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(71) Applicant(s)
University of Washington through its Center for Commercialization

(72) Inventor(s)
Russell, David W.;Hirata, Roli K.

(74) Agent / Attorney
Spruson & Ferguson, GPO Box 3898, Sydney, NSW, 2001, AU

(56) Related Art
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(71) Applicant: **UNIVERSITY OF WASHINGTON THROUGH ITS CENTER FOR COMMERCIALIZATION** [US/US]; 4311 11th Avenue NE, Suite 500, Seattle, WA 98105 (US).

(72) Inventor: **RUSSELL, David, W.**; 2219 East Howe Street, Seattle, WA 98112 (US).

(74) Agent: **HARPER, David, S.**; Mcdonnell Boehnen Hulbert & Berghoff LLP, 300 South Wacker Drive, Suite 3100, Chicago, IL 60606 (US).

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(54) **Title**: HLA CLASS II DEFICIENT CELLS, HLA CLASS I DEFICIENT CELLS CAPABLE OF EXPRESSING HLA CLASS II PROTEINS, AND USES THEREOF

(57) **Abstract**: The invention provides isolated primate cells preferably human cells that comprise a genetically engineered disruption in a human leukocyte antigen (HLA) class II-related gene, which results in deficiency in MHC class II expression and function. This invention also provides isolated cells further comprising a genetically engineered disruption in a beta-2 microglobulin (B2M) gene, which results in HLA class I/class II deficiency. Also provided are the method of using the cells for transplantation and treating a disease condition.

HLA CLASS II DEFICIENT CELLS, HLA CLASS I DEFICIENT CELLS CAPABLE OF EXPRESSING HLA CLASS II PROTEINS, AND USES THEREOF

Cross Reference

[001] This application claims priority to U.S. provisional patent application Serial No. 61/625,314 filed April 17, 2012, incorporated by reference herein in its entirety.

Statement of Government Rights

[002] This invention was made with government support under grant numbers R01GM086497 and R01DK55759 awarded by the National Institutes of Health. The government has certain rights in the invention.

Background of the Invention

[003] Human pluripotent stem cells have the potential to treat diseases affecting almost every organ system. However, the clinical use of human pluripotent stem cells and their derivatives has a major limitation - rejection of transplanted cells by the recipient due to differences in the major histocompatibility complex.

[004] The major histocompatibility complex (MHC) is a cell surface multi-component molecule found in all vertebrates that mediates interactions of leukocytes with other leukocytes or other cells. The MHC gene family is divided into three groups: class I, class II and class III. In humans, MHC is referred to as human leukocyte antigen (HLA). HLA class II molecules (HLA-II) are transmembrane protein found only on professional antigen-presenting cells (APCs) including macrophages, dendritic cells and B cells. In addition, solid organ may sometimes express HLA class II genes that participate in immune rejection. The HLA class I (HLA-I) protein is expressed on all nucleated cells and consists of an HLA class I heavy chain (or α chain) and β-2 microglobulin (B2M). HLA class I protein presents peptides on the cell surface to CD8+ cytotoxic T cells. Six HLA class I α chains have been identified to date, including three classical (HLA-A, HLA-B and HLA-C) and three non-classical (HLA-E, HLA-F and HLA-G) α chains. The specificity for peptide binding on the HLA class I molecule peptide binding cleft is determined by the α chain. Recognition by

CD8+ T cells of the peptides presented by the HLA class I molecule mediates cellular immunity.

[005] HLA class II molecules and class I molecules are both heterodimers. Class I molecules consist of an alpha chain (or heavy chain) and β-2 microglobuin (B2M), whereas the class II molecules consist of two homologous subunits: the alpha subunit and beta subunit.

