of 100 mM ammonium acetate pH 7. The washes were collected for analysis.

[0116] The captured RNA then was eluted by adding 200 μ L of elution buffer (15 mM 7-methyl guanosine in a solution of 300 mM ammonium chloride). The apparatus was allowed to tumble for ten minutes at room temperature. The apparatus was centrifuged as described above
15 in the wash steps and the eluate collected for diagnostic analysis.

[0117] The column can be regenerated, although regeneration is not presently preferred when performing diagnostic tests. To regenerate the column, 200 μ L of low pH buffer (0.1 M glycine-HCl pH 2.45) were added. The column was allowed to tumble as in the wash and elution steps and the volume can be collected for analysis of the protocol. The column is washed with 400 μ L
20 of standard PBS as with the previous wash steps. 400 μ L of 1.4 M NaCl were added and the column was stored at 4°C.

[0118] RT-PCR was performed on the diagnostic eluate using the Titanium™ One-Step RT-PCR Kit (Clontech/BD Biosciences catalog number 639504 K1403) and the RT-PCR primers of SEQ ID NO. 86 and SEQ ID NO. 87. RNA-primer mixtures for 75°C heat treatment were
25 prepared. The primer mixtures were each 7.5 μ L total and included 1 μ L of primers (45 μ M), 1 μ L of RNA sample or control, and Kit RT buffer (RNAse inhibitor, GC melt dNTP's, RT). The heat treatment program on the MJ 100 Thermal Cycler was run. 42.5 μ L of PCR Master Mix were added to each tube; Kit PCR buffer with Taq enzyme was used. The Thermal Cycler Program "2-Step" was run with the following parameters: 50°C x 1 hour; 95°C x 5 minutes;
30 95°C x 30 seconds; 58°C x 30 seconds; repeat 35 times; 68°C x 2 minutes; hold at 4°C.

- 37 -

[0119] Samples were subsequently evaluated by gel electrophoresis. U2 snRNA abundance could be determined by examination of the gel image and threshold dilution analysis. It is contemplated that RT-PCR can also be used to measure the product. An example of such a gel appears in Figure 5.

- 5 [0120] Fifty patient samples comprising 14 from patients with cancer and 36 with benign disease or no detectable disease were tested with an RT-PCR assay for U2 snRNA. The results are shown in Table 2. RT-PCR detected the presence of U2 snRNA in 30 of the samples. U2 snRNA was amplified in thirteen of the fourteen samples from cancer patients and in 19 of 36 samples from patients with benign or no detectable disease.

10

TABLE 2

Truth Table for PCR Assay (U2 snRNA)			
	CANCER (+)	CANCER (-)	
PCR Test (+)	True Positive (TP) 13	False Positive (FP) 17	Total PCR (+) 30
PCR Test (-)	False Negative (FN) 1	True Negative (TN) 19	Total PCR (-) 20
	Total Cancer 14	Total Non-Cancer 36	Total Population 50

[0121] The sensitivity for the assay was calculated as $TP/(TP+FN)$: $13/14 = 93\%$; the specificity was calculated as $TN/(TN+FP)$: $19/36 = 53\%$; the positive predictive value was calculated as $TP/(TP+FP)$: $13/30 = 43\%$; the negative predictive value was calculated as $TN/(TN+FN)$: $19/20 = 95\%$; and the diagnostic accuracy was calculated as

- 15 $TP+TN/(TP+TN+FP+FN)$: $32/50 = 64\%$

Example 4 Morpholino Purification and Screening Method

[0122] This Example provides a protocol for capturing U2 particles.

[0123] The affinity resin was prepared as follows. U2 specific morpholinos, as set forth in SEQ ID NO. 88, with a primary amine synthesized at the 3' end (GeneTools, LLC Philomath

- 20 OR) were obtained in 300 nmol amounts. The morpholinos were immobilized on agarose-4CLB

- 38 -

using the AminoLink[®] Immobilization Kit and AminoLink[®] Coupling Gel (Pierce Biotechnology, Inc., Rockford, IL) in accordance with the manufacturer's instructions.

[0124] Serum samples were diluted in a mild salt and detergent solution (e.g., 10mM NaCl, 30 mM sucrose, 1 mM PIPES pH 6.8, 0.5 mM MgCl₂, 0.05% Triton X-100) at a mixture of not less than 1:1. In addition, 10 µL of RNase inhibitor (Ambion Inc. Austin TX Catalog # 2682) were added to each sample.

[0125] Then, each sample was pre-cleared using a column packed with Agarose-4Clb (Amersham Pharmacia). The pre-clearing was performed on at least 1.0 mL of diluted sample. The vessel used for performing the pre-clearing was a vial or a tube made of unwettable material that had a capacity of at least 5 times the volume of the sample and resin to be used in the pre-clearing. An amount of resin 6 times greater than the sample was selected. The pre-clearing column matrix (agarose 4clb) agarose resin was washed with an equal volume of WB 250 buffer (250mM NaCl, 20mM HEPES, pH 7.9, 0.05% NP-40, 5mM PMSF, 0.5mM DTT). The resin was centrifuged using a table-top centrifuge (National Labnet Company model C-1200) at 1000g for 5 minutes, and the supernatant buffer was removed. An equal volume of fresh WB250 then was added. The resulting beads were divided into five aliquots, each aliquot corresponding to at least 0.6 volumes of the total amount of diluted sample to be pre-cleared. The aliquots were centrifuged as before and the supernatant buffer removed from each resin. The serum sample to be tested, diluted 1:1 with WB250, was added to one of the aliquots. The sample and resin mix was slowly rotated for one hour. Subsequently, the sample and resin mix was centrifuged at 1000g for 2 minutes and the supernatant removed. The supernatant was added to a fresh aliquot of WB250 washed agarose. The steps of rotation mixing, centrifugation and supernatant transfer were repeated three more times. The final supernatants were designated "pre-cleared extracts" or PCEs, and were analyzed immediately or frozen at minus 80 °C

[0126] 70 µL of premix was prepared containing the following components: 15 µL of 0.1M ATP, 10 µL of 0.5M creatine phosphate, 2 µL of 1M MgCl₂, complete with H₂O to final volume of 70 µL, 150 µL of affinity resin. 70 µL premix was added to 0.9 mL of PCE and mixed gently. 30 µL of 5M NaCl was added to bring the PCE mixture to a final concentration of 250 mM NaCl. The mixture was incubated at 30°C for 2.5 hours at room temperature. The extract then was centrifuged at 1300g. The supernatant was removed and the residual gel was washed 5 times with 200 µL of WB100 (the composition was identical to WB250, with the exception that the

- 39 -

concentration of NaCl was 100 mM). The gel then was washed 5 times with 200 μ L of WB250. The U2 particles were first eluted by incubation at 75°C, 10 minutes in WB100 (E1). The remaining U2 particles were eluted with 200 μ L water (E2). The elutes were centrifuged and the supernatants collected. The collected samples were concentrated to dryness in Speed-Vac
5 (Savant) vacuum evaporator. The pellets then were re-suspended in an appropriate buffer for analysis (eg., PCR, ELISA).

[0127] It is contemplated that resulting E1 and E2 fractions can be used for diagnostic purposes. For example, the E1 fraction may be used in quantitative RT-PCR measurements, or other nucleic acid-based measurements. The E2 fraction may be used in protein measurements
10 including immunoassays such as ELISAs. The results from nucleic acid and/or protein methods may be used to diagnose cancer in an individual.

Equivalents

[0128] The invention may be embodied in other specific forms without departing from the spirit or essential characteristics thereof. The foregoing embodiments are therefore to be
15 considered in all respects illustrative rather than limiting on the invention described herein. Scope of the invention is thus indicated by the appended claims rather than by the foregoing description, and all changes that come within the meaning and range of equivalency of the claims are intended to be embraced by reference therein.

Incorporation By Reference

20 [0129] The entire disclosure of each of the aforementioned patent and scientific documents cited hereinabove is expressly incorporated by reference herein for all purposes.

- 40 -

What is claimed is:

- 1 1. A method of diagnosing cancer in a mammal, the method comprising the steps of:
 - 2 (a) disrupting a complex in a tissue or body fluid sample from a mammal, the complex
 - 3 comprising one or more components of spliceosomal particle U2; and
 - 4 (b) detecting a component of spliceosomal particle U2, wherein the presence of the
 - 5 component is indicative of the presence of cancer in the mammal.
- 1 2. A method of diagnosing cancer in a mammal, the method comprising the steps of:
 - 2 (a) disrupting a complex in a tissue or body fluid sample from a mammal, the complex
 - 3 comprising one or more components of spliceosomal particle U2; and
 - 4 (b) measuring the amount of the component of spliceosomal particle U2, wherein the
 - 5 amount of the component is indicative of the presence of cancer in the mammal.
- 1 3. The method of claim 1 or 2, wherein the complex is disrupted by mixing the complex with a
- 2 denaturant.
- 1 4. The method of claim 3, wherein the denaturant is urea.
- 1 5. A method of diagnosing cancer in a mammal, the method comprising the step of detecting in a
- 2 tissue or body fluid sample isolated from the mammal the presence of a component of
- 3 spliceosomal particle U2, which if present is indicative of cancer in the mammal, provided that
- 4 the component is not U2 snRNP B".
- 1 6. A method of diagnosing cancer in a mammal, the method comprising the step of measuring in
- 2 a tissue or body fluid sample isolated from the mammal an amount of a component of
- 3 spliceosomal particle U2, wherein the amount is indicative of cancer in the mammal, provided
- 4 that the component is not U2 snRNP B".
- 1 7. The method of claim 2 or 6, wherein the amount, when greater than or equal to a threshold
- 2 value, is indicative of the presence of cancer in the mammal.
- 1 8. A method of diagnosing cancer in a mammal, the method comprising the steps of:
 - 2 (a) combining a tissue or body fluid sample isolated from the mammal with a purified
 - 3 binding moiety capable of binding specifically to a component of spliceosomal particle U2
 - 4 thereby to form a complex comprising the binding moiety and the component, provided that the
 - 5 component is not U2 snRNP B"; and

- 41 -

(b) detecting the presence of the complex, which, if present, is indicative of the presence of cancer in the mammal.

9. A method of diagnosing cancer in a mammal, the method comprising the steps of:

(a) combining a tissue or body fluid sample isolated from the mammal with a purified binding moiety capable of binding specifically to a component of spliceosomal particle U2 thereby to form a complex comprising the binding moiety and the component, provided that the component is not U2 snRNP B"; and

(b) measuring the amount of the complex, wherein an amount of the complex greater than or equal to a threshold value is indicative of the presence of cancer in the mammal.

10. The method of any one of claims 1-4, wherein the component is U2 snRNP B".

11. The method of any one of claims 1-9, wherein the component is U2 snRNA.

12. The method of any one of claims 1-9, wherein the component is SAP155.

13. The method of any one of claims 1-9, wherein the component is SAP145.

14. The method of any one of claims 1-9, wherein the component is SPF31.

15. The method of any one of claims 1-9, wherein the component is selected from the group consisting of SAP130, SAP114, SAP62, SAP61, SAP49, U2 snRNP A', p14, U2AF35, U2AF65, U2AF1-RS2, hPrp5p, hPrp19, HuR, ALY, SR140, CHERP, hPrp43, HSP75, PUF60, Hsp60, SPF45, BRAF35, SF2/ASF, SF3b14b, SF3b10, SF3a120, SF3a66, SF3a60, and SPF30.

16. The method of claim 11, wherein the detecting step comprises amplifying the U2 snRNA.

17. The method of any one of claims 1-16, wherein the detecting or measuring step comprises detecting or measuring the amount of a plurality of components of the U2 spliceosomal particle.

18. The method of anyone of claims 1-17, wherein the detecting or measuring step comprises detecting or measuring a second, different component of the U2 spliceosomal particle.

19. The method of claim 18, wherein the second, different component is selected from the group consisting of SAP155, SAP145, SPF31, SAP130, SAP114, SAP62, SAP61, SAP49, U2 snRNP A', p14, U2AF35, U2AF65, U2AF1-RS2, hPrp5p, hPrp19, HuR, ALY, SR140, CHERP, hPrp43, HSP75, PUF60, Hsp60, SPF45, BRAF35, SF2/ASF, SF3b14b, SF3b10, SF3a120, SF3a66, SF3a60, and SPF30.

- 42 -

- 1 20. The method of claim 18, wherein the second, different component is selected from the group
2 consisting of U2 snRNP B'' and U2 snRNA.
- 1 21. The method of claim 8 or 9, wherein the binding moiety is selected from the group
2 consisting of a nucleic acid, a nucleic acid analog, and a protein.
- 1 22. The method of claim 21, wherein the protein is a snurportin protein.
- 1 23. The method of claim 21, wherein the protein is an antibody or an antigen-binding fragment
2 thereof.
- 1 24. The method of claim 23, wherein the antibody is selected from the group consisting of an
2 anti-2,2,7-trimethylguanosine antibody, an anti-Sm antibody, an anti-SMN antibody, an anti-
3 Importin B antibody, an anti-snurportin antibody, an anti-Ran antibody, and an anti-Ran-GTP
4 antibody.
- 1 25. The method of any one of claims 1-24, wherein the detecting step comprises mass
2 spectrometry.
- 1 26. The method of claim 2, 6, and 9, wherein the amount is a relative amount.
- 1 27. A method of detecting one or more snRNAs comprising 2,2,7-trimethylguanosine in a body
2 fluid sample isolated from a mammal, the method comprising:
3 (a) contacting the sample with a binding moiety that specifically binds 2,2,7-
4 trimethylguanosine, such that, if an snRNA comprising 2,2,7-trimethylguanosine is present in
5 the sample, the snRNA binds to the moiety to produce a complex; and
6 (b) detecting the presence, absence or amount of the complex.
- 1 28. The method of claim 27, wherein the presence or amount of the complex is indicative of the
2 presence of cancer.
- 1 29. The method of claim 27 or 28, wherein the binding moiety is an antibody or an antigen-
2 binding fragment thereof.
- 1 30. The method of any one of claims 1-29, wherein the mammal is a human.
- 1 31. The method of any one of claims 1-30, wherein the sample is a breast tissue sample.
- 1 32. The method of any one of claims 1-26 and 28-31, wherein the cancer is breast cancer.

- 43 -

1 33. The method of any one of claims 1-30, wherein the sample is a body fluid sample selected
2 from the group consisting of blood, serum, plasma, nipple aspirate, ductal lavage fluid, fine
3 needle aspirate, sweat, tears, urine, peritoneal fluid, lymph, vaginal secretions, semen, spinal
4 fluid, ascitic fluid, saliva and sputum.

1 34. A kit comprising:

- 2 (a) a purified binding moiety that specifically binds 2,2,7-trimethylguanosine; and
3 (b) one or more molecules complementary to at least a portion of a U2 snRNA.

1 35. The kit of claim 34, wherein the binding moiety is an antibody or an antigen-binding
2 fragment thereof.

1 36. A kit for detecting cancer, the kit comprising:

- 2 (a) a purified binding moiety that specifically binds U2 snRNA; and
3 (b) a reference sample having an amount of U2 snRNA indicative of the presence of
4 cancer.

1 37. The kit of claim 36, further comprising a receptacle for receiving a sample from a patient.

1 38. The kit of claim 36, wherein the binding moiety is a nucleic acid or nucleic acid analog
2 complementary to at least a portion of the U2 snRNA.

1 39. The kit of claim 36, wherein the binding moiety is an antibody or an antigen-binding
2 fragment thereof.