[006] HLA class II (HLA-II) molecules or proteins present on the cell surface peptide antigens from extracellular proteins including proteins of an extracellular pathogen, while HLA class I proteins present peptides from intracellular proteins or pathogens. Loaded HLA class II proteins on the cell surface interact with CD4+ helper T cells. The interaction leads to recruitment of phagocytes, local inflammation, and/or humoral responses through the activation of B cells. Several HLA class II gene loci have been identified to date, including HLA-DM (HLA-DMA and HLA-DMB that encode HLA-DM α chain and HLA-DM β chain, respectively), HLA-DO (HLA-DOA and HLA-DOB that encode HLA-DO α chain and HLA-DO β chain, respectively), HLA-DP (HLA-DPA and HLA-DPB that encode HLA-DP α chain and HLA-DP β chain, respectively), HLA-DQ (HLA-DQA and HLA-DQB that encode HLA-DQ α chain and HLA-DQ β chain, respectively), and HLA-DR (HLA-DRA and HLA-DRB that encode HLA-DR α chain and HLA-DR β chain, respectively).

[007] The HLA class I and /or class II proteins from an allogeneic source constitutes a foreign antigen in the context of transplantation. The recognition of non-self HLA class I and/or class II proteins is a major hurdle in using pluripotent cells for transplantation or replacement therapies.

[008] Thus, although individualized stem cell preparations or HLA-diverse stem cell banks may address the current problem of transplantation, they require that multiple cell lines be characterized, differentiated into therapeutic cell products, and approved for human administration. This time-consuming, technically difficult, and expensive process is a major factor preventing stem cell-based therapies from entering clinical trials. Thus, there exists a need for a more effective and less expensive cell-based therapies that are not impeded by rejection.

Summary of the Invention

[009] In a first aspect, the present invention provides isolated cells comprising a genetically engineered disruption in a human leukocyte antigen (HLA) class II-related gene, wherein the cell is a primate cell. In one embodiment, the HLA class II-related gene is selected from the group consisting of regulatory factor X-associated ankyrin-containing protein *(RFXANK)*, regulatory factor 5 (*RFX5*), regulatory factor X-associated protein (*RFXAP*), class II transactivator (*CIITA*), HLA-DPA (α chain), HLA-DPB (β chain), HLA-DQA, HLA-DQB, HLA-DRA, HLA-DRB, HLA-DMA, HLA-DMB, HLA-DOA and HLA-DOB. In another embodiment, the cell comprises genetically engineered disruptions in at least two, at least three, or in all four of the HLA class II-related genes. In a further embodiment, the HLA class II-related gene is regulatory factor X-associated ankyrin-containing protein *(RFXANK)*. In a still further embodiment, the cell comprises genetically engineered disruptions in all copies of the HLA class II-related gene. In another embodiment the cell further comprises one or more recombinant immunomodulatory genes, each capable of expressing an immunomodulatory polypeptide in the human cell. In a further embodiment, the one or more immunomodulatory genes comprise a polynucleotide capable of encoding an HLA II protein. In another embodiment, the one or more immunomodulatory genes comprise a polynucleotide capable of encoding a single chain fusion HLA class II protein. In a further embodiment, the cell further comprises a genetically engineered disruption in the β2-microglobulin (*B2M*) gene.

[0010] In another aspect, the present invention provides isolated cells comprising (a) a genetically engineered disruption in a beta-2 microglobulin (*B2M)* gene; and (b) one or more polynucleotides capable of encoding an HLA class II protein, or a single chain fusion HLA class II protein; wherein the cell is a primate cell.

[0011] In one embodiment of either of these aspects, the cell comprises genetically engineered disruptions of all copies of the *B2M* gene. In a further embodiment, the HLA II gene encodes an HLA protein selected from the group consisting of an HLA-DM α chain, an HLA-DM β chain, an HLA-DO α chain, an HLA-DO β chain, an HLA-DP α chain, an HLA-DP β chain, an HLA-DQ α chain, an HLA-DQ β chain, an HLA-DR α chain and an HLA-DR β chain.