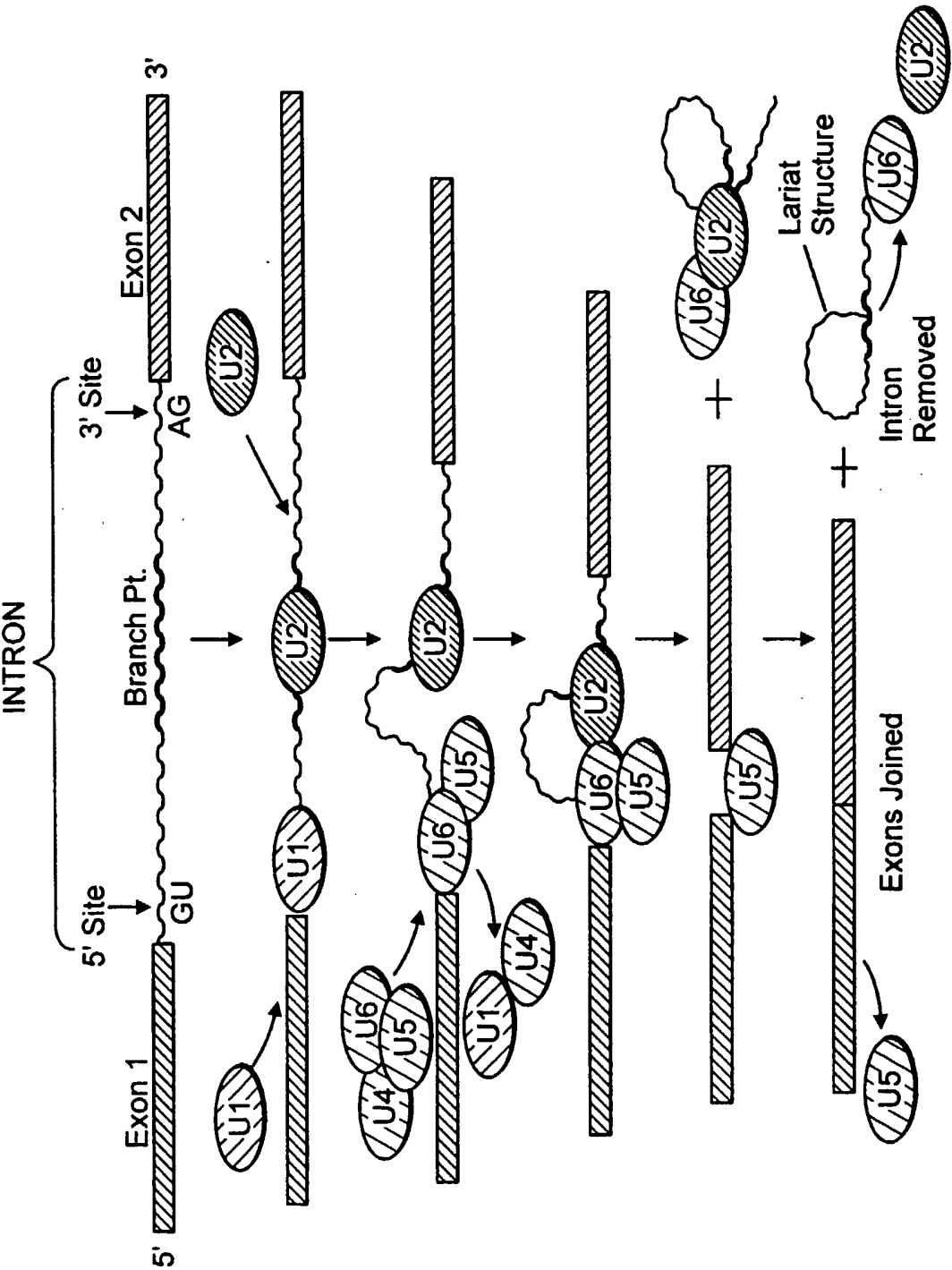


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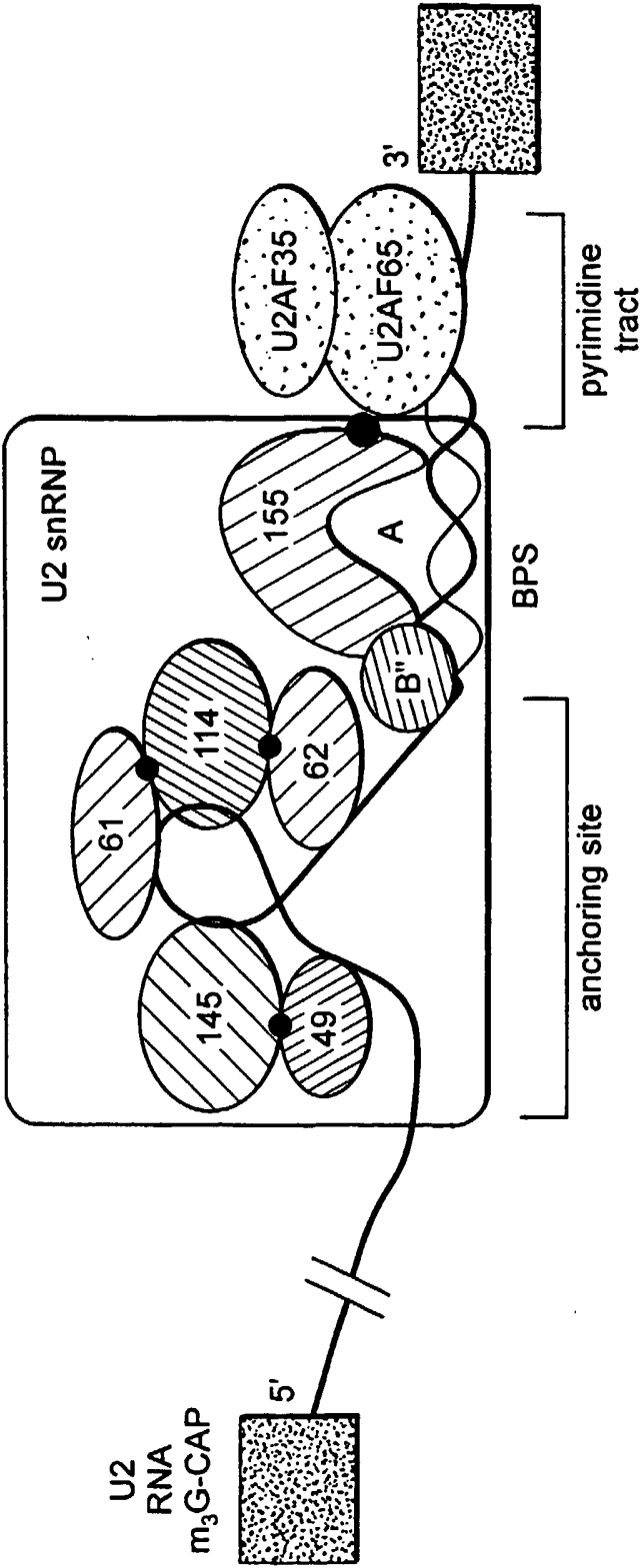


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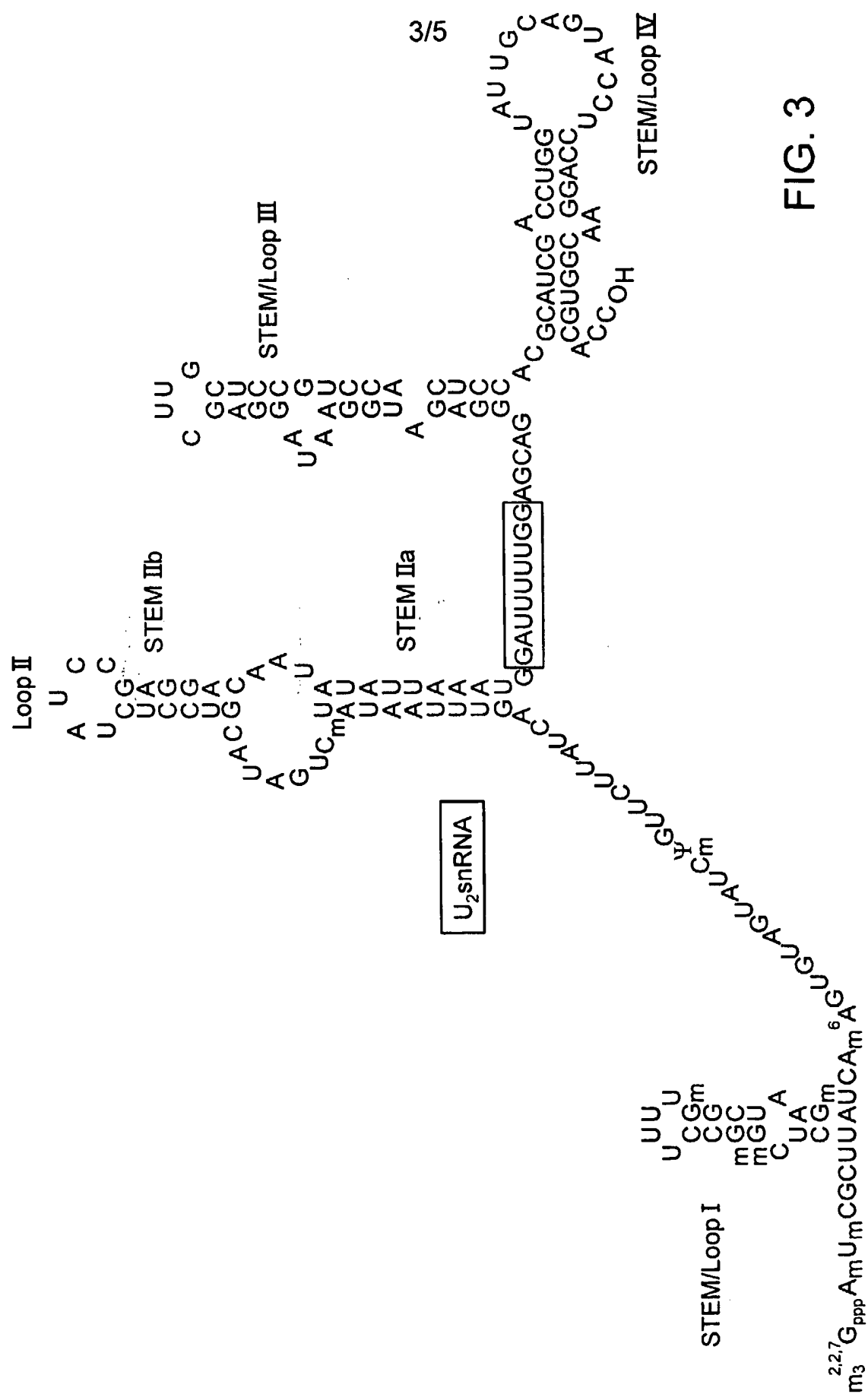


FIG. 3

4/5

Morpholine

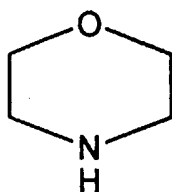


FIG. 4A

Morpholino Oligo

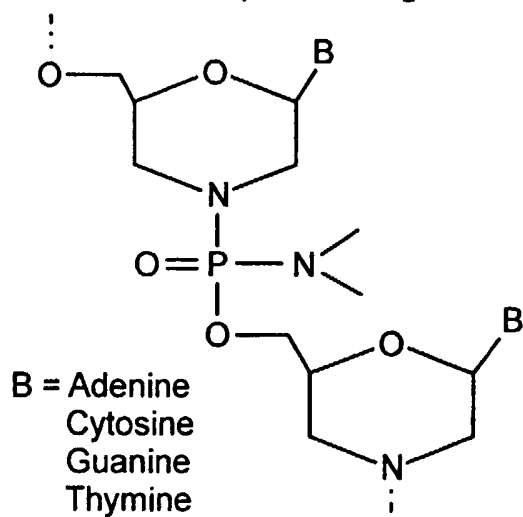
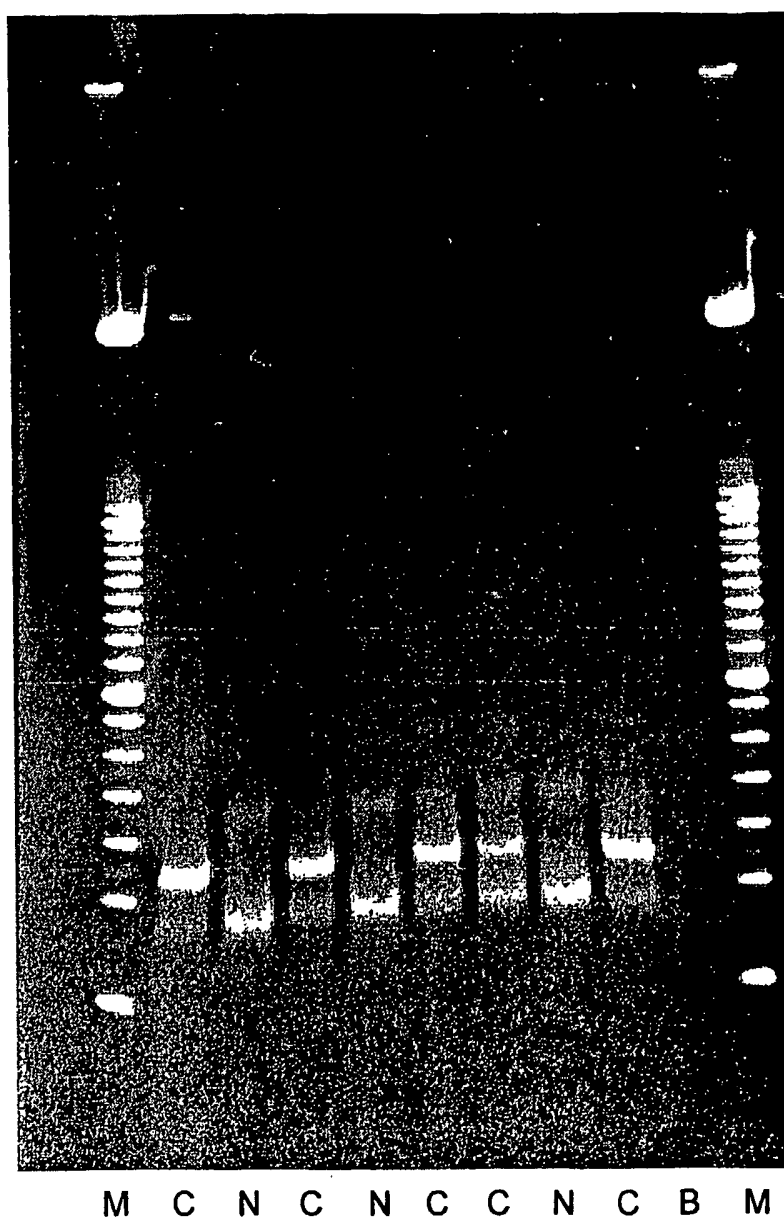


FIG. 4B

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FIG. 5

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Ala Asp Arg₁₁₅ Glu Asp Glu Tyr Lys₁₂₀ Lys His Arg Arg Thr₁₂₅ Met Ile Ile