[0012] In another embodiment, the single chain fusion HLA class II protein comprises at least a portion of an HLA class II gene α chain covalently linked to at least a portion of an HLA class II gene β chain, wherein the HLA class II gene is selected from the group consisting of HLA-DP, HLA-DQ, HLA-DR, HLA-DM, and HLA-DO. In a further embodiment, the single chain fusion HLA class II protein comprises a plurality of different single chain fusion HLA class II proteins. In another embodiment, the single chain fusion HLA class II protein comprises at least a portion of HLA-DQ α chain and at least a portion of HLA-DQ β chain. In a still further embodiment, the single chain fusion HLA class II protein comprises at least a portion of HLA-DQ α chain allele HLA-DQA1*01 and at least a portion of HLA-DQ β chain allele HLA-DQB1*02.

[0013] In a further embodiment of either aspect of the cells of the invention, the HLA protein or the single chain fusion HLA class II protein presents a first target peptide antigen on the cell surface. In one such embodiment, the first target peptide antigen is covalently linked to the single chain fusion HLA class II protein.

[0014] In another embodiment the cell further comprises a polynucleotide capable of encoding a single chain fusion HLA class I protein. In one such embodiment, the single chain fusion HLA class I protein comprises at least a portion of B2M covalently linked to at least a portion of an HLA class I α chain selected from the group consisting of HLA-A, HLA-B, HLA-C, HLA-E, HLA-F and HLA-G. In another such embodiment, the single chain fusion HLA class I protein comprises at least a portion of B2M covalently linked to at least a portion of HLA-A. In a further embodiment the single chain fusion HLA class I protein comprises at least a portion of B2M covalently linked to at least a portion of HLA-A0201. In another embodiment the cell further expresses a second target peptide antigen that is presented by the single chain fusion HLA class I protein on the cell surface. For example, the second target peptide antigen may be covalently linked to the single chain fusion HLA class I protein.

[0015] In another embodiment of either aspect of the cells of the invention, the cell further comprises one or more recombinant genes capable of encoding a suicide gene product. For example, the suicide gene product may comprise a protein selected from the group consisting of thymidine kinase and an apoptotic signaling protein.

[0016] The cells of either aspect of the invention may have a normal karyotype and may be non-transformed cells. The cells may be stem cells, such as hematopoietic stem cells, embryonic stem cells, pluripotent stem cells, induced pluripotent stem cells, liver stem cells, neural stem cells, pancreatic stem cells or mesenchymal stem cells. The stem cell may be differentiated, such as dendritic cells, pancreatic islet cells, liver cells, muscle cells, keratinocytes, neuronal cells, hematopoietic cells, lymphocytes, red blood cells, platelets, skeletal muscle cells, ocular cells, mesenchymal cells, fibroblasts, lung cells, gastrointestinal (GI) tract cells, vascular cells, endocrine cells, adipocytes or cardiomyocytes. The cells may be human cells.

[0017] In another aspect, the present invention provides vaccines comprising the cell of any one embodiment or combinations of embodiments of the cells of the present invention that include at least one target peptide antigen on the cell surface, wherein the vaccine is capable of eliciting in a primate an immune response specific for the target peptide antigen(s).

[0018] In a further aspect, the invention provides methods of transplantation in a patient in need thereof comprising the step of administering to the patient an effective amount of the cell or vaccine of any embodiment or combination of embodiments of the cells of the invention. In one such embodiment, the patient may be immune competent. In another embodiment, the cell or vaccine may comprise a differentiated cell.

[0018A] In another aspect, the present invention provides an isolated cell comprising a genetically engineered disruption in a human leukocyte antigen (HLA) class II-related gene, wherein the cell is a primate cell wherein:

(a) the cell further comprises one or more recombinant immunomodulatory genes, each capable of expressing an immunomodulatory polypeptide in the human cell, and wherein the one or more immunomodulatory genes comprise a polynucleotide capable of encoding a single chain fusion HLA class II protein, or an HLA class II protein; and/or

(b) the cell further comprises genetically engineered disruption in all copies of the β2-microglobulin (*B2M*) gene (SEQ ID NO: 1).

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[0018B] In a further aspect, the present invention provides a vaccine comprising the cell of the previous aspect, wherein the vaccine is capable of eliciting in a primate an immune response specific for the first and/or second target peptide antigen.

[0018C] In yet another aspect, the present invention provides a method of transplantation in a patient in need thereof comprising the step of administering to the patient an effective amount of the cell of the aspect defined in paragraph [0018A] or the vaccine defined in paragraph [0018B].

[0018D] The term "comprise" and variants of the term such as "comprises" or "comprising" are used herein to denote the inclusion of a stated integer or stated integers but not to exclude any other integer or any other integers, unless in the context or usage an exclusive interpretation of the term is required.

[0018E] Any reference to publications cited in this specification is not an admission that the disclosures constitute common general knowledge in Australia.

Description of the Figures

[0019] **Figure 1** shows the structure of exemplary two adeno-associated virus (AAV) gene targeting vectors, designed to insert either a TKNeo (AAV-RFXANK-ETKNpA) or HyTK (AAV-RFXANK-HyTK) gene controlled by an EF1alpha promoter (EF) into exon 3 of the RFXANK gene, which is also shown below the vectors. Selection of vector-infected cells with G418 or hygromycin (Hygro) allows one to isolate cells targeted by the TKNeo or HyTK vectors respectively. Subsequent expression of Cre recombinase and selection with gancyclovir (GCV) then allows one to isolate clones that have removed the TKNeo or HyTK genes, leaving behind two inactivated RFXANK alleles with stop codons in all 3 reading frames, a loxP site, and a polyadenylation site (StopX3-loxP-pA). LoxP is the recombination site for Cre recombinase. ITR is a vector inverted terminal repeat. Similar vectors could be designed to target other genes.

[0020] **Figure 2 (A)** Schematic depiction of targeting strategy for infection of human embryonic stem cells with construct AAV-RFXANK-ETKNpA. (**B**) Photograph of stained gel showing polymerase chain reaction (PCR) products obtained after infection of human embryonic stem cells with AAV-RFXANK-ETKNpA and PCR using a forward primer homologous to the neomycin sequence of the selection cassette and a reverse primer homologous to the RFXANK gene which was outside the targeting homology arm, as indicated by the arrows above.

Detailed Description of the Invention

[0021] All references cited are herein incorporated by reference in their entirety. Within this application, unless otherwise stated, the techniques utilized may be found in any of several well-known references such as: *Molecular Cloning: A Laboratory Manual* (Sambrook, et al., 1989, Cold Spring Harbor Laboratory Press), *Gene Expression Technology* (Methods in Enzymology, Vol. 185, edited by D. Goeddel, 1991. Academic Press, San Diego, CA), "Guide to Protein Purification" in *Methods in Enzymology* (M.P. Deutshcer, ed., (1990) Academic Press, Inc.); *PCR Protocols: A Guide to Methods and Applications* (Innis, et al. 1990. Academic Press, San Diego, CA), *Culture of Animal Cells: A Manual of Basic Technique, 2nd Ed.* (R.I. Freshney. 1987. Liss, Inc. New York, NY), *Gene Transfer and Expression Protocols*, pp. 109-128, ed. E.J. Murray, The Humana Press Inc., Clifton, N.J.), and the Ambion 1998 Catalog (Ambion, Austin, TX).

[0022] As used herein, the singular forms "a", "an" and "the" include plural referents unless the context clearly dictates otherwise. "And" as used herein is interchangeably used with "or" unless expressly stated otherwise.

[0023] All embodiments of any aspect of the invention can be used in combination, unless the context clearly dictates otherwise.