Ser Pro Glu Arg Leu Asp Pro₁₃₅ Phe Ala Asp Gly₁₄₀ Lys Thr Pro Asp

Pro Lys Met Asn Val₁₅₀ Arg Thr Tyr Met Asp Val₁₅₅ Met Arg Glu Gln His₁₆₀

Leu Thr Lys Glu Glu₁₆₅ Arg Glu Ile Arg Gln₁₇₀ Gln Leu Ala Glu Lys₁₇₅ Ala

Lys Ala Gly Glu₁₈₀ Leu Lys Val Val₁₈₅ Asn Gly Ala Ala Ala Ser₁₉₀ Gln Pro

Pro Ser Lys₁₉₅ Arg Lys Arg Arg Trp₂₀₀ Asp Gln Thr Ala Asp₂₀₅ Gln Thr Pro

Gly Ala Thr Pro Lys Lys₂₁₅ Leu Ser Ser Trp Asp Gln₂₂₀ Ala Glu Thr Pro

Gly His Thr Pro Ser₂₃₀ Leu Arg Trp Asp Glu Thr₂₃₅ Pro Gly Arg Ala Lys₂₄₀

Gly Ser Glu Thr Pro₂₄₅ Gly Ala Thr Pro Gly₂₅₀ Ser Lys Ile Trp Asp₂₅₅ Pro

Thr Pro Ser His₂₆₀ Thr Pro Ala Gly Ala₂₆₅ Ala Thr Pro Gly Arg₂₇₀ Gly Asp

Thr Pro Gly₂₇₅ His Ala Thr Pro Gly₂₈₀ His Gly Gly Ala Thr₂₈₅ Ser Ser Ala

Arg Lys₂₉₀ Asn Arg Trp Asp Glu₂₉₅ Thr Pro Lys Thr Glu₃₀₀ Arg Asp Thr Pro

Gly His Gly Ser Gly₃₁₀ Trp Ala Glu Thr Pro Arg₃₁₅ Thr Asp Arg Gly Gly₃₂₀

Asp Ser Ile Gly Glu₃₂₅ Thr Pro Thr Pro Gly₃₃₀ Ala Ser Lys Arg Lys₃₃₅ Ser

Arg Trp Asp Glu₃₄₀ Thr Pro Ala Ser Gln₃₄₅ Met Gly Gly Ser Thr₃₅₀ Pro Val

Leu Thr Pro Gly Lys Thr Pro Ile₃₆₀ Gly Thr Pro Ala Met₃₆₅ Asn Met Ala

Thr Pro Thr Pro Gly His Ile₃₇₅ Met Ser Met Thr Pro₃₈₀ Glu Gln Leu Gln

Ala Trp Arg Trp Glu Arg₃₉₀ Glu Ile Asp Glu Arg₃₉₅ Asn Arg Pro Leu Ser₄₀₀

Asp Glu Glu Leu Asp₄₀₅ Ala Met Phe Pro Glu₄₁₀ Gly Tyr Lys Val Leu₄₁₅ Pro

Pro Pro Ala Gly Tyr Val Pro Ile Arg₄₂₅ Thr Pro Ala Arg Lys₄₃₀ Leu Thr

Ala Thr Pro Thr Pro Leu Gly Gly₄₄₀ Met Thr Gly Phe His₄₄₅ Met Gln Thr

MTP-031PC.TXT

Glu Asp Arg Thr Met Lys Ser Val Asn Asp Gln Pro Ser Gly Asn Leu
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 Pro Phe Leu Lys Pro Asp Asp Ile Gln Tyr Phe Asp Lys Leu Leu Val
 465 470 475 480
 Asp Val Asp Glu Ser Thr Leu Ser Pro Glu Glu Gln Lys Glu Arg Lys
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 Ile Met Lys Leu Leu Leu Lys Ile Lys Asn Gly Thr Pro Pro Met Arg
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 Lys Ala Ala Leu Arg Gln Ile Thr Asp Lys Ala Arg Glu Phe Gly Ala
 515 520 525
 Gly Pro Leu Phe Asn Gln Ile Leu Pro Leu Leu Met Ser Pro Thr Leu
 530 535 540
 Glu Asp Gln Glu Arg His Leu Leu Val Lys Val Ile Asp Arg Ile Leu
 545 550 555 560
 Tyr Lys Leu Asp Asp Leu Val Arg Pro Tyr Val His Lys Ile Leu Val
 565 570 575
 Val Ile Glu Pro Leu Leu Ile Asp Glu Asp Tyr Tyr Ala Arg Val Glu
 580 585 590
 Gly Leu Glu Ile Ile Ser Asn Leu Ala Lys Ala Ala Gly Leu Ala Thr
 595 600 605
 Met Ile Ser Thr Met Arg Pro Asp Ile Asp Asn Met Asp Glu Tyr Val
 610 615 620
 Arg Asn Thr Thr Ala Arg Ala Phe Ala Val Val Ala Ser Ala Leu Gly
 625 630 635 640
 Ile Pro Ser Leu Leu Pro Phe Leu Lys Ala Val Cys Lys Ser Lys Lys
 645 650 655
 Ser Trp Gln Ala Arg His Thr Gly Ile Lys Ile Val Gln Gln Ile Ala
 660 665 670
 Ile Leu Met Gly Cys Ala Ile Leu Pro His Leu Arg Ser Leu Val Glu
 675 680 685
 Ile Ile Glu His Gly Leu Val Asp Glu Gln Gln Lys Val Arg Thr Ile
 690 695 700
 Ser Ala Leu Ala Ile Ala Ala Leu Ala Glu Ala Ala Thr Pro Tyr Gly
 705 710 715 720
 Ile Glu Ser Phe Asp Ser Val Leu Lys Pro Leu Trp Lys Gly Ile Arg
 725 730 735
 Gln His Arg Gly Lys Gly Leu Ala Ala Phe Leu Lys Ala Ile Gly Tyr
 740 745 750
 Leu Ile Pro Leu Met Asp Ala Glu Tyr Ala Asn Tyr Tyr Thr Arg Glu
 755 760 765
 Val Met Leu Ile Leu Ile Arg Glu Phe Gln Ser Pro Asp Glu Glu Met
 770 775 780
 Lys Lys Ile Val Leu Lys Val Val Lys Gln Cys Cys Gly Thr Asp Gly
 785 790 795 800
 Val Glu Ala Asn Tyr Ile Lys Thr Glu Ile Leu Pro Pro Phe Phe Lys

MTP-031PC.TXT

805	810	815
His Phe Trp Gln 820	His Arg Met Ala Leu Asp Arg Arg Asn Tyr Arg Gln 825	
Leu Val Asp Thr Thr Val Glu Leu Ala Asn Lys Val Gly Ala Ala Glu 835		
Ile Ile Ser Arg Ile Val Asp Asp Leu Lys Asp Glu Ala Glu Gln Tyr 850		
Arg Lys Met Val Met Glu Thr Ile Glu Lys Ile Met Gly Asn Leu Gly 865		
Ala Ala Asp Ile Asp His Lys Leu Glu Glu Gln Leu Ile Asp Gly Ile 885		
Leu Tyr Ala Phe Gln Glu Gln Thr Thr Glu Asp Ser Val Met Leu Asn 900		
Gly Phe Gly Thr Val Val Asn Ala Leu Gly Lys Arg Val Lys Pro Tyr 915		
Leu Pro Gln Ile Cys Gly Thr Val Leu Trp Arg Leu Asn Asn Lys Ser 930		
Ala Lys Val Arg Gln Gln Ala Ala Asp Leu Ile Ser Arg Thr Ala Val 945		
Val Met Lys Thr Cys Gln Glu Glu Lys Leu Met Gly His Leu Gly Val 965		
Val Leu Tyr Glu Tyr Leu Gly Glu Glu Tyr Pro Glu Val Leu Gly Ser 980		
Ile Leu Gly Ala Leu Lys Ala Ile Val Asn Val Ile Gly Met His Lys 995		
Met Thr Pro Pro Ile Lys Asp Leu Leu Pro Arg Leu Thr Pro Ile Leu 1010		
Lys Asn Arg His Glu Lys Val Gln Glu Asn Cys Ile Asp Leu Val Gly 1025		
Arg Ile Ala Asp Arg Gly Ala Glu Tyr Val Ser Ala Arg Glu Trp Met 1045		
Arg Ile Cys Phe Glu Leu Leu Glu Leu Leu Lys Ala His Lys Lys Ala 1060		
Ile Arg Arg Ala Thr Val Asn Thr Phe Gly Tyr Ile Ala Lys Ala Ile 1075		
Gly Pro His Asp Val Leu Ala Thr Leu Leu Asn Asn Leu Lys Val Gln 1090		
Glu Arg Gln Asn Arg Val Cys Thr Thr Val Ala Ile Ala Ile Val Ala 1105		
Glu Thr Cys Ser Pro Phe Thr Val Leu Pro Ala Leu Met Asn Glu Tyr 1125		
Arg Val Pro Glu Leu Asn Val Gln Asn Gly Val Leu Lys Ser Leu Ser 1140		
Phe Leu Phe Glu Tyr Ile Gly Glu Met Gly Lys Asp Tyr Ile Tyr Ala 1155		

MTP-031PC.TXT

Val Thr Pro Leu Leu Glu Asp Ala Leu Met Asp Arg Asp Leu Val His
 1170 1175 1180

Arg Gln Thr Ala Ser Ala Val Val Gln His Met Ser Leu Gly Val Tyr
 1185 1190 1195 1200

Gly Phe Gly Cys Glu Asp Ser Leu Asn His Leu Leu Asn Tyr Val Trp
 1205 1210 1215

Pro Asn Val Phe Glu Thr Ser Pro His Val Ile Gln Ala Val Met Gly
 1220 1225 1230

Ala Leu Glu Gly Leu Arg Val Ala Ile Gly Pro Cys Arg Met Leu Gln
 1235 1240 1245

Tyr Cys Leu Gln Gly Leu Phe His Pro Ala Arg Lys Val Arg Asp Val
 1250 1255 1260

Tyr Trp Lys Ile Tyr Asn Ser Ile Tyr Ile Gly Ser Gln Asp Ala Leu
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Ile Ala His Tyr Pro Arg Ile Tyr Asn Asp Asp Lys Asn Thr Tyr Ile
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Arg Tyr Glu Leu Asp Tyr Ile Leu
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 SAP155 consensus sequence

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MTP-031PC.TXT

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<223> Variable residue or not present

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

MTP-031PC.TXT

Pro Gly Ala Ser Lys Arg Lys Ser Arg Trp Asp Glu Thr Pro Ala Ser
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 Gln Met Gly Gly Ser Thr Pro Val Leu Thr Pro Gly Lys Thr Pro Ile
 355 360 365
 Gly Thr Pro Ala Met Asn Met Ala Thr Pro Thr Pro Gly His Ile Met
 370 375 380
 Ser Met Thr Pro Glu Gln Leu Gln Ala Trp Arg Trp Glu Arg Glu Ile
 385 390 395 400
 Asp Glu Arg Asn Arg Pro Leu Ser Asp Glu Glu Leu Asp Ala Met Phe
 405 410 415
 Pro Glu Gly Tyr Lys Val Leu Pro Pro Pro Ala Gly Tyr Val Pro Ile
 420 425 430
 Arg Thr Pro Ala Arg Lys Leu Thr Ala Thr Pro Thr Pro Leu Gly Gly
 435 440 445
 Met Thr Gly Phe His Met Gln Thr Glu Asp Arg Thr Met Lys Ser Val
 450 455 460
 Asn Asp Gln Pro Ser Gly Asn Leu Pro Phe Leu Lys Pro Asp Asp Ile
 465 470 475 480
 Gln Tyr Phe Asp Lys Leu Leu Val Asp Val Asp Glu Ser Thr Leu Ser
 485 490 495
 Pro Glu Glu Gln Lys Glu Arg Lys Ile Met Lys Leu Leu Leu Lys Ile
 500 505
 Lys Asn Gly Thr Pro Pro Met Arg Lys Ala Ala Leu Arg Gln Ile Thr
 515 520 525
 Asp Lys Ala Arg Glu Phe Gly Ala Gly Pro Leu Phe Asn Gln Ile Leu
 530 535 540
 Pro Leu Leu Met Ser Pro Thr Leu Glu Asp Gln Glu Arg His Leu Leu
 545 550 555 560
 Val Lys Val Ile Asp Arg Ile Leu Tyr Lys Leu Asp Asp Leu Val Arg
 565 570 575
 Pro Tyr Val His Lys Ile Leu Val Val Ile Glu Pro Leu Leu Ile Asp
 580 585 590
 Glu Asp Tyr Tyr Ala Arg Val Glu Gly Xaa Glu Ile Ile Ser Asn Leu
 595 600 605
 Ala Lys Ala Ala Gly Leu Ala Thr Met Ile Ser Thr Met Arg Pro Asp
 610 615 620
 Ile Asp Asn Met Asp Glu Tyr Val Arg Asn Thr Thr Ala Arg Ala Phe
 625 630 635 640
 Ala Val Val Ala Ser Ala Leu Gly Ile Pro Ser Leu Leu Pro Phe Leu
 645 650 655
 Lys Ala Val Cys Lys Ser Lys Lys Ser Trp Gln Ala Arg His Thr Gly
 660 665 670
 Ile Lys Ile Val Gln Gln Ile Ala Ile Leu Met Gly Cys Ala Ile Leu
 675 680 685
 Pro His Leu Arg Ser Leu Val Glu Ile Ile Glu His Gly Leu Val Asp

MTP-031PC.TXT
700

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Glu Gln Gln Lys Val	Arg Thr Ile Ser Ala	Leu Ala Ile Ala Ala Leu
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Ala Glu Ala Ala Thr	Pro Tyr Gly Ile Glu	Ser Phe Asp Ser Val Leu
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Lys Pro Leu Trp	Lys Gly Ile Arg Gln	His Arg Gly Lys Gly Leu Ala
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Ala Phe Leu Lys Ala Ile	Gly Tyr Leu Ile Pro Leu	Met Asp Ala Glu
	755	760 765
Tyr Ala Asn Tyr Tyr Thr	Arg Glu Val Met Leu	Ile Leu Ile Arg Glu
	770	775 780
Phe Gln Ser Pro Asp	Glu Glu Met Lys Lys	Ile Val Leu Lys Val Xaa
	785	790 795 800
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Tyr Ile Lys Thr	Glu Ile Leu Pro	Pro Phe Phe Lys His Phe Trp Gln
	820	825 830
His Arg Met	Ala Leu Asp Arg	Arg Asn Tyr Arg Gln Leu Val Asp Thr
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Thr Val Glu Leu Ala	Asn Lys Val Gly Ala Ala	Glu Ile Ile Ser Arg
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Ile Val Asp Asp Leu	Lys Asp Glu Ala Glu	Gln Tyr Arg Lys Met Val
	865	870 875 880
Met Glu Thr Ile	Glu Lys Ile Met Gly	Asn Leu Gly Ala Ala Asp Ile
	885	890 895
Asp His Lys Leu	Glu Glu Gln Leu	Ile Asp Gly Ile Leu Tyr Ala Phe
	900	905 910
Gln Glu Gln Thr Thr	Glu Asp Ser Val	Met Leu Asn Gly Phe Gly Thr
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Val Val Asn Ala Leu	Gly Lys Arg Val	Lys Pro Tyr Leu Pro Gln Ile
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Cys Gly Thr Val Leu	Trp Arg Leu Asn Asn	Lys Ser Ala Lys Val Arg
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Gln Gln Ala Ala	Asp Leu Ile Ser Arg	Thr Ala Val Val Met Lys Thr
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Cys Gln Glu Glu Lys	Leu Met Gly His	Leu Gly Val Val Leu Tyr Glu
	980	985 990
Tyr Leu Gly Glu Glu Tyr	Pro Glu Val Leu Gly	Ser Ile Leu Gly Ala
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Leu Lys Ala Ile Val	Asn Xaa Xaa Xaa	Val Ile Gly Met His Lys Met
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Thr Pro Pro Ile Lys	Asp Leu Leu Pro Arg	Leu Thr Pro Ile Leu Lys
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Asn Arg His Glu Lys	Val Gln Glu Asn	Cys Ile Asp Leu Val Gly Arg
	1045	1050 1055

MTP-031PC.TXT

Ile Ala Asp Arg Gly Ala Glu Tyr Val Ser Ala Arg Glu Trp Met Arg
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 Ile Cys Phe Glu Leu Leu Glu Leu Lys Ala His Lys Lys Ala Ile
 1075 1080 1085
 Arg Arg Ala Thr Val Asn Thr Phe Gly Tyr Ile Ala Lys Ala Ile Gly
 1090 1095 1100
 Pro His Asp Val Leu Ala Thr Leu Leu Asn Asn Leu Lys Val Gln Glu
 1105 1110 1115 1120
 Arg Gln Asn Arg Val Cys Thr Thr Val Ala Ile Ala Ile Val Ala Glu
 1125 1130 1135
 Thr Cys Ser Pro Phe Thr Val Leu Pro Ala Leu Met Asn Glu Tyr Arg
 1140 1145 1150
 Val Pro Glu Leu Asn Val Gln Asn Gly Val Leu Lys Ser Leu Ser Phe
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 Thr Pro Leu Leu Glu Asp Ala Leu Met Asp Arg Asp Leu Val His Arg
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 Gln Thr Ala Ser Ala Val Val Gln His Met Ser Leu Gly Val Tyr Gly
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 Asn Val Phe Glu Thr Ser Pro His Val Ile Gln Ala Val Met Gly Ala
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 Leu Glu Gly Leu Arg Val Ala Ile Gly Pro Cys Arg Met Leu Gln Tyr
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 Trp Lys Ile Tyr Asn Ser Ile Tyr Ile Gly Ser Gln Asp Ala Leu Ile
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<212> DNA

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MTP-031PC.TXT

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 Gly Glu Asp Gly Asp Lys Ala Ala Pro Pro Pro Met Ser Ala Gln Leu
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 Pro Gly Ile Pro Met Pro Pro Pro Pro Leu Gly Leu Pro Pro Leu Gln
 65 70 75 80
 Pro Pro Pro Pro Pro Pro Pro Pro Gly Leu Gly Leu Gly Phe
 85 90 95
 Pro Met Ala His Pro Pro Asn Leu Gly Pro Pro Pro Pro Leu Arg Val
 100 105 110
 Gly Glu Pro Val Ala Leu Ser Glu Glu Glu Arg Leu Lys Leu Ala Gln

MTP-031PC.TXT

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Pro Thr Pro Thr Val Leu Pro Met	Gly Ala Pro Val Pro Arg Pro Arg	
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Gly Pro Pro Pro Pro Pro Gly Asp	Glu Asn Arg Glu Met Asp Asp Pro	
	225	230
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Pro Glu Ile Tyr Glu Pro Asn Phe	Ile Phe Phe Lys Arg Ile Phe Glu	
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Phe Glu Glu Glu His Lys Asp Ser	Asp Asp Ser Ser Asp Asp Glu	
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Gln Glu Lys Lys Pro Glu Ala Pro	Lys Leu Ser Lys Lys Lys Leu Arg	
	345	350
Arg Met Asn Arg Phe Thr Val Ala	Glu Leu Lys Gln Leu Val Ala Arg	
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Pro Asp Val Val Glu Met His Asp	Val Thr Ala Gln Asp Pro Lys Leu	
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Leu Val His Leu Lys Ala Thr Arg	Asn Ser Val Pro Val Pro Arg His	
	375	380

MTP-031PC.TXT

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500 505 510

Met Arg Glu Ala Leu Gln Glu Lys Glu Glu Gln Lys Thr Met Lys Ser
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Lys Met Arg Glu Lys Val Arg Pro Lys Met Gly Lys Ile Asp Ile Asp
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Tyr Gln Lys Leu His Asp Ala Phe Phe Lys Trp Gln Thr Lys Pro Lys
545 550 555 560

Leu Thr Ile His Gly Asp Leu Tyr Tyr Glu Gly Lys Glu Phe Glu Thr
565 570 575

Arg Leu Lys Glu Lys Lys Pro Gly Asp Leu Ser Asp Glu Leu Arg Ile
580 585 590

Ser Leu Gly Met Pro Val Gly Pro Asn Ala His Lys Val Pro Pro Pro
595 600 605

Trp Leu Ile Ala Met Gln Arg Tyr Gly Pro Pro Pro Ser Tyr Pro Asn
610 615 620

Leu Lys Ile Pro Gly Leu Asn Ser Pro Ile Pro Glu Ser Cys Ser Phe
625 630 635 640

Gly Tyr His Ala Gly Gly Trp Gly Lys Pro Pro Val Asp Glu Thr Gly
645 650 655

Lys Pro Leu Tyr Gly Asp Val Phe Gly Thr Asn Ala Ala Glu Phe Gln
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Gly Leu Ile Thr Pro Gly Gly Phe Ser Ser Val Pro Ala Gly Met Glu
725 730 735

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740 745 750

Asp Gly Ser Glu Thr Pro Gln Leu Phe Thr Val Leu Pro Glu Lys Arg
755 760 765

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 275 280 285
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 290 295 300
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 305 310 315 320
 Lys Lys Lys Lys Pro Gln Arg Val Arg Xaa Ser Ser Glu Ser Xaa Gly
 325 330 335
 Asp Arg Glu Lys Xaa Ser Xaa Arg Ser Arg Gly Ser Asp Xaa Pro Ala
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          50             55             60
Phe Asn Leu Asn Pro Phe Glu Val Leu Gln Ile Asp Pro Glu Val Thr
          65             70             75             80
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Thr Ser Lys Asn Gln Ile Glu Arg Leu Thr Arg Pro Gly Ser Ser Tyr
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Phe Asn Leu Asn Pro Phe Glu Val Leu Gln Ile Asp Pro Glu Val Thr
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Asp Glu Glu Ile Lys Lys Xaa Phe Arg Gln Leu Ser Ile Leu Val His
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MTP-031PC.TXT

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145 150 155 160

His Lys Ala Asn Thr Leu Val Tyr His Val Val Gly Val Asp Val Gly
165 170 175

Phe Glu Asn Pro Met Phe Ala Cys Leu Glu Met Asp Tyr Glu Glu Ala
180 185 190

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Gly Ser Asp Gly Pro Ser Gly Val Leu Ile Cys Ser Glu Asn Tyr Ile
245 250 255

Thr Tyr Lys Asn Phe Gly Asp Gln Pro Asp Ile Arg Cys Pro Ile Pro
260 265 270

Arg Arg Arg Asn Asp Leu Asp Asp Pro Glu Arg Gly Met Ile Phe Val
275 280 285

Cys Ser Ala Thr His Lys Thr Lys Ser Met Phe Phe Phe Trp Ala Gln
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Thr Glu Gln Gly Asp Ile Phe Lys Ile Thr Leu Glu Thr Asp Glu Asp
305 310 315 320

Met Val Thr Glu Ile Arg Leu Lys Tyr Phe Asp Thr Val Pro Val Ala
325 330 335

Ala Ala Met Cys Val Leu Lys Thr Gly Phe Leu Phe Val Ala Ser Glu
340 345 350

Phe Gly Asn His Tyr Leu Tyr Gln Ile Ala His Leu Gly Asp Asp Asp
355 360 365

Glu Glu Pro Glu Phe Ser Ser Ala Met Pro Leu Glu Glu Gly Asp Thr
370 375 380

Phe Phe Phe Gln Pro Arg Pro Leu Lys Asn Leu Val Leu Val Asp Glu
385 390 395 400

Leu Asp Ser Leu Ser Pro Ile Leu Phe Cys Gln Ile Ala Asp Leu Ala
405 410 415

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

Ser Ser Leu Arg Val Leu Arg His Gly Leu Glu Val Ser Glu Met Ala
435 440 445

Val Ser Glu Leu Pro Gly Asn Pro Asn Ala Val Trp Thr Val Arg Arg
450 455 460

His Ile Glu Asp Glu Phe Asp Ala Tyr Ile Ile Val Ser Phe Val Asn
465 470 475 480

MTP-031PC.TXT

Ala Thr Leu Val₄₈₅ Leu Ser Ile Gly Glu Thr Val Glu Glu Val Thr Asp₄₉₅
 Ser Gly Phe Leu₅₀₀ Gly Thr Thr Pro Thr₅₀₅ Leu Ser Cys Ser Leu₅₁₀ Leu Gly
 Asp Asp Ala₅₁₅ Leu Val Gln Val Tyr₅₂₀ Pro Asp Gly Ile Arg₅₂₅ His Ile Arg
 Ala Asp Lys Arg Val Asn Glu₅₃₅ Trp Lys Thr Pro Gly₅₄₀ Lys Lys Thr Ile
 Val Lys Cys Ala Val Asn₅₅₀ Gln Arg Gln Val Val₅₅₅ Ile Ala Leu Thr Gly₅₆₀
 Gly Glu Leu Val Tyr₅₆₅ Phe Glu Met Asp Pro₅₇₀ Ser Gly Gln Leu Asn Glu₅₇₅
 Tyr Thr Glu Arg₅₈₀ Lys Glu Met Ser Ala₅₈₅ Asp Val Val Cys Met₅₉₀ Ser Leu
 Ala Asn Val₅₉₅ Pro Pro Gly Glu Gln Arg Ser Arg Phe Leu₆₀₅ Ala Val Gly
 Leu Val Asp Asn Thr Val Arg₆₁₅ Ile Ile Ser Leu Asp₆₂₀ Pro Ser Asp Cys
 Leu Gln Pro Leu Ser Met₆₃₀ Gln Ala Leu Pro Ala₆₃₅ Gln Pro Glu Ser Leu₆₄₀
 Cys Ile Val Glu Met₆₄₅ Gly Gly Thr Glu Lys₆₅₀ Gln Asp Glu Leu Gly Glu₆₅₅
 Arg Gly Ser Ile₆₆₀ Gly Phe Leu Tyr Leu₆₆₅ Asn Ile Gly Leu Gln Asn Gly₆₇₀
 Val Leu Leu₆₇₅ Arg Thr Val Leu Asp₆₈₀ Pro Val Thr Gly Asp₆₈₅ Leu Ser Asp
 Thr Arg Thr Arg Tyr Leu Gly₆₉₅ Ser Arg Pro Val Lys₇₀₀ Leu Phe Arg Val
 Arg Met Gln Gly Gln Glu₇₁₀ Ala Val Leu Ala Met₇₁₅ Ser Ser Arg Ser Trp₇₂₀
 Leu Ser Tyr Ser Tyr₇₂₅ Gln Ser Arg Phe His₇₃₀ Leu Thr Pro Leu Ser Tyr₇₃₅
 Glu Thr Leu Glu Phe Ala Ser Gly Phe₇₄₅ Ala Ser Glu Gln Cys₇₅₀ Pro Glu
 Gly Ile Val Ala Ile Ser Thr Asn₇₆₀ Thr Leu Arg Ile Leu₇₆₅ Ala Leu Glu
 Lys Leu Gly Ala Val Phe Asn₇₇₅ Gln Val Ala Phe Pro₇₈₀ Leu Gln Tyr Thr
 Pro Arg Lys Phe Val Ile₇₉₀ His Pro Glu Ser Asn₇₉₅ Asn Leu Ile Ile Ile₈₀₀
 Glu Thr Asp His Asn₈₀₅ Ala Tyr Thr Glu Ala₈₁₀ Thr Lys Ala Gln Arg Lys
 Gln Gln Met Ala Glu Glu Met Val Glu₈₂₅ Ala Ala Gly Glu Asp₈₃₀ Glu Arg
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MTP-031PC.TXT

835		840		845
Glu Ser Ile Phe Gly Ala Pro Lys Ala Gly Asn Gly Gln Trp Ala Ser	850	855	860	
Val Ile Arg Val Met Asn Pro Ile Gln Gly Asn Thr Leu Asp Leu Val	865	870	875	880
Gln Leu Glu Gln Asn Glu Ala Ala Phe Ser Val Ala Val Cys Arg Phe		885	890	895
Ser Asn Thr Gly Glu Asp Trp Tyr Val Leu Val Gly Val Ala Lys Asp		900	905	910
Leu Ile Leu Asn Pro Arg Ser Val Ala Gly Gly Phe Val Tyr Thr Tyr	915	920	925	
Lys Leu Val Asn Asn Gly Glu Lys Leu Glu Phe Leu His Lys Thr Pro	930	935	940	
Val Glu Glu Val Pro Ala Ala Ile Ala Pro Phe Gln Gly Arg Val Leu	945	950	955	960
Ile Gly Val Gly Lys Leu Leu Arg Val Tyr Asp Leu Gly Lys Lys Lys		965	970	975
Leu Leu Arg Lys Cys Glu Asn Lys His Ile Ala Asn Tyr Ile Ser Gly	980	985	990	
Ile Gln Thr Ile Gly His Arg Val Ile Val Ser Asp Val Gln Glu Ser	995	1000	1005	
Phe Ile Trp Val Arg Tyr Lys Arg Asn Glu Asn Gln Leu Ile Ile Phe	1010	1015	1020	
Ala Asp Asp Thr Tyr Pro Arg Trp Val Thr Thr Ala Ser Leu Leu Asp	1025	1030	1035	1040
Tyr Asp Thr Val Ala Gly Ala Asp Lys Phe Gly Asn Ile Cys Val Val		1045	1050	1055
Arg Leu Pro Pro Asn Thr Asn Asp Glu Val Asp Glu Asp Pro Thr Gly	1060	1065	1070	
Asn Lys Ala Leu Trp Asp Arg Gly Leu Leu Asn Gly Ala Ser Gln Lys	1075	1080	1085	
Ala Glu Val Ile Met Asn Tyr His Val Gly Glu Thr Val Leu Ser Leu	1090	1095	1100	
Gln Lys Thr Thr Leu Ile Pro Gly Gly Ser Glu Ser Leu Val Tyr Thr	1105	1110	1115	1120
Thr Leu Ser Gly Gly Ile Gly Ile Leu Val Pro Phe Thr Ser His Glu		1125	1130	1135
Asp His Asp Phe Phe Gln His Val Glu Met His Leu Arg Ser Glu His	1140	1145	1150	
Pro Pro Leu Cys Gly Arg Asp His Leu Ser Phe Arg Ser Tyr Tyr Phe	1155	1160	1165	
Pro Val Lys Asn Val Ile Asp Gly Asp Leu Cys Glu Gln Phe Asn Ser	1170	1175	1180	
Met Glu Pro Asn Lys Gln Lys Asn Val Ser Glu Glu Leu Asp Arg Thr	1185	1190	1195	1200

MTP-031PC.TXT

Pro Pro Glu Val Ser Lys Lys Leu Glu Asp Ile Arg Thr Arg Tyr Ala
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Phe

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 <212> DNA
 <213> Homo sapiens

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MTP-031PC.TXT

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 Ser Ala Pro₃₅ Ser Lys Pro Val Val₄₀ Gly Ile Ile Tyr Pro₄₅ Pro Pro Glu
 Val Arg₅₀ Asn Ile Val Asp Lys₅₅ Thr Ala Ser Phe Val₆₀ Ala Arg Asn Gly
 Pro Glu Phe Glu Ala Arg₇₀ Ile Arg Gln Asn Glu₇₅ Ile Asn Asn Pro Lys₈₀
 Phe Asn Phe Leu Asn₈₅ Pro Asn Asp Pro Tyr₉₀ His Ala Tyr Tyr Arg₉₅ His
 Lys Val Ser Glu₁₀₀ Phe Lys Glu Gly Lys₁₀₅ Ala Gln Glu Pro Ser₁₁₀ Ala Ala
 Ile Pro Lys₁₁₅ Val Met Gln Gln Gln₁₂₀ Gln Gln Thr Thr Gln₁₂₅ Gln Gln Leu
 Pro Gln Lys Val Gln Ala Gln₁₃₅ Val Ile Gln Glu Thr₁₄₀ Ile Val Pro Lys
 Glu₁₄₅ Pro Pro Pro Glu Phe₁₅₀ Glu Phe Ile Ala Asp₁₅₅ Pro Pro Ser Ile Ser₁₆₀
 Ala Phe Asp Leu Asp₁₆₅ Val Val Lys Leu Thr₁₇₀ Ala Gln Phe Val₁₇₅ Ala Arg
 Asn Gly Arg Gln₁₈₀ Phe Leu Thr Gln₁₈₅ Leu Met Gln Lys Glu₁₉₀ Gln Arg Asn
 Tyr Gln Phe₁₉₅ Asp Phe Leu Arg Pro₂₀₀ Gln His Ser Leu Phe₂₀₅ Asn Tyr Phe
 Thr Lys₂₁₀ Leu Val Glu Gln Tyr₂₁₅ Thr Lys Ile Leu Ile₂₂₀ Pro Pro Lys Gly
 Leu₂₂₅ Phe Ser Lys Leu Lys₂₃₀ Lys Glu Ala Glu Asn₂₃₅ Pro Arg Glu Val Leu₂₄₀
 Asp Gln Val Cys Tyr₂₄₅ Arg Val Glu Trp Ala₂₅₀ Lys Phe Gln Glu Arg₂₅₅ Glu
 Arg Lys Lys Glu₂₆₀ Glu Glu Glu Lys Glu₂₆₅ Lys Glu Arg Val Ala₂₇₀ Tyr Ala
 Gln Ile Asp Trp His Asp Phe Val₂₈₀ Val Val Glu Thr Val₂₈₅ Asp Phe Gln
 Pro Asn Glu Gln Gly Asn Phe₂₉₅ Pro Pro Pro Thr Thr₃₀₀ Pro Glu Glu Leu
 Gly Ala Arg Ile Leu Ile₃₁₀ Gln Glu Arg Tyr Glu₃₁₅ Lys Phe Gly Glu Ser₃₂₀
 Glu Glu Val Glu Met₃₂₅ Glu Val Glu Ser Asp₃₃₀ Glu Glu Asp Asp Lys₃₃₅ Gln
 Glu Lys Ala Glu₃₄₀ Glu Pro Pro Ser Gln₃₄₅ Leu Asp Gln Asp Thr₃₅₀ Gln Val
 Gln Asp Met₃₅₅ Asp Glu Gly Ser Asp₃₆₀ Asp Glu Glu Glu Gly₃₆₅ Gln Lys Val
 Pro Pro Pro Pro Glu Thr Pro₃₇₅ Met Pro Pro Pro Leu₃₈₀ Pro Pro Thr Pro

MTP-031PC.TXT

Asp Gln Val Ile Val Arg Lys Asp Tyr Asp Pro Lys Ala Ser Lys Pro
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 Leu Pro Pro Ala Pro Ala Pro Asp Glu Tyr Leu Val Ser Pro Ile Thr
 405 410 415
 Gly Glu Lys Ile Pro Ala Ser Lys Met Gln Glu His Met Arg Ile Gly
 420 425 430
 Leu Leu Asp Pro Arg Trp Leu Glu Gln Arg Asp Arg Ser Ile Arg Glu
 435 440 445
 Lys Gln Ser Asp Asp Glu Val Tyr Ala Pro Gly Leu Asp Ile Glu Ser
 450 455 460
 Ser Leu Lys Gln Leu Ala Glu Arg Arg Thr Asp Ile Phe Gly Val Glu
 465 470 475 480
 Glu Thr Ala Ile Gly Lys Lys Ile Gly Glu Glu Glu Ile Gln Lys Pro
 485 490 495
 Glu Glu Lys Val Thr Trp Asp Gly His Ser Gly Ser Met Ala Arg Thr
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 Gln Gln Ala Ala Gln Ala Asn Ile Thr Leu Gln Glu Gln Ile Glu Ala
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 Ile His Lys Ala Lys Gly Leu Val Pro Glu Asp Asp Thr Lys Glu Lys
 530 535 540
 Ile Gly Pro Ser Lys Pro Asn Glu Ile Pro Gln Gln Pro Pro Pro Pro
 545 550 555 560
 Ser Ser Ala Thr Asn Ile Pro Ser Ser Ala Pro Pro Ile Thr Ser Val
 565 570 575
 Pro Arg Pro Pro Thr Met Pro Pro Pro Val Arg Thr Thr Val Val Ser
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 Ala Val Pro Val Met Pro Arg Pro Pro Met Ala Ser Val Val Arg Leu
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 Pro Pro Gly Ser Val Ile Ala Pro Met Pro Pro Ile Ile His Ala Pro
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 Arg Ile Asn Val Val Pro Met Pro Pro Ser Ala Pro Pro Ile Met Ala
 625 630 635 640
 Pro Arg Pro Pro Pro Met Ile Val Pro Thr Ala Phe Val Pro Ala Pro
 645 650 655
 Pro Val Ala Pro Val Pro Ala Pro Ala Pro Met Pro Pro Val His Pro
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 Pro Pro Pro Met Glu Asp Glu Pro Thr Ser Lys Lys Leu Lys Thr Glu
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 Asp Ser Leu Met Pro Glu Glu Glu Phe Leu Arg Arg Asn Lys Gly Pro
 690 695 700
 Val Ser Ile Lys Val Gln Val Pro Asn Met Gln Asp Lys Thr Glu Trp
 705 710 715 720
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Asn His Leu Gly Ser Tyr Glu Cys Lys Leu Cys Leu Thr Leu His Asn
50 55 60
Asn Glu Gly Ser Tyr Leu Ala His Thr Gln Gly Lys Lys His Gln Thr
65 70 75 80
Asn Leu Ala Arg Arg Ala Ala Lys Glu Ala Lys Glu Ala Pro Ala Gln
85 90 95