[0024] In a first aspect, the present invention provides isolated cells comprising a genetically engineered disruption in a human leukocyte antigen (HLA) class II-related gene, wherein the cell is a primate cell. The HLA class II related genes as used in the instant application broadly refer to genes that encode proteins involved in the HLA class II mediated immune responses. Thus, HLA class II related genes encompass genes that encode the HLA class II molecules such as HLA-DM (SEQ ID NO: 48, 50), HLA-DO (SEQ ID NO: 52, 54), HLA-DP (SEQ ID

NO: 36, 38), HLA-DQ (SEQ ID NO: 40, 42), and HLA-DR (SEQ ID NO: 44, 46). The sequences of exemplary HLA class II genes/proteins can be found in publicly available database under GenBank or IMGT/HLA database numbers NM_033554.3 (SEQ ID NOs:36, 37) for HLA-DPA, HLA00514 (SEQ ID NOs:38, 39) for HLA-DPB, HLA00601 (SEQ ID NOs:40, 41) for HLA-DQA, HLA00622 (SEQ ID NOs:42, 43) for HLA-DQB, NM_019111 (SEQ ID NOs:44, 45) for HLA-DRA, HLA00664 (SEQ ID NOs:46, 47) for HLA-DRB, NM_006120 (SEQ ID NOs:48, 49) for HLA-DMA, NM_002118 (SEQ ID NOs:50, 51) for HLA-DMB, NM_002119 (SEQ ID NOs:52, 53) for HLA-DOA, and NM_002120 (SEQ ID NOs:54, 55) for HLA-DOB.

[0025] In addition, HLA class II related genes also include genes that encode HLA class II regulatory proteins that regulate the expression of HLA class II molecules, including without limitation regulatory factor X-associated ankyrin-containing protein *(RFXANK)*, regulatory factor 5 (*RFX5*), regulatory factor X-associated protein (*RFXAP*), and class II transactivator (*CIITA*). For example, regulatory factor X-associated ankyrin-containing protein *(RFXANK)* together with regulatory factor X-associated protein and regulatory factor-5 form a complex that binds to the X box motif of HLA class II gene promoters and activates transcription of the HLA class II genes. The sequences of exemplary HLA class II-related genes that regulate the expression of HLA class II molecules can be found in publicly available database under GenBank Accession Numbers NM_134440.1 (SEQ ID NOs:24, 25) and NM_003721.2 (SEQ ID NOs:26, 27) for RFXANK, NM_000449.3 (SEQ ID NOs:28, 29) and NM_001025603.1 (SEQ ID NOs:30, 31) for RFX5, NM_000538.3 (SEQ ID NOs:32, 33) for RFXAP and NM_000246.3 (SEQ ID NOs:34, 35) for CIITA. All the sequences disclosed under these GenBank Accession Numbers are herein incorporated by reference.

[0026] In certain embodiments, the invention provides an isolated primate preferably human cell that comprises a genetically engineered disruption in at least one HLA class II-related gene as defined herein. In certain particular embodiments, the cell comprises genetically engineered disruptions of all copies of the at least one HLA class II-related gene. In certain other embodiments, the cell comprises a plurality of genetically engineered disruptions in a plurality of HLA class II-related genes.

[0027] In certain embodiments, the HLA class II-related gene is selected from the group consisting of regulatory factor X-associated ankyrin-containing protein *(RFXANK)*,

regulatory factor 5 (*RFX5*), regulatory factor X-associated protein (*RFXAP*), and class II transactivator (*CIITA*). In certain particular embodiments, the cell comprises at least one genetically engineered disruption in at least one, at least two, at least three, or all of the HLA class II-related genes selected from the group consisting of regulatory factor X-associated ankyrin-containing protein *(RFXANK)*, regulatory factor 5 (*RFX5*), regulatory factor X-associated protein (*RFXAP*), and class II transactivator (*CIITA*). Any combinations of these four HLA class II-related genes as target for genetic disruption to create HLA class II deficient cell are within the scope of the invention.

[0028] In certain other embodiments, the cell comprises at least one genetically engineered disruption of an HLA class II-related genes selected from the group consisting of regulatory factor X-associated ankyrin-containing protein *(RFXANK)(SEQ ID NO: 24-27)*, regulatory factor 5 (*RFX5*) (SEQ ID NO: 28-31), regulatory factor X-associated protein (*RFXAP*) (SEQ ID NO: 32, 33), class II transactivator (*CIITA*) (SEQ ID NO: 34, 35), HLA-DPA (α chain)(SEQ ID NO: 36, 37), HLA-DPB (β chain) (SEQ ID NO: 38, 39), HLA-DQA (SEQ ID NO: 40, 41), HLA-DQB (SEQ ID NO: 42, 43), HLA-DRA (SEQ ID NO: 44, 45), HLA-DRB (SEQ ID NO: 46-47), HLA-DMA (SEQ ID NO: 48, 49), HLA-DMB (SEQ ID NO: 50, 51), HLA-DOA (SEQ ID NO: 52, 53) and HLA-DOB (SEQ ID NO: 54, 55).

[0029] The genetically engineered disruptions include without limitation deletions, insertions, substitutions and truncations of a target HLA class II-related gene that result in no expression of the target gene or expression of a truncated or mutated protein with no function or much reduced function as compared to the wild type protein. In certain embodiments, the genetically engineered disruption of a HLA class II-related gene leads to the expression of a truncated HLA class II-related protein. In certain particular embodiments, the HLA class II-related gene is *RFXANK (SEQ ID NO: 24-27)*. In certain other particular embodiments, the HLA-related gene is selected from the group consisting of HLA-DPA (α chain)(SEQ ID NO: 36, 37), HLA-DPB (β chain) (SEQ ID NO: 38, 39), HLA-DQA (SEQ ID NO: 40, 41), HLA-DQB (SEQ ID NO: 42, 43), HLA-DRA (SEQ ID NO: 44, 45), HLA-DRB (SEQ ID NO: 46-47), HLA-DMA (SEQ ID NO: 48, 49), HLA-DMB (SEQ ID NO: 50, 51), HLA-DOA (SEQ ID NO: 52, 53) and HLA-DOB (SEQ ID NO: 54, 55). In certain further embodiments the cell comprises genetically engineered disruptions in all copies of the HLA class II-related gene.

[0030] In another aspect, the invention provides HLA class I and HLA class II deficient cells. In certain embodiments, the invention provides a primate cell, preferably a human cell that comprises a genetically engineered disruption in an HLA class II-related gene and further comprises a genetically engineered disruption in the β2-microglobulin (B2M) gene (SEQ ID NO: 1). In other particular embodiments, the cell further comprises genetically engineered disruptions of all copies of the B2M gene (SEQ ID NO: 1). In certain embodiments, the genetic disruptions in the B2M (SEQ ID NO: 1) gene result in defective or no expression of the B2M protein (SEQ ID NO: 2). In other particular embodiments, the cell further comprises genetically engineered disruptions of all copies of the B2M gene. In certain embodiments, the genetic disruptions in the B2M gene result in defective or no expression of the B2M protein. Since B2M is a common component of all HLA class I proteins, the disruptions preclude the expression of all natural HLA class I proteins on the cell surface. Thus, in this aspect of the invention an HLA class I/class II deficient cell is provided. The B2M coding sequence is shown in SEQ ID NO:1 (GenBank Accession Number NM_004048) and the B2M protein sequence is shown in SEQ ID NO:2. There may be many single nucleotide polymorphisms (SNPs) in the gene; as will be understood by those of skill in the art, the human cells and methods of the invention are applicable to any such B2M gene and SNPs.

[0031] Any suitable technique for introducing a genetically engineered disruption (in an HLA class II-related gene, in B2M gene or any other suitable gene) can be used; exemplary techniques for gene disruptions are disclosed throughout the application and are within the level of skill in the art based on the teachings herein and the teachings known in the art. Other exemplary techniques can be found, for example, in U.S. Patent Application Publication Number US2008/0219956, published September 11, 2008, and incorporated by reference herein in its entirety. These techniques may optionally include steps to remove non-human DNA sequences from the cells after disruption of an HLA class II-related gene and optionally disruption of B2M gene.