MTP-031PC.TXT

Pro Ala Pro Glu Lys Val Lys Val Glu Val Lys Lys Phe Val Lys Ile
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Gly Arg Pro Gly Tyr Lys Val Thr Lys Gln Arg Asp Ser Glu Met Gly
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Gln Gln Ser Leu Leu Phe Gln Ile Asp Tyr Pro Glu Ile Ala Glu Gly
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Ile Met Pro Arg His Arg Phe Met Ser Ala Tyr Glu Gln Arg Ile Glu
 145 150 155 160

Pro Pro Asp Arg Arg Trp Gln Tyr Leu Leu Met Ala Ala Glu Pro Tyr
 165 170 175

Glu Thr Ile Ala Phe Lys Val Pro Ser Arg Glu Ile Asp Lys Ala Glu
 180 185 190

Gly Lys Phe Trp Thr His Trp Asn Arg Glu Thr Lys Gln Phe Phe Leu
 195 200 205

Gln Phe His Phe Lys Met Glu Lys Pro Pro Ala Pro Pro Ser Leu Pro
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Ala Gly Pro Pro Gly Val Lys Arg Pro Pro Pro Pro Leu Met Asn Gly
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Leu Pro Pro Arg Pro Pro Leu Pro Glu Ser Leu Pro Pro Pro Pro Pro
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Gly Gly Leu Pro Leu Pro Pro Met Pro Pro Thr Gly Pro Ala Pro Ser
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Gly Pro Pro Gly Pro Pro Gln Leu Pro Pro Pro Ala Pro Gly Val His
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Pro Pro Ala Pro Val Val His Pro Pro Ala Ser Gly Val His Pro Pro
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Ala Pro Gly Val His Pro Pro Ala Pro Gly Val His Pro Pro Ala Pro
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Gly Val His Pro Pro Thr Ser Gly Val His Pro Pro Ala Pro Gly Val
 325 330 335

His Pro Pro Ala Pro Gly Val His Pro Pro Ala Pro Gly Val His Pro
 340 345 350

Pro Ala Pro Gly Val His Pro Pro Ala Pro Gly Val His Pro Pro Pro
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Ser Ala Gly Val His Pro Gln Ala Pro Gly Val His Pro Ala Ala Pro
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Ala Val His Pro Gln Ala Pro Gly Val His Pro Pro Ala Pro Gly Met
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His Pro Gln Ala Pro Gly Val His Pro Gln Pro Pro Gly Val His Pro
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Ser Ala Pro Gly Val His Pro Gln Pro Gly Val His Pro Ser Asn
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Pro Gly Val His Pro Pro Thr Pro Met Pro Pro Met Leu Arg Pro Pro
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Leu Pro Ser Glu Gly Pro Gly Asn Ile Pro Pro Pro Pro Pro Thr Asn
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 agctacttgg gaggctgagg caggagggtt gcttgagact agcctaggta acatagttag 2160
 accctgtctc attaaaaaaa aaaaaaaaag gcctgggtggc acgcactgta gtcccagcta 2220
 ctcaggagac tgaggctaga agatcctttg aacctaggag tttagacca gcctgggcga 2280
 tatagttagg ccccatctca aaaaaaaaaa aaagcggggg gggggagttg ggctgtgttg 2340
 gaatgggcct gcagcccaac aaacaaggga actaggaccg acagtgactt caccagcttg 2400
 ctaggctaga atgagagact ggtgggtctg tctacctgtt tcttctacaa gatccctatt 2460
 tgactgtaaa agtagctaact actcacatgt tctccaatcc caggtagcca tggtagagtt 2520
 gggtagagtt gagcagccgc cccaggatcc aaatgtggtg tctgaaatgg aaagaactaa 2580
 ggcaaccagg aaggcactga tctgccttat aagcacagtc atctgaaagt caggcctgct 2640
 gcaggacagg atccccaga gacccccatt gcctctcaac actcagacct tcaactgttt 2700
 ttaataaat ctacttttta aaaaaaaaaa ata 2733

<210> 21
 <211> 501
 <212> PRT
 <213> Homo sapiens

<400> 21
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 1 5 10 15

MTP-031PC.TXT

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

MTP-031PC.TXT

Leu Gly Trp Asp Gly Lys Pro Ile Pro Tyr Trp Leu Tyr Lys Leu His
 385 390 395 400
 Gly Leu Asn Ile Asn Tyr Asn Cys Glu Ile Cys Gly Asn Tyr Thr Tyr
 405 410 415
 Arg Gly Pro Lys Ala Phe Gln Arg His Phe Ala Glu Trp Arg His Ala
 420 425 430
 His Gly Met Arg Cys Leu Gly Ile Pro Asn Thr Ala His Phe Ala Asn
 435 440 445
 Val Thr Gln Ile Glu Asp Ala Val Ser Leu Trp Ala Lys Leu Lys Leu
 450 455 460
 Gln Lys Ala Ser Glu Arg Trp Gln Pro Asp Thr Glu Glu Glu Tyr Glu
 465 470 475 480
 Asp Ser Ser Gly Asn Val Val Asn Lys Lys Thr Tyr Glu Asp Leu Lys
 485 490 495
 Arg Gln Gly Leu Leu
 500

<210> 22
 <211> 1275
 <212> DNA
 <213> Homo sapiens

<400> 22
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 gatgagaagg ttagtgaacc gctgctgtgg gaactgtttc tccaggctgg accagtagtc 120
 aacaccacaca tgccaaagga tagagtcact ggccagcacc aaggctatgg ctttgtggaa 180
 ttcttgagtg aggaagatgc tgactatgcc attaagatca tgaacatgat caaactctat 240
 gggaagccaa tacgggtgaa caaagcatca gctcacaaca aaaacctgga tgtaggggcc 300
 aacattttca ttgggaacct ggacctgag attgatgaga agttgcttta tgatactttc 360
 agcgcctttg gggtcattctt acaaaccctc aaaattatgc gggacctga cacaggcaac 420
 tccaaagggtt atgcctttat taattttgct tcatttgatg cttcggatgc agcaattgaa 480
 gccatgaatg ggcagtacct ctgtaaccgt cctatcaccg tatcttatgc cttcaagaag 540
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 catccccacg ctggaccccc aggcctctggg ggccagccac cgccccgacc accacctgga 1020
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 cccatgggtc acccaggtcc tatgcctccg catggtatgc gtggacctcc tccactgatg 1140
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<210> 23
 <211> 424
 <212> PRT
 <213> Homo sapiens

<400> 23
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 20 25 30

MTP-031PC.TXT

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

MTP-031PC.TXT

Leu Pro Pro Pro Arg Pro Thr Pro Arg Pro Pro Val Pro Pro Arg Gly
 405 410 415

Pro Leu Arg Gly Pro Leu Pro Gln
 420

<210> 24
 <211> 1054
 <212> DNA
 <213> Homo sapiens

<400> 24
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 tcaagctgac ggcggagctg atcgagcagg cggcgagcag caccaacgcg gtgcgcgacc 120
 gggagctgga cctccggggg tataaaattc ccgtcattga aaatctagggt gctacgttag 180
 accagtttga tgctattgat ttttctgaca atgagatcag gaaactggat ggttttcctt 240
 tgttgagaag actgaaaaca ttgttagtga acaacaacag aatatgccgt ataggtgagg 300
 gacttgatca ggctctgccc tgtctgacag aactcattct caccaataat agtctcgtgg 360
 aactgggtga tctggaccct ctggcatctc tcaaactcgt gacttaccta agtatcctaa 420
 gaaatccggt aaccaataag aagcattaca gattgtaigt gatttataaa gttccgcaag 480
 tcagagtact ggatttccag aaagtgaaac taaaagagcg tcaggaagca gagaaaatgt 540
 tcaagggcaa acgggggtgca cagcttgcaa aggatattgc caggagaagc aaaactttta 600
 atccaggtgc tggtttgcca actgacaaaa agagaggtgg gccatctcca ggggatgtag 660
 aagcaatcaa gaatgccata gcaaattgctt caactctggc tgaagtggag aggttgaagg 720
 ggttgctgca gtctggtcag atccctggca gagaacgcag atcagggccc actgatgatg 780
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 tgtgttagca aagtggaaatc tatcagcatt gttgaaatgc ttaagactgc tgctgataat 960
 tttgtaatat aagttttgaa atctaaatgt caattttcta caaattataa aaataaaactc 1020
 cactctctat gctaaaaaaa aaaaaaaggaa attc 1054

<210> 25
 <211> 255
 <212> PRT
 <213> Homo sapiens

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

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<210> 26
<211> 378
<212> DNA
<213> Homo sapiens
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<400> 26
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ttgtatataa gaaatttgcc atacaaaatc acagctgaag aaatgtatga tatatttggg 120
aaatatggac ctattcgtca aatcagagtg gggaacacac ctgaaactag aggaacagct 180
tatgtggtct atgaggacat ctttgatgcc aagaatgcat gtgatcacct atcgggattc 240
aatgttttga acagatacct tgtggttttg tactataatg ccaacagggc atttcgaag 300
atggacacaa agaagaagga ggaacagttg aagcttctca aggagaaata tggcatcaac 360
acagatcctc ccaagtga                                     378
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<210> 27
<211> 125
<212> PRT
<213> Homo sapiens
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<400>	27															
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			20					25					30			
Glu	Glu	Met	Tyr	Asp	Ile	Phe	Gly	Lys	Tyr	Gly	Pro	Ile	Arg	Gln	Ile	
		35					40					45				
Arg	Val	Gly	Asn	Thr	Pro	Glu	Thr	Arg	Gly	Thr	Ala	Tyr	Val	Val	Tyr	
	50					55					60					
Glu	Asp	Ile	Phe	Asp	Ala	Lys	Asn	Ala	Cys	Asp	His	Leu	Ser	Gly	Phe	
65					70					75					80	
Asn	Val	Cys	Asn	Arg	Tyr	Leu	Val	Val	Leu	Tyr	Tyr	Asn	Ala	Asn	Arg	
				85					90					95		
Ala	Phe	Gln	Lys	Met	Asp	Thr	Lys	Lys	Lys	Glu	Glu	Gln	Leu	Lys	Leu	
			100					105					110			
Leu	Lys	Glu	Lys	Tyr	Gly	Ile	Asn	Thr	Asp	Pro	Pro	Lys				
		115					120					125				

<210> 28

MTP-031PC.TXT

<211> 904
 <212> DNA
 <213> Homo sapiens

<400> 28
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 gtcattggaga caggtgtctt cggttgacaca ataaaccgac gtttagccag accattgccc 180
 tcttgaacat ttaccgtaac cctcaaaact cttcccagtc tgctgacggt ttgcgctgtg 240
 ccgtgagcga tgtggagatg caggaacact atgatgagtt ttttgaggag gtttttacag 300
 aaatggagga gaagtatggg gaagtagagg agatgaacgt ctgtgacaac ctgggagacc 360
 acctgggtggg gaacgtgtac gtcaagtttc gccgtgagga agatgcggaa aaggctgtga 420
 ttgacttgaa taaccgttgg tttaatggac agccgatcca cgccgagctg tcacccgtga 480
 cggacttcag agaagcctgc tgccgtcagt atgagatggg agaatgcaca cgaggcggct 540
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 gccgtcgcaa gaagcataga tcaagatccc gatcccggga gcgtcgttct cggctctagag 660
 accgtgggtcg tggcgggtggc ggtggcgggtg gtggagggtg cggcggacgg gagcgtgaca 720
 ggaggcgggtc gagagatcgt gaaagatctg ggcgattctg agccatgcca tttttacctt 780
 atgtctgcta gaaagtgttg tagttgattg accaaaccag ttcataaggg gaatttttta 840
 aaaaacaaca aaaaaaaac atacaaagat gggtttctga ataaaaattt gtagtgataa 904
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<210> 29
 <211> 240
 <212> PRT
 <213> Homo sapiens

<400> 29
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 20 25 30
 Cys Ser Arg Leu His Asn Lys Pro Thr Phe Ser Gln Thr Ile Ala Leu
 35 40 45
 Leu Asn Ile Tyr Arg Asn Pro Gln Asn Ser Ser Gln Ser Ala Asp Gly
 50 55 60
 Leu Arg Cys Ala Val Ser Asp Val Glu Met Gln Glu His Tyr Asp Glu
 65 70 75 80
 Phe Phe Glu Glu Val Phe Thr Glu Met Glu Glu Lys Tyr Gly Glu Val
 85 90 95
 Glu Glu Met Asn Val Cys Asp Asn Leu Gly Asp His Leu Val Gly Asn
 100 105 110
 Val Tyr Val Lys Phe Arg Arg Glu Glu Asp Ala Glu Lys Ala Val Ile
 115 120 125
 Asp Leu Asn Asn Arg Trp Phe Asn Gly Gln Pro Ile His Ala Glu Leu
 130 135 140
 Ser Pro Val Thr Asp Phe Arg Glu Ala Cys Cys Arg Gln Tyr Glu Met
 145 150 155 160
 Gly Glu Cys Thr Arg Gly Gly Phe Cys Asn Phe Met His Leu Lys Pro
 165 170 175
 Ile Ser Arg Glu Leu Arg Arg Glu Leu Tyr Gly Arg Arg Arg Lys Lys
 180 185 190
 His Arg Ser Arg Ser Arg Ser Arg Glu Arg Arg Ser Arg Ser Arg Asp
 195 200 205

MTP-031PC.TXT

Arg Gly Arg Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Arg
 210 215 220

Glu Arg Asp Arg Arg Arg Ser Arg Asp Arg Glu Arg Ser Gly Arg Phe
 225 230 235 240

<210> 30
 <211> 1707
 <212> DNA
 <213> Homo sapiens

<400> 30
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 cagccacagc cgctctcggg gccgggaccg caaacgccgg agccggagcc gcgaccggcg 180
 caaccgggac cagcggagcg cctcccggga caggcgacga cgcagcaaac ctttgaccag 240
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 ggtcggtaaa tactgggacg tgccaccccc aggccttgag cacatcaccc caatgcagta 360
 caaggccatg caagctgcgg gtcagattcc agccactgct cttctcccca ccatgacccc 420
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 agcccggcgc ctctacgtgg gcaacatccc ctttggcatac actgaggagg ccatgatgga 540
 tttcttcaac gcccagatgc gcctgggggg gctgacccag gcccctggca acccagtgtt 600
 ggctgtgcag attaacagg acaagaattt tgcttttttg gaggttccgct cagtggacga 660
 gactaccag gctatggcct ttgatggcat catcttcag ggccagtcac taaagatccg 720
 caggcctcac gactaccagc cgcttcctgg catgtcagag aaccctccg tctatgtgcc 780
 tgggggtgtg tccactgtgg tccccgactc tgcccacaag ctgttcatac ggggcttacc 840
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 taagaagctg ctggtccaga gggcgagtgt gggagccaag aatgccacgc tggtagccc 1080
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 cacagcccca cacagacaac acgcacg 1707

<210> 31
 <211> 475
 <212> PRT
 <213> Homo sapiens

<400> 31
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Glu Arg Asp Lys Glu Asn Arg His Arg Lys Arg Ser His Ser Arg Ser
 20 25 30