[0032] One such techniques employs an adeno-associated virus gene targeting vector, optionally including removing the transgene used for targeting via techniques such as those described below, or by removing the transgene used for targeting by Cre-mediated loxP recombination, or other suitable recombination techniques. *See* Khan *et al.* 2011, Protocol, 6:482-501, which is incorporated by reference in its entirety. Exemplary targeting vectors

and exemplary vector diagrams are also disclosed herein. It is within the level of those of skill in the art, based on the teachings herein and known in the art, to utilize a variety of techniques for making the HLA class II, preferably human cells, of the invention.

[0033] In certain embodiments, the cell genome of HLA class II deficient cells may comprise no more than 100, no more than 50 or no more than 30 nucleotides of non-human DNA sequences. In certain other embodiments, the cell genome may comprise 6, 5, 4, 3, 2, 1, or 0 nucleotides of non-human DNA sequences. Exemplary strategy for genetically disrupting the RFXANK gene is shown in **Figure 1**. The non-human DNA sequences can be removed by a second round of targeting to delete the HyTK or TKNeo transgenes in the first vectors or by the Cre-mediated loxP recombination.

[0034] In certain other embodiments, the HLA class II or HLA class I/class II deficient cells further comprise one or more recombinant immunomodulatory genes. Suitable immunomodulatory genes include without limitation a gene encoding a viral protein that inhibits antigen presentation, a microRNA gene, a gene that encodes an HLA class II protein, or a gene that encodes a single chain (SC) fusion HLA class II protein. The term "single chain fusion HLA class II protein," "single chain fusion HLA class II molecule" or "single chain fusion HLA class II antigen" refers to a fusion protein comprising at least a portion of the HLA class II α chain covalently linked, either directly or via a linker sequence, to at least a portion of an HLA class II β chain or a class II α or β chain linked to a peptide antigen, or linked class II α and β chains also linked to a peptide antigen. On the other hand, the term "HLA class II protein," "HLA class II molecule" or "HLA class II antigen" refers to a non-covalently associated heterodimer of an HLA class II α chain and an HLA β chain expressed on the surface of a wild type cell. In embodiments wherein the gene encodes an HLA class II protein (as opposed to a single chain fusion HLA class II protein), the gene is under control of a promoter not involved in normal class II expression in the cell. In one embodiment, the gene is episomally expressed; in another embodiment, the gene is integrated into the cell's genome. In either embodiment, the gene is operatively linked (i.e.: under transcriptional control) to a promoter not involved in normal class II expression in the cell. Any suitable promoter may be used, as may be determined by one of skill in the art based on the specific intended design and use of the constructs and cells.

[0035] In another aspect, the present invention provides isolated cells comprising (a) a genetically engineered disruption in a beta-2 microglobulin (*B2M)* gene; and (b) one or more polynucleotides capable of encoding an HLA II protein (alpha or beta chains) or a single chain fusion HLA class II protein; wherein the cell is a primate cell. Cells according to this aspect of the invention are HLA class I deficient cells.

[0036] HLA class II deficient cells, HLA class I deficient cells, or HLA class I/class II deficient cells can be used as universal donor cells. In certain particular embodiments, the HLA class II deficient cells, HLA class I deficient cells, or HLA class I/class II deficient cells are hematopoietic cells or dendritic cells for use in transplantation. In addition, solid organ cells may sometimes express HLA class II genes that participate in immune rejection. Thus, in certain advantageous embodiments, the invention provides HLA class II, HLA class I deficient cells, or HLA class I/class II deficient cells for transplantation for treatment of diseases or injuries associated with solid organs.