Arg Ser Arg Asp Arg Lys Arg Arg Ser Arg Ser Arg Asp Arg Arg Asn
 35 40 45

Arg Asp Gln Arg Ser Ala Ser Arg Asp Arg Arg Arg Arg Ser Lys Pro
 50 55 60

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

MTP-031PC.TXT

Arg His Glu Lys Lys Lys Lys Val Arg Lys Tyr Trp Asp Val Pro Pro
 85 90 95
 Pro Gly Phe Glu His Ile Thr Pro Met Gln Tyr Lys Ala Met Gln Ala
 100 105 110
 Ala Gly Gln Ile Pro Ala Thr Ala Leu Leu Pro Thr Met Thr Pro Asp
 115 120 125
 Gly Leu Ala Val Thr Pro Thr Pro Val Pro Val Val Gly Ser Gln Met
 130 135 140
 Thr Arg Gln Ala Arg Arg Leu Tyr Val Gly Asn Ile Pro Phe Gly Ile
 145 150 155 160
 Thr Glu Glu Ala Met Met Asp Phe Phe Asn Ala Gln Met Arg Leu Gly
 165 170 175
 Gly Leu Thr Gln Ala Pro Gly Asn Pro Val Leu Ala Val Gln Ile Asn
 180 185 190
 Gln Asp Lys Asn Phe Ala Phe Leu Glu Phe Arg Ser Val Asp Glu Thr
 195 200 205
 Thr Gln Ala Met Ala Phe Asp Gly Ile Ile Phe Gln Gly Gln Ser Leu
 210 215 220
 Lys Ile Arg Arg Pro His Asp Tyr Gln Pro Leu Pro Gly Met Ser Glu
 225 230 235 240
 Asn Pro Ser Val Tyr Val Pro Gly Val Val Ser Thr Val Val Pro Asp
 245 250 255
 Ser Ala His Lys Leu Phe Ile Gly Gly Leu Pro Asn Tyr Leu Asn Asp
 260 265 270
 Asp Gln Val Lys Glu Leu Leu Thr Ser Phe Gly Pro Leu Lys Ala Phe
 275 280 285
 Asn Leu Val Lys Asp Ser Ala Thr Gly Leu Ser Lys Gly Tyr Ala Phe
 290 295 300
 Cys Glu Tyr Val Asp Ile Asn Val Thr Asp Gln Ala Ile Ala Gly Leu
 305 310 315 320
 Asn Gly Met Gln Leu Gly Asp Lys Lys Leu Leu Val Gln Arg Ala Ser
 325 330 335
 Val Gly Ala Lys Asn Ala Thr Leu Val Ser Pro Pro Ser Thr Ile Asn
 340 345 350
 Gln Thr Pro Val Thr Leu Gln Val Pro Gly Leu Met Ser Ser Gln Val
 355 360 365
 Gln Met Gly Gly His Pro Thr Glu Val Leu Cys Leu Met Asn Met Val
 370 375 380
 Leu Pro Glu Glu Leu Leu Asp Asp Glu Glu Tyr Glu Glu Ile Val Glu
 385 390 395 400
 Asp Val Arg Asp Glu Cys Ser Lys Tyr Gly Leu Val Lys Ser Ile Glu
 405 410 415
 Ile Pro Arg Pro Val Asp Gly Val Glu Val Pro Gly Cys Gly Lys Ile
 420 425 430
 Phe Val Glu Phe Thr Ser Val Phe Asp Cys Gln Lys Ala Met Gln Gly
 435 440 445

MTP-031PC.TXT

Leu Thr Gly Arg Lys Phe Ala Asn Arg Val Val Val Thr Lys Tyr Cys
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Asp Pro Asp Ser Tyr His Arg Arg Asp Phe Trp
 465 470 475

<210> 32
 <211> 1488
 <212> DNA
 <213> Homo sapiens

<400> 32
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 gaacttgctc gactgagaga ctcaggactc tcacagaagg aggaagagga ggacactttt 180
 attgaagaac aacaactaga agaagagaag ctattggaaa gagagaggca aagattacat 240
 gaggagtggg tgctaagaga gcagaaggca caagaagaat tcagaataaa gaaggaaaaag 300
 gaagaggcgg ctaaaaaacg gcaagaagaa caagagagaa agttaagga acaatgggaa 360
 gaacagcaga ggaagagag agaagaggag gacaggaac gacaggagaa gaaagaaaaa 420
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 Glu Leu Ala Arg Leu Arg Asp Ser Gly Leu Ser Gln Lys Glu Glu Glu
 35 40 45
 Glu Asp Thr Phe Ile Glu Glu Gln Gln Leu Glu Glu Glu Lys Leu Leu
 50 55 60
 Glu Arg Glu Arg Gln Arg Leu His Glu Glu Trp Leu Leu Arg Glu Gln
 65 70 75 80
 Lys Ala Gln Glu Glu Phe Arg Ile Lys Lys Glu Lys Glu Glu Ala Ala
 85 90 95
 Lys Lys Arg Gln Glu Glu Gln Glu Arg Lys Leu Lys Glu Gln Trp Glu
 100 105 110

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Glu Gln Gln Arg Lys Glu Arg Glu Glu Glu Gln Lys Arg Gln Glu
115 120 125

Lys Lys Glu Lys Glu Glu Ala Leu Gln Lys Met Leu Asp Gln Ala Glu
130 135 140

Asn Glu Leu Glu Asn Gly Thr Thr Trp Gln Asn Pro Glu Pro Pro Val
145 150 155 160

Asp Phe Arg Val Met Glu Lys Asp Arg Ala Asn Cys Pro Phe Tyr Ser
165 170 175

Lys Thr Gly Ala Cys Arg Phe Gly Asp Arg Cys Ser Arg Lys His Asn
180 185 190

Phe Pro Thr Ser Ser Pro Thr Leu Leu Ile Lys Ser Met Phe Thr Thr
195 200 205

Phe Gly Met Glu Gln Cys Arg Arg Asp Asp Tyr Asp Pro Asp Ala Ser
210 215 220

Leu Glu Tyr Ser Glu Glu Glu Thr Tyr Gln Gln Phe Leu Asp Phe Tyr
225 230 235 240

Glu Asp Val Leu Pro Glu Phe Lys Asn Val Gly Lys Val Ile Gln Phe
245 250 255

Lys Val Ser Cys Asn Leu Glu Pro His Leu Arg Gly Asn Val Tyr Val
260 265 270

Gln Tyr Gln Ser Glu Glu Glu Cys Gln Ala Ala Leu Ser Leu Phe Asn
275 280 285

Gly Arg Trp Tyr Ala Gly Arg Gln Leu Gln Cys Glu Phe Cys Pro Val
290 295 300

Thr Arg Trp Lys Met Ala Ile Cys Gly Leu Phe Glu Ile Gln Gln Cys
305 310 315 320

Pro Arg Gly Lys His Cys Asn Phe Leu His Val Phe Arg Asn Pro Asn
325 330 335

Asn Glu Phe Trp Glu Ala Asn Arg Asp Ile Tyr Leu Ser Pro Asp Arg
340 345 350

Thr Gly Ser Ser Phe Gly Lys Asn Ser Glu Arg Arg Glu Arg Met Gly
355 360 365

His His Asp Asp Tyr Tyr Ser Arg Leu Arg Gly Arg Arg Asn Pro Ser
370 375 380

Pro Asp His Ser Tyr Lys Arg Asn Gly Glu Ser Glu Arg Lys Ser Ser
385 390 395 400

Arg His Arg Gly Lys Lys Ser His Lys Arg Thr Ser Lys Ser Arg Glu
405 410 415

Arg His Asn Ser Arg Ser Arg Gly Arg Asn Arg Asp Arg Ser Arg Asp
420 425 430

Arg Ser Arg Gly Arg Gly Ser Arg Ser Arg Ser Arg Ser Arg Ser Arg
435 440 445

Arg Ser Arg Arg Ser Arg Ser Gln Ser Ser Ser Arg Ser Arg Ser Arg
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Ser Lys

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 35 40 45
 Arg Glu Arg Ser Arg Ser Arg Asp Lys Arg Arg Ser Arg Ser Arg Asp
 50 55 60
 Arg Lys Arg Leu Arg Arg Ser Arg Ser Arg Glu Arg Asp Arg Ser Arg
 65 70 75 80
 Glu Arg Arg Arg Ser Arg Ser Arg Asp Arg Arg Arg Ser Arg Ser Arg
 85 90 95
 Ser Arg Gly Arg Arg Ser Arg Ser Ser Ser Pro Gly Asn Lys Ser Lys
 100 105 110
 Lys Thr Glu Asn Arg Ser Arg Ser Lys Glu Lys Thr Asp Gly Gly Glu

MTP-031PC.TXT

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Glu Lys Asp Ala Gly Asn Phe Asp Gln Asn Lys Leu Glu Glu Glu Met		
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Arg Lys Arg Lys Glu Arg Val Glu Lys Trp Arg Glu Glu Gln Arg Lys		
165	170	175
Lys Ala Met Glu Asn Ile Gly Glu Leu Lys Lys Glu Ile Glu Glu Met		
180	185	190
Lys Gln Gly Lys Lys Trp Ser Leu Glu Asp Asp Asp Asp Asp Glu Asp		
195	200	205
Asp Pro Ala Glu Ala Glu Lys Glu Gly Asn Glu Met Glu Gly Glu Glu		
210	215	220
Leu Asp Pro Leu Asp Ala Tyr Met Glu Glu Val Lys Glu Glu Val Lys		
225	230	235
Lys Phe Asn Met Arg Ser Val Lys Gly Gly Gly Gly Asn Glu Lys Lys		
245	250	255
Ser Gly Pro Thr Val Thr Lys Val Val Thr Val Val Thr Thr Lys Lys		
260	265	270
Ala Val Val Asp Ser Asp Lys Lys Lys Gly Glu Leu Met Glu Asn Asp		
275	280	285
Gln Asp Ala Met Glu Tyr Ser Ser Glu Glu Glu Glu Val Asp Leu Gln		
290	295	300
Thr Ala Leu Thr Gly Tyr Gln Thr Lys Gln Arg Lys Leu Leu Glu Pro		
305	310	315
Val Asp His Gly Lys Ile Glu Tyr Glu Pro Phe Arg Lys Asn Phe Tyr		
325	330	335
Val Glu Val Pro Glu Leu Ala Lys Met Ser Gln Glu Glu Val Asn Val		
340	345	350
Phe Arg Leu Glu Met Glu Gly Ile Thr Val Lys Gly Lys Gly Cys Pro		
355	360	365
Lys Pro Ile Lys Ser Trp Val Gln Cys Gly Ile Ser Met Lys Ile Leu		
370	375	380
Asn Ser Leu Lys Lys His Gly Tyr Glu Lys Pro Thr Pro Ile Gln Thr		
385	390	395
Gln Ala Ile Pro Ala Ile Met Ser Gly Arg Asp Leu Ile Gly Ile Ala		
405	410	415
Lys Thr Gly Ser Gly Lys Thr Ile Ala Phe Leu Leu Pro Met Phe Arg		
420	425	430
His Ile Met Asp Gln Arg Ser Leu Glu Glu Gly Glu Gly Pro Ile Ala		
435	440	445
Val Ile Met Thr Pro Thr Arg Glu Leu Ala Leu Gln Ile Thr Lys Glu		
450	455	460
Cys Lys Lys Phe Ser Lys Thr Leu Gly Leu Arg Val Val Cys Val Tyr		
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Gly Gly Thr Gly Ile Ser Glu Gln Ile Ala Glu Leu Lys Arg Gly Ala
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Glu Ile Ile Val Cys Thr Pro Gly Arg Met Ile Asp Met Leu Ala Ala
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Asn Ser Gly Arg Val Thr Asn Leu Arg Arg Val Thr Tyr Val Val Leu
515 520 525

Asp Glu Ala Asp Arg Met Phe Asp Met Gly Phe Glu Pro Gln Val Met
530 535 540

Arg Ile Val Asp Asn Val Arg Pro Asp Arg Gln Thr Val Met Phe Ser
545 550 555 560

Ala Thr Phe Pro Arg Ala Met Glu Ala Leu Ala Arg Arg Ile Leu Ser
565 570 575

Lys Pro Ile Glu Val Gln Val Gly Gly Arg Ser Val Val Cys Ser Asp
580 585 590

Val Glu Gln Gln Val Ile Val Ile Glu Glu Glu Lys Lys Phe Leu Lys
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Leu Leu Glu Leu Leu Gly His Tyr Gln Glu Ser Gly Ser Val Ile Ile
610 615 620

Phe Val Asp Lys Gln Glu His Ala Asp Gly Leu Leu Lys Asp Leu Met
625 630 635 640

Arg Ala Ser Tyr Pro Cys Met Ser Leu His Gly Gly Ile Asp Gln Tyr
645 650 655

Asp Arg Asp Ser Ile Ile Asn Asp Phe Lys Asn Gly Thr Cys Lys Leu
660 665 670

Leu Val Ala Thr Ser Val Ala Ala Arg Gly Leu Asp Val Lys His Leu
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Thr Phe Ile Thr Glu Asp Gln Ala Arg Tyr Ala Gly Asp Ile Ile Lys
725 730 735

Ala Leu Glu Leu Ser Gly Thr Ala Val Pro Pro Asp Leu Glu Lys Leu
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Trp Ser Asp Phe Lys Asp Gln Gln Lys Ala Glu Gly Lys Ile Ile Lys
755 760 765

Lys Ser Ser Gly Phe Ser Gly Lys Gly Phe Lys Phe Asp Glu Thr Glu
770 775 780

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785 790 795 800

Leu Gln Asp Ser Asp Glu Asp Ala Ala Val Asp Ile Asp Glu Gln
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 Ala Glu Gln Leu Ala Glu Lys Ile Asn Ala Lys Leu Asn Tyr Val Pro
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 Ala Arg Trp Lys Val Thr Ser Lys Glu Ala Leu Gln Arg Ile Ser Glu
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 965 970 975
 Lys Glu Pro Lys Glu Gly Glu Arg Lys Ile Tyr Leu Ala Ile Glu Ser
 980 985 990
 Ala Asn Glu Leu Ala Val Gln Lys Ala Lys Ala Glu Ile Thr Arg Leu
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 <213> Homo sapiens

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 Glu Glu Gln Leu Ile Asp Ile Lys Val Ala His Pro Ile Arg Pro Lys
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MTP-031PC.TXT
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MTP-031PC.TXT

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MTP-031PC.TXT

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MTP-031PC.TXT

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 Thr Asn Leu Tyr Leu Gly Asn Ile Asn Pro Gln Met Asn Glu Glu Met
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MTP-031PC.TXT
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Pro	Pro	His	Cys 420	Pro	Pro	Trp	Asn	Asn 425	Ser	His	Glu	Gly	Met 430	Trp	Gly				
Glu	Gln	Arg 435	Gly	Asp	Pro	Gly	Trp 440	Asn	Gly	Gln	Arg	Asp 445	Ala	Pro	Trp				
Asn 450	Asn	Gln	Pro	Asp	Ala	Ala 455	Trp	Asn	Ser	Gln	Phe 460	Glu	Gly	Pro	Trp				
Asn 465	Ser	Gln	His	Glu	Gln 470	Pro	Pro	Trp	Gly	Gly 475	Gly	Gln	Arg	Glu	Pro 480				
Pro	Phe	Arg	Met	Gln 485	Arg	Pro	Pro	His	Phe 490	Arg	Gly	Pro	Phe	Pro 495	Pro				

MTP-031PC.TXT

His Gln Gln His Pro Gln Phe Asn Gln Pro Pro His Pro His Asn Phe
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 Asn Arg Phe Pro Pro Arg Phe Met Gln Asp Asp Phe Pro Pro Arg His
 515 520 525
 Pro Phe Glu Arg Pro Pro Tyr Pro His Arg Phe Asp Tyr Pro Gln Gly
 530 535 540
 Asp Phe Pro Ala Glu Met Gly Pro Pro His His His Pro Gly His Arg
 545 550 555 560
 Met Pro His Pro Gly Ile Asn Glu His Pro Pro Trp Ala Gly Pro Gln
 565 570 575
 His Pro Asp Phe Gly Pro Pro Pro His Gly Phe Asn Gly Gln Pro Pro
 580 585 590
 His Met Arg Arg Gln Gly Pro Pro His Ile Asn His Asp Asp Pro Ser
 595 600 605
 Leu Val Pro Asn Val Pro Tyr Phe Asp Leu Pro Ala Gly Leu Met Ala
 610 615 620
 Pro Leu Val Lys Leu Glu Asp His Glu Tyr Lys Pro Leu Asp Pro Lys
 625 630 635 640
 Asp Ile Arg Leu Pro Pro Pro Met Pro Pro Ser Glu Arg Leu Leu Ala
 645 650 655
 Ala Val Glu Ala Phe Tyr Ser Pro Pro Ser His Asp Arg Pro Arg Asn
 660 665 670
 Ser Glu Gly Trp Glu Gln Asn Gly Leu Tyr Glu Phe Phe Arg Ala Lys
 675 680 685
 Met Arg Ala Arg Arg Arg Lys Gly Gln Glu Lys Arg Asn Ser Gly Pro
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 705 710 715 720
 Ser Asn Ser Arg Ser Ser Lys Ser Ser Gly Ser Tyr Ser Arg Ser Arg
 725 730 735
 Ser Arg Ser Cys Ser Arg Ser Tyr Ser Arg Ser Arg Ser Arg Ser Arg
 740 745 750
 Ser Arg Ser Arg Ser Ser Arg Ser Arg Ser Arg Ser Gln Ser Arg Ser
 755 760 765
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 770 775 780
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 785 790 795 800
 Pro Ile Pro Asp Ser Arg Leu Gly Glu Glu Asn Lys Gly His Gln Met
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 Leu Val Lys Met Gly Trp Ser Gly Ser Gly Gly Leu Gly Ala Lys Glu
 820 825 830
 Gln Gly Ile Gln Asp Pro Ile Lys Gly Gly Asp Val Arg Asp Lys Trp
 835 840 845
 Asp Gln Tyr Lys Gly Val Gly Val Ala Leu Asp Asp Pro Tyr Glu Asn
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MTP-031PC.TXT

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Asp Glu Cys Lys

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 <211> 2441
 <212> DNA
 <213> Homo sapiens

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 <212> PRT
 <213> Homo sapiens

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MTP-031PC.TXT

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 Arg Glu Arg Glu Arg Glu Lys Glu Lys Glu Lys Glu Leu Arg Ala Ser
 50 55 60
 Thr Asn Ala Met Leu Ile Ser Ala Gly Leu Pro Pro Leu Lys Ala Ser
 65 70 75 80
 His Ser Ala His Ser Thr His Ser Ala His Ser Thr His Ser Thr His
 85 90 95
 Ser Ala His Ser Thr His Ala Gly His Ala Gly His Thr Ser Leu Pro
 100 105 110
 Gln Cys Ile Asn Pro Phe Thr Asn Leu Pro His Thr Pro Arg Tyr Tyr
 115 120 125
 Asp Ile Leu Lys Lys Arg Leu Gln Leu Pro Val Trp Glu Tyr Lys Asp
 130 135 140
 Arg Phe Thr Asp Ile Leu Val Arg His Gln Ser Phe Val Leu Val Gly
 145 150 155 160
 Glu Thr Gly Ser Gly Lys Thr Thr Gln Ile Pro Gln Trp Cys Val Glu
 165 170 175
 Tyr Met Arg Ser Leu Pro Gly Pro Lys Arg Gly Val Ala Cys Thr Gln
 180 185 190
 Pro Arg Arg Val Ala Ala Met Ser Val Ala Gln Arg Val Ala Asp Glu
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 Met Asp Val Met Leu Gly Gln Glu Val Gly Tyr Ser Ile Arg Phe Glu
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 Asp Cys Ser Ser Ala Lys Thr Ile Leu Lys Tyr Met Thr Asp Gly Met
 225 230 235 240
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 245 250 255
 Ile Ile Leu Asp Glu Ala His Glu Arg Thr Leu Ala Thr Asp Ile Leu
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 275 280 285
 Ile Val Met Ser Ala Thr Leu Asp Ala Gly Lys Phe Gln Ile Tyr Phe
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 Asp Asn Cys Pro Leu Leu Thr Ile Pro Gly Arg Thr His Pro Val Glu
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 Ile Phe Tyr Thr Pro Glu Pro Glu Arg Asp Tyr Leu Glu Ala Ala Ile
 325 330 335
 Arg Thr Val Ile Gln Ile His Met Cys Glu Glu Glu Glu Gly Asp Leu
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 355 360 365
 Ile Lys Arg Glu Val Asp Asp Leu Gly Pro Glu Val Gly Asp Ile Lys
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 Ile Ile Pro Leu Tyr Ser Thr Leu Pro Pro Gln Gln Gln Gln Arg Ile

MTP-031PC.TXT
395

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val val Phe Val Ile Asp Pro Gly Phe Ala Lys Gln Lys Val Tyr Asn
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Pro Arg Ile Arg Val Glu Ser Leu Leu Val Thr Ala Ile Ser Lys Ala
      450      455      460
Ser Ala Gln Gln Arg Ala Gly Arg Ala Gly Arg Thr Arg Pro Gly Lys
      465      470      475      480
Cys Phe Arg Leu Tyr Thr Glu Lys Ala Tyr Lys Thr Glu Met Gln Asp
      485      490      495
Asn Thr Tyr Pro Glu Ile Leu Arg Ser Asn Leu Gly Ser Val Val Leu
      500      505      510
Gln Leu Lys Lys Leu Gly Ile Asp Asp Leu Val His Phe Asp Phe Met
      515      520      525
Asp Pro Pro Ala Pro Glu Thr Leu Met Arg Ala Leu Glu Leu Leu Asn
      530      535      540
Tyr Leu Ala Ala Leu Asn Asp Asp Gly Asp Leu Thr Glu Leu Gly Ser
      545      550      555      560
Met Met Ala Glu Phe Pro Leu Asp Pro Gln Leu Ala Lys Met Val Ile
      565      570      575
Ala Ser Cys Asp Tyr Asn Cys Ser Asn Glu Val Leu Ser Ile Thr Ala
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Met Leu Ser Val Pro Gln Cys Phe Val Arg Pro Thr Glu Ala Lys Lys
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Ala Ala Asp Glu Ala Lys Met Arg Phe Ala His Ile Asp Gly Asp His
      610      615      620
Leu Thr Leu Leu Asn Val Tyr His Ala Phe Lys Gln Asn His Glu Ser
      625      630      635      640
Val Gln Trp Cys Tyr Asp Asn Phe Ile Asn Tyr Arg Ser Leu Met Ser
      645      650      655
Ala Asp Asn Val Arg Gln Gln Leu Ser Arg Ile Met Asp Arg Phe Asn
      660      665      670
Leu Pro Arg Arg Ser Thr Asp Phe Thr Ser Arg Asp Tyr Tyr Ile Asn
      675      680      685
Ile Arg Lys Ala Leu Val Thr Gly Tyr Phe Met Gln Val Ala His Leu
      690      695      700
Glu Arg Thr Gly His Tyr Leu Thr Val Lys Asp Asn Gln Val Val Gln
      705      710      715      720
Leu His Pro Ser Thr Val Leu Asp His Lys Pro Glu Trp Val Leu Tyr
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Asn Glu Phe Val Leu Thr Thr Lys Asn Tyr Ile Arg Thr Cys Thr Asp
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MTP-031PC.TXT

Ile Lys Pro Glu Trp Leu Val Lys Ile Ala Pro Gln Tyr Tyr Asp Met
 755 760 765

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Ala Lys Leu Gln Ser Lys Glu Tyr Ser Gln Tyr
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 <211> 2225
 <212> DNA
 <213> Homo sapiens

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 aaaaa 2225

<210> 49
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 <212> PRT
 <213> Homo sapiens

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MTP-031PC.TXT

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 Glu Asp Lys Glu Glu Pro Leu His Ser Ile Ile Ser Ser Thr Glu Ser
 65 70 75 80
 Val Gln Gly Ser Thr Ser Lys His Glu Phe Gln Ala Glu Thr Lys Lys
 85 90 95
 Leu Leu Asp Ile Val Ala Arg Ser Leu Tyr Ser Glu Lys Glu Val Phe
 100 105 110
 Ile Arg Glu Leu Ile Ser Asn Ala Ser Asp Ala Leu Glu Lys Leu Arg
 115 120 125
 His Lys Leu Val Ser Asp Gly Gln Ala Leu Pro Glu Met Glu Ile His
 130 135 140
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 145 150 155 160
 Ile Gly Met Thr Gln Glu Glu Leu Val Ser Asn Leu Gly Thr Ile Ala
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 Ala Ser Ser Lys Ile Ile Gly Gln Phe Gly Val Gly Phe Tyr Ser Ala
 195 200 205
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 Gly Ser Leu Gly Tyr Gln Trp Leu Ser Asp Gly Ser Gly Val Phe Glu
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 245 250 255
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 260 265 270
 Val Val Thr Lys Tyr Ser Asn Phe Val Ser Phe Pro Leu Tyr Leu Asn
 275 280 285
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 290 295 300
 Asp Val Gly Glu Trp Gln His Glu Glu Phe Tyr Arg Tyr Val Ala Gln
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 Phe Asp Val Ser Arg Glu Leu Gly Ser Ser Val Ala Leu Tyr Ser Arg
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 385 390 395 400

MTP-031PC.TXT

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 435 440 445
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 Ala Lys Leu Leu Arg Tyr Glu Ser Ser Ala Leu Pro Ser Gly Gln Leu
 465 470 475 480
 Thr Ser Leu Ser Glu Tyr Ala Ser Arg Met Arg Ala Gly Thr Arg Asn
 485 490 495
 Ile Tyr Tyr Leu Cys Ala Pro Asn Arg His Leu Ala Glu His Ser Pro
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 Lys Lys Leu Ile Ser Val Glu Thr Asp Ile Val Val Asp His Tyr Lys
 545 550 555 560
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 565 570 575
 Lys Glu Thr Glu Glu Leu Met Ala Trp Met Arg Asn Val Leu Gly Ser
 580 585 590
 Arg Val Thr Asn Val Lys Val Thr Leu Arg Leu Asp Thr His Pro Ala
 595 600 605
 Met Val Thr Val Leu Glu Met Gly Ala Ala Arg His Phe Leu Arg Met
 610 615 620
 Gln Gln Leu Ala Lys Thr Gln Glu Glu Arg Ala Gln Leu Leu Gln Pro
 625 630 635 640
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 645 650 655
 Leu Arg Ala Ser Glu Pro Gly Leu Ala Gln Leu Leu Val Asp Gln Ile
 660 665 670
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 675 680 685
 Met Val Gly Arg Leu Asn Glu Leu Leu Val Lys Ala Leu Glu Arg His
 690 695 700

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 <212> DNA
 <213> Homo sapiens

<400> 50

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 Ser Thr Ala Ala Lys Leu Gly Leu Pro Pro Leu Thr Pro Glu Gln Gln
 50 55 60
 Glu Ala Leu Gln Lys Ala Lys Lys Tyr Ala Met Glu Gln Ser Ile Lys
 65 70 75 80
 Ser Val Leu Val Lys Gln Thr Ile Ala His Gln Gln Gln Gln Leu Thr
 85 90 95
 Asn Leu Gln Met Ala Ala Gln Arg Gln Arg Ala Leu Ala Ile Met Cys
 100 105 110
 Arg Val Tyr Val Gly Ser Ile Tyr Tyr Glu Leu Gly Glu Asp Thr Ile
 115 120 125
 Arg Gln Ala Phe Ala Pro Phe Gly Pro Ile Lys Ser Ile Asp Met Ser
 130 135 140
 Trp Asp Ser Val Thr Met Lys His Lys Gly Phe Ala Phe Val Glu Tyr
 145 150 155 160

MTP-031PC.TXT

Glu Val Pro Glu Ala Ala Gln Leu Ala Leu Glu Gln Met Asn Ser Val
 165 170 175
 Met Leu Gly Gly Arg Asn Ile Lys Val Gly Arg Pro Ser Asn Ile Gly
 180 185 190
 Gln Ala Gln Pro Ile Ile Asp Gln Leu Ala Glu Glu Ala Arg Ala Phe
 195 200 205
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 465 470 475 480
 Ile Tyr Gln Glu Lys Gln Gly Glu Glu Glu Asp Ala Glu Ile Ile Val
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MTP-031PC.TXT

515

520

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MTP-031PC.TXT
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 245 250 255
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 Gly Gly Ala Val Phe Gly Glu Glu Gly Leu Thr Leu Asn Leu Glu Asp
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 340 345 350
 Asp Asp Ala Met Leu Leu Lys Gly Lys Gly Asp Lys Ala Gln Ile Glu
 355 360 365
 Lys Arg Ile Gln Glu Ile Ile Glu Gln Leu Asp Val Thr Thr Ser Glu
 370 375 380
 Tyr Glu Lys Glu Lys Leu Asn Glu Arg Leu Ala Lys Leu Ser Asp Gly
 385 390 395 400
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MTP-031PC.TXT

Lys Lys Asp Arg Val Thr Asp Ala Leu Asn Ala Thr Arg Ala Ala Val
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 450 455 460
 Ile Glu Ile Ile Lys Arg Thr Leu Lys Ile Pro Ala Met Thr Ile Ala
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 485 490 495
 Ser Ser Ser Glu Val Gly Tyr Asp Ala Met Ala Gly Asp Phe Val Asn
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MTP-031PC.TXT

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<212> PRT

<213> Homo sapiens

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

Asp Arg Gln Ile Val Asp Thr Pro Pro His Val Ala Ala Gly Leu Lys
65 70 75 80

Asp Pro Val Pro Ser Gly Phe Ser Ala Gly Glu Val Leu Ile Pro Leu
85 90 95

Ala Asp Glu Tyr Asp Pro Met Phe Pro Asn Asp Tyr Glu Lys Val Val
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Lys Arg Gln Arg Glu Glu Arg Gln Arg Gln Arg Glu Leu Glu Arg Gln
115 120 125

Lys Glu Ile Glu Glu Arg Glu Lys Arg Arg Lys Asp Arg His Glu Ala
130 135 140

Ser Gly Phe Ala Arg Arg Pro Asp Pro Asp Ser Asp Glu Asp Glu Asp
145 150 155 160

Tyr Glu Arg Glu Arg Arg Lys Arg Ser Met Gly Gly Ala Ala Ile Ala
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Pro Pro Thr Ser Leu Val Glu Lys Asp Lys Glu Leu Pro Arg Asp Phe
180 185 190

Pro Tyr Glu Glu Asp Ser Arg Pro Arg Ser Gln Ser Ser Lys Ala Ala
195 200 205

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<213> Homo sapiens
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<213> Homo sapiens
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<212> DNA
<213> Homo sapiens
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MTP-031PC.TXT

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<210> 59

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<212> PRT

<213> Homo sapiens

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Pro Pro Ser Gly Ser Trp Gln Asp Leu Lys Asp His Met Arg Glu Ala
          130          135          140
Gly Asp Val Cys Tyr Ala Asp Val Tyr Arg Asp Gly Thr Gly Val Val
          145          150          155          160
Glu Phe Val Arg Lys Glu Asp Met Thr Tyr Ala Val Arg Lys Leu Asp
          165          170          175
Asn Thr Lys Phe Arg Ser His Glu Gly Glu Thr Ala Tyr Ile Arg Val
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Lys Val Asp Gly Pro Arg Ser Pro Ser Tyr Gly Arg Ser Arg Ser Arg
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MTP-031PC.TXT

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 <212> DNA
 <213> Homo sapiens

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 <212> PRT
 <213> Homo sapiens

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 Cys Asn Tyr Gly Ser Tyr Gln Gly Arg Cys Val Ile Cys Gly Gly Pro
 50 55 60
 Gly Val Ser Asp Ala Tyr Tyr Cys Lys Glu Cys Thr Ile Gln Glu Lys
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<210> 62
 <211> 786

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<212> DNA

<213> Homo sapiens

<400> 62

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<212> PRT

<213> Homo sapiens

<400> 63

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<213> Homo sapiens

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5136

<210> 65

<211> 793

<212> PRT

<213> Homo sapiens

<400> 65

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Val Arg Asn Ile Val Asp Lys Thr Ala Ser Phe Val Ala Arg Asn Gly
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Pro Glu Phe Glu Ala Arg Ile Arg Gln Asn Glu Ile Asn Asn Pro Lys
 65 70 75 80

Phe Asn Phe Leu Asn Pro Asn Asp Pro Tyr His Ala Tyr Tyr Arg His
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Lys Val Ser Glu Phe Lys Glu Gly Lys Ala Gln Glu Pro Ser Ala Ala
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Ile Pro Lys Val Met Gln Gln Gln Gln Thr Thr Gln Gln Gln Leu
 115 120 125

Pro Gln Lys Val Gln Ala Gln Val Ile Gln Glu Thr Ile Val Pro Lys
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Glu Pro Pro Pro Glu Phe Glu Phe Ile Ala Asp Pro Pro Ser Ile Ser
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Ala Phe Asp Leu Asp Val Val Lys Leu Thr Ala Gln Phe Val Ala Arg
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Tyr Gln Phe Asp Phe Leu Arg Pro Gln His Ser Leu Phe Asn Tyr Phe
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Thr Lys Leu Val Glu Gln Tyr Thr Lys Ile Leu Ile Pro Pro Lys Gly
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Leu Phe Ser Lys Leu Lys Lys Glu Ala Glu Asn Pro Arg Glu Val Leu
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Asp Gln Val Cys Tyr Arg Val Glu Trp Ala Lys Phe Gln Glu Arg Glu
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Arg Lys Lys Glu Glu Glu Glu Lys Glu Lys Glu Arg Val Ala Tyr Ala
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Gln Ile Asp Trp His Asp Phe Val Val Val Glu Thr Val Asp Phe Gln
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Gly Ala Arg Ile Leu Ile Gln Glu Arg Tyr Glu Lys Phe Gly Glu Ser
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 Lys Gln Ser Asp Asp Glu Val Tyr Ala Pro Gly Leu Asp Ile Glu Ser
 450 455 460
 Ser Leu Lys Gln Leu Ala Glu Arg Arg Thr Asp Ile Phe Gly Val Glu
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 485 490 495
 Glu Glu Lys Val Thr Trp Asp Gly His Ser Gly Ser Met Ala Arg Thr
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 Ile Gly Pro Ser Lys Pro Asn Glu Ile Pro Gln Gln Pro Pro Pro Pro
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 Ala Val Pro Val Met Pro Arg Pro Pro Met Ala Ser Val Val Arg Leu
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 Pro Pro Gly Ser Val Ile Ala Pro Met Pro Pro Ile Ile His Ala Pro
 610 615 620
 Arg Ile Asn Val Val Pro Met Pro Pro Ser Ala Pro Pro Ile Met Ala
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 Pro Arg Pro Pro Pro Met Ile Val Pro Thr Ala Phe Val Pro Ala Pro
 645 650 655
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 660 665 670
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675 680 685

Asp Ser Leu Met Pro Glu Glu Glu Phe Leu Arg Arg Asn Lys Gly Pro
690 695 700

Val Ser Ile Lys Val Gln Val Pro Asn Met Gln Asp Lys Thr Glu Trp
705 710 715 720

Lys Leu Asn Gly Gln Val Leu Val Phe Thr Leu Pro Leu Thr Asp Gln
725 730 735

Val Ser Val Ile Lys Val Lys Ile His Glu Ala Thr Gly Met Pro Ala
740 745 750

Gly Lys Gln Lys Leu Gln Tyr Glu Gly Ile Phe Ile Lys Asp Ser Asn
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<212> PRT
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<400> 67
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MTP-031PC.TXT

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Asn	His 50	Leu	Gly	Ser	Tyr	Glu 55	Cys	Lys	Leu	Cys	Leu 60	Thr	Leu	His	Asn
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MTP-031PC.TXT
380

370 375 380

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385 390 395 400

His Pro Gln Ala Pro Gly Val His Pro Gln Pro Pro Gly Val His Pro
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Ser Ala Pro Gly Val His Pro Gln Pro Pro Gly Val His Pro Ser Asn
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Pro Gly Val His Pro Pro Thr Pro Met Pro Pro Met Leu Arg Pro Pro
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Leu Pro Ser Glu Gly Pro Gly Asn Ile Pro Pro Pro Pro Thr Asn
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<210> 68
<211> 2855
<212> DNA
<213> Homo sapiens

<400> 68

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tgtctcatta	aaaaaaaaaa	aaaggcatgg	tggcacgcac	tgtagtccca	gctactcagg	2340
agactgaggc	tagaagatcc	tttgaacctt	ggagtttgag	accagcctgg	gcgatatagt	2400
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MTP-031PC.TXT

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gtaaaagtag ctaataactca catgttctcc aatcccaggt agccatggta gagttgggta 2640
gagttgagca gctgccccag gatccaaatg tgggtgtctga aatggaaaga actaaggcaa 2700
ccaggaaggc actgatctgc cttataagca cagtcactctg aaagtcaggc ctgctgcagg 2760
acaggatccc ccagagaccc catttgccctc tcaacactca gaccttcaac tgttttttaa 2820
taaacttact ttttaaaaaa aaaaaaaaaa aaaaaa 2855

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<210> 69

<211> 501

<212> PRT

<213> Homo sapiens

<400> 69

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

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MTP-031PC.TXT

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

<210> 70
 <211> 717
 <212> DNA
 <213> Homo sapiens

<400> 70
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 gaagttatag aactaaccac agaccttctg tcaactcaac cttctgagac gcttgcaagt 180
 tcagacagtt ttgcttctac tcaacctact cattcatgga aagtaggaga caagtgtatg 240
 gcagctctgga gtgaagatgg acagtgttat gaagcggaga ttgaggagat agatgaagaa 300
 aatggcaccg ctgcaatcac ctttgctggt tatggcaatg ctgaagtgc tccactgttg 360
 aacctcaagc ctgtagaaga aggaaggaag gcaaaggagg acagtggcaa caaacccatg 420
 tcaaaaaaag aaatgattgc ccagcagcgt gaatatataaaa agaagaaagc tttgaaaaaa 480
 gctcagagaa taaaagaact tgagcaggaa agagaggacc agaaagtga atggcaacaa 540
 ttcaacaaca gagcctattc taaaaacaaa aaaggccagg taaagaggag tatttttgct 600
 tcacctgaga gtgtgactgg taaagtggga gtaggaacct gtggaattgc tgataaacct 660
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<210> 71
 <211> 238
 <212> PRT
 <213> Homo sapiens

MTP-031PC.TXT

<400> 71

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

<210> 72

<211> 1153

<212> DNA

<213> Homo sapiens

<400> 72

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 ggaggcgaat ccggcgggta tcagagccat cagaaccgcc accatgacgg tgggcaagag 180
 cagcaagatg ctgcagcata ttgattacag gatgagggtgc atcctgcagg acggccggat 240
 cttcattggc accttcaagg ctttgacaa gcacatgaat ttgatcctct gtgactgtga 300
 tgagttcaga aagatcaagc caaagaactc caaacaagca gaaagggag agaacgcagt 360
 cctcggctctg gtgctgctgc gaggggagaa tctggtctca atgacagtag agggacctcc 420
 tcccaaagat actggtattg ctcgagtcc acttgctgga gctgccgggg gccagggat 480
 cggcagggct gctggcagag gaatcccagc tggggttccc atgccccagg ctctgcagg 540
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 ccagtaccca cctggccgtg ggggtcctcc ccacctatg ggccgaggag cccccctcc 720
 aggcattgat ggcccacctc ctggtatgag acctcctatg ggtcccccaa tggggatccc 780
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MTP-031PC.TXT

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gatgcgaggc cttctttgac ccttgggccac agagtatgga agtagctccg cagagggcgtg 900
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acattataat tgc 1153

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<210> 73

<211> 231

<212> PRT

<213> Homo sapiens

<400> 73

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Met Thr Val Gly Lys Ser Ser Lys Met Leu Gln His Ile Asp Tyr Arg
  1           5           10           15

```

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Met Arg Cys Ile Leu Gln Asp Gly Arg Ile Phe Ile Gly Thr Phe Lys
          20           25           30

```

```

Ala Phe Asp Lys His Met Asn Leu Ile Leu Cys Asp Cys Asp Glu Phe
          35           40           45

```

```

Arg Lys Ile Lys Pro Lys Asn Ser Lys Gln Ala Glu Arg Glu Glu Lys
          50           55           60

```

```

Arg Val Leu Gly Leu Val Leu Leu Arg Gly Glu Asn Leu Val Ser Met
          65           70           75           80

```

```

Thr Val Glu Gly Pro Pro Lys Asp Thr Gly Ile Ala Arg Val Pro
          85           90           95

```

```

Leu Ala Gly Ala Ala Gly Gly Pro Gly Ile Gly Arg Ala Ala Gly Arg
          100          105          110

```

```

Gly Ile Pro Ala Gly Val Pro Met Pro Gln Ala Pro Ala Gly Leu Ala
          115          120          125

```

```

Gly Pro Val Arg Gly Val Gly Gly Pro Ser Gln Gln Val Met Thr Pro
          130          135          140

```

```

Gln Gly Arg Gly Thr Val Ala Ala Ala Ala Ala Ala Ala Thr Ala Ser
          145          150          155          160

```

```

Ile Ala Gly Ala Pro Thr Gln Tyr Pro Pro Gly Arg Gly Gly Pro Pro
          165          170          175

```

```

Pro Pro Met Gly Arg Gly Ala Pro Pro Pro Gly Met Met Gly Pro Pro
          180          185          190

```

```

Pro Gly Met Arg Pro Pro Met Gly Pro Pro Met Gly Ile Pro Pro Gly
          195          200          205

```

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Arg Gly Thr Pro Met Gly Met Pro Pro Pro Gly Met Arg Pro Pro Pro
          210          215          220

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Pro Gly Met Arg Gly Leu Leu
          225          230

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<210> 74

<211> 1385

<212> DNA

<213> Homo sapiens

<400> 74

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MTP-031PC.TXT

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cgaactctct tcctgccaaag atgtctattg gtgtgccgat taaagtactg catgaggccg 480
agggccacat tgtgacatgt gagacgaaca ccggtgaggt atatcggggg aagctcattg 540
aagcagagga caacatgaac tgccagatgt ccaacatcac agtcacatac agagatggcc 600
gagtggcaca gctggagcag gtatacatcc gtggcagcaa aatccgcttt ctgattttgc 660
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cggat 1385

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<210> 75
 <211> 126
 <212> PRT
 <213> Homo sapiens

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

<210> 76
 <211> 762
 <212> DNA
 <213> Homo sapiens

<400> 76
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 tcattgtgca ccgttgggtg ggaatgctgt ggcaacaggc cacgcctcca cttactggtt 180
 ggctttgctc aggcgccaac ggaagtgggt cgcaggaaga ggaagtccc cctctctctc 240
 ctgaggcagc agcaacgcgg aggaaacggg agtgaacgga gagcgtagt accatcatga 300
 gcctctctca caagcccaag agtgagatga ccccagagga gctgcagaag cgagaggagg 360
 aggaatttaa caccggtcca ctctctgtgc tcacacagtc agtcaagaac aatacccaag 420

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agggcaagaa	gaagtccaag	ccagtcaaca	aagaccgcta	catctccaag	atgttcctgc	600
gcggggactc	agtcctcgtg	gtcctgcgga	acccgctcat	cgccggcaag	taggggcccgc	660
ctgtctgttg	acagaactca	ctcctctgtc	ctatgaagac	cgctgccatt	ggtgttgaga	720
ataataaagc	tctgtgtttt	tttctaaaaa	aaaaaaaaaa	aa		762

<210> 77

<211> 118

<212> PRT

<213> Homo sapiens

<400> 77

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Gln	Lys	Arg	Glu	Glu	Glu	Glu	Phe	Asn	Thr	Gly	Pro	Leu	Ser	Val	Leu
			20					25					30		

Thr	Gln	Ser	Val	Lys	Asn	Asn	Thr	Gln	Val	Leu	Ile	Asn	Cys	Arg	Asn
		35					40					45			

Asn	Lys	Lys	Leu	Leu	Gly	Arg	Val	Lys	Ala	Phe	Asp	Arg	His	Cys	Asn
50					55						60				

Met	Val	Leu	Glu	Asn	Val	Lys	Glu	Met	Trp	Thr	Glu	Val	Pro	Lys	Ser
65					70					75					80

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

Ser	Lys	Met	Phe	Leu	Arg	Gly	Asp	Ser	Val	Ile	Val	Val	Leu	Arg	Asn
			100					105					110		

Pro	Leu	Ile	Ala	Gly	Lys
					115

<210> 78

<211> 1614

<212> DNA

<213> Homo sapiens

<400> 78

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atacacatct	taaagctgtg	aaaatgaccc	tgaagaacag	agaacctgta	cagctggaaa	300
cgctgagtat	tcgaggaaat	aacattcggg	attttattct	accagacagt	ttacctctgg	360
atacactact	tgttgatggt	gaacctaagg	tgaaatctaa	gaaaagggaa	gctgttgacg	420
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ctaggcgata	atgtctctca	agatttcaaa	gtcatatgag	atttgggata	ttttttgtac	540
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tttttctttt	tctttttatg	atgaataagg	ttaaaaataaa	agccttagac	aaattaaatt	780
tggcagagtt	taattgagca	aaggacaatt	cacaaatcag	gtagcccctg	aaccataata	840
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caagagttag	gtaccgtctg	tttacacgtc	cagttaggct	acagttctat	gtactgagaa	1080
acctttaagc	tgaacttgag	atatgtaaag	agacttttag	ctaaacttaa	caatatatat	1140
aggatatata	cccttctact	tcacatgcac	tgaatatgca	ttttattgct	ttactcttca	1200
ttctgtggca	cctaccacac	ggggaagtaa	gaagtgtgtt	ttggtatttc	ggaaactaaa	1260
gtccttatgg	gatggggctc	agaattgatt	ctcctttcct	gagttttact	ccacggagtc	1320
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MTP-031PC.TXT

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aaaatctcct attaatgtgt aatgtacctg tcagtgcctc ctttattaag gggttctttg 1560
agaataaaaag agaaaagacc tactttattt gacagcaaaa aaaaaaagga attc 1614

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<210> 79
 <211> 119
 <212> PRT
 <213> Homo sapiens

<400> 79
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 20 25 30
 Asp Val Ser Met Asn Thr His Leu Lys Ala Val Lys Met Thr Leu Lys
 35 40 45
 Asn Arg Glu Pro Val Gln Leu Glu Thr Leu Ser Ile Arg Gly Asn Asn
 50 55 60
 Ile Arg Tyr Phe Ile Leu Pro Asp Ser Leu Pro Leu Asp Thr Leu Leu
 65 70 75 80
 Val Asp Val Glu Pro Lys Val Lys Ser Lys Lys Arg Glu Ala Val Ala
 85 90 95
 Gly Arg Gly Arg Gly Arg Gly Arg Gly Arg Gly Arg Gly Arg
 100 105 110
 Gly Arg Gly Gly Pro Arg Arg
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<210> 80
 <211> 1593
 <212> DNA
 <213> Homo sapiens

<400> 80
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 tcatcatttg tagttctgga tgctggaata ccagagtttc taacctaaat acgttgggta 780
 cattatttaa tggggtcagt attgctcaac actctcattg agtcaactgt aggtccttgt 840
 gaattttatc gctaagatca gaatgtgaga agtatttggga tatagggaag gaatgaagt 900
 ctttcaagt acattaaaaa tcagttaaga gtttacagga aagagactga gattggtaat 960
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 tgctggttga attcttatat ggacaggttt cccttcccc agtatcgac atggttctag 1140
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 cgggtgagga aggaccaaga agtctggctc ctgcttttct acatgcctgt gaaggagact 1380
 tttcatgaaa ctgaataaaa gaaatcctt ccgagataga ggagatttgt aggtgaatgc 1440
 agaagtgtat ccagctttga accatgcatt ccactatat tcttcctgtc tgaactcatg 1500

MTP-031PC.TXT

ctcttttgat tatgttttga aataaaagggc tgcattagtt cttttaaaaa aaaaaaaaaa 1560
 aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaa 1593

<210> 81
 <211> 92
 <212> PRT
 <213> Homo sapiens

<400> 81
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 1 5 10 15
 Pro Ile Asn Leu Ile Phe Arg Tyr Leu Gln Asn Arg Ser Arg Ile Gln
 20 25 30
 Val Trp Leu Tyr Glu Gln Val Asn Met Arg Ile Glu Gly Cys Ile Ile
 35 40 45
 Gly Phe Asp Glu Tyr Met Asn Leu Val Leu Asp Asp Ala Glu Glu Ile
 50 55 60
 His Ser Lys Thr Lys Ser Arg Lys Gln Leu Gly Arg Ile Met Leu Lys
 65 70 75 80
 Gly Asp Asn Ile Thr Leu Leu Gln Ser Val Ser Asn
 85 90

<210> 82
 <211> 462
 <212> DNA
 <213> Homo sapiens

<400> 82
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 ttacccttc aatcccaaac ctttctcaa tggactaaca ggaaagccag tgatggtgaa 180
 acttaagtgg ggaatggagt acaagggcta tctggtatct gtagatggct acatgaacat 240
 gcagcttgca aatacagaag aatacataga tggagctttg tctggacatc tgggtgaagt 300
 ttaataaagg tgtaataatg tcctttatat cagaggtgtg gaagaagagg aagaagatgg 360
 ggaaatgaga gaatagcatc ttttgtgggg gatttttttt atatatattt ctagacaata 420
 aagatttggt tgtttttcaa cttgaaaaaa aaaaaaaaaa aa 462

<210> 83
 <211> 86
 <212> PRT
 <213> Homo sapiens

<400> 83
 Met Ser Leu Pro Leu Asn Pro Lys Pro Phe Leu Asn Gly Leu Thr Gly
 1 5 10 15
 Lys Pro Val Met Val Lys Leu Lys Trp Gly Met Glu Tyr Lys Gly Tyr
 20 25 30
 Leu Val Ser Val Asp Gly Tyr Met Asn Met Gln Leu Ala Asn Thr Glu
 35 40 45
 Glu Tyr Ile Asp Gly Ala Leu Ser Gly His Leu Gly Glu Val Leu Ile
 50 55 60
 Arg Cys Asn Asn Val Leu Tyr Ile Arg Gly Val Glu Glu Glu Glu Glu
 65 70 75 80
 Asp Gly Glu Met Arg Glu
 85

MTP-031PC.TXT

<210> 84
 <211> 606
 <212> DNA
 <213> Homo sapiens

<400> 84
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 gcattctgtga gcccgcggag tatacaccat gagcaaagct caccctccc agttgaaaaa 120
 atttatggac aagaagttat cattgaaatt aaatgggtggc agacatgtcc aaggaatatt 180
 gcggggattt gatcccttta tgaaccttgt gatagatgaa tgtgtggaga tggcgactag 240
 tggacaacag aacaatattg gaatgggtgg aatacgagga aatagtatca tcatgttaga 300
 agccttgga cgagtataaa taatggctgt tcagcagaga aacccatgtc ctctctccat 360
 agggcctgtt ttactatgat gtaaaaatta ggcatgtac attttcatat tagacttttt 420
 gttaaataaa cttttgtaat agtcaaaaat gctttctcag atgttctgaa tatagaatat 480
 cagctctcat tccagttttt tctaaccatga attttcctgg ttgacattga tttcaaaggg 540
 ttttatgcat taaagtgaag gaatcttatt aaatgcgaaa aaaaaaaaaa aaaaaaaaaa 600
 aaaaaa 606

<210> 85
 <211> 76
 <212> PRT
 <213> Homo sapiens

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

<210> 86
 <211> 21
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: Synthetic PCR
 primer U2 Foward

<400> 86
 agtgtagtat ctgttcatca g 21

<210> 87
 <211> 21
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: Synthetic PCR
 U2 Reverse

<400> 87
 atctccctgc tccaaaaatc c 21

MTP-031PC.TXT

<210> 88

<211> 23

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
anti-sense oligonucleotide

<400> 88

ataagaacag atactacact tga

23