[0037] In certain particular embodiments of any of the cells of the present invention, the HLA α and β chains are selected from the group consisting of α and β chains of HLA-DM, HLA-DR, HLA-DP, HLA-DQ, and HLA-DO. The α and β chains can be but do not have to be from the same HLA class II gene. For example, an HLA class II protein or a single chain fusion HLA class II protein may comprise at least a portion of an HLA-DQ α chain and at least a portion of an HLA-DQ β chain (also referred to as a dimeric construct). HLA class II proteins and single chain fusion HLA class II proteins comprising mismatching HLA class II alleles are also contemplated. In certain particular embodiments, an HLA class II protein or a single chain fusion HLA class II protein may comprise at least a portion of the HLA-DQ α chain allele HLA-DQA1*01 (SEQ ID NO:41) and at least a portion of the HLA-DQ β chain allele HLA-DQB1*02 (SEQ ID NO:43). In certain preferred embodiments, the leader sequence (or signal peptide) of the second portion of the fusion protein is removed in the fusion construct. For example, in a single chain fusion HLA class II protein that comprises at least a portion of HLA-DQA1*01 (SEQ ID NO: 41) at the N-terminus covalently linked to at least a portion of HLA-DQB1*02 (SEQ ID NO: 43) at the C-terminus, the HLA-DQA1*01 (SEQ ID NO: 41) leader sequence is left in, and the HLA-DQB1*02 (SEQ ID NO: 43) leader sequence is removed from the construct. In certain other embodiments, the cell further expresses at least two, at least three, or at least four or more different single chain fusion

HLA class II proteins. In certain particular embodiments, the HLA class II protein or single chain fusion HLA class II protein also comprises a first target peptide antigen that occupies the peptide binding site of the HLA class II protein or single chain fusion HLA class II protein, wherein the peptide antigen is covalently linked to the HLA class II protein or single chain fusion HLA class II protein (also referred to as a trimeric construct). In certain other embodiments, the covalently linked peptide antigen is cleaved via a built-in protease cleavage site, and the cleaved peptide antigen can bind to the peptide binding site of the single chain fusion HLA-II protein for presentation.

[0038] Thus, HLA class II, HLA class I deficient cells, or HLA class I/class II deficient cells also encompass cells having genetically engineered disruptions in all copies of an HLA class II gene (e.g., disruptions in all copies of HLA-DQ α and/or β chain), wherein one HLA class II allele is genetically engineered to express, instead of the wild type HLA class II protein, an HLA class II protein of interest or a single chain fusion HLA class II protein (i.e., genetically targeted knockin in one HLA-II allele). Take HLA-DQ as an example, in certain embodiments, *HLA-DQ*$^{-/-}$ cells express HLA-DQ protein only in the context of a single chain fusion HLA-DQ protein from an *HLA-DQ* genetic locus. In certain advantageous embodiments, the expression of the single chain fusion HLA class II protein is regulated by the endogenous *HLA-DQ* regulatory sequence located at the *HLA-DQ* locus.

[0039] In related embodiments, HLA class II, HLA class I deficient cells, or HLA class I/class II deficient cells further encompass cells having genetically engineered disruptions in all copies of a certain HLA-II gene, wherein all alleles of the specific HLA-II gene are genetically engineered to express, instead of the wild type HLA-II protein, single chain fusion HLA class II proteins (i.e., genetically targeted knockin in all HLA-II alleles). HLA class II, HLA class I deficient cells, or HLA class I/class II deficient cells with such genetic disruptions express a particular HLA-II protein only in the context of single chain fusion HLA class II proteins from the genetic loci of all the alleles of the particular *HLA-II* gene.

[0040] HLA class II proteins and single chain fusion HLA class II proteins comprising sequence variants and fragments of HLA class II α chains and β chains are contemplated by the instant invention, wherein such HLA class II proteins or single chain fusion constructs nevertheless possess normal HLA class II functions, *e.g.*, forming proper secondary structure of the heterodimer on the cell surface, presenting peptides in the peptide binding site,

interacting with CD4+ helper T cells and triggering HLA class II-mediated immune responses. In certain embodiments, the variants share at least 75%, 78%, 80%, 81%, 85%, 88%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or complete sequence homology with the naturally occurring HLA class II α or β chain sequences, wherein the variants possess normal HLA class II functions. In certain other embodiments, the variants share at least 75%, 80%, 81%, 85%, 88%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or complete sequence homology with the sequences of HLA class II α or β chains as shown in SEQ ID NOs:37, 39, 41, 43, 45, 47, 49, 51, 53 and 55.

[0041] Further, the HLA class II, HLA class I deficient cells, or HLA class I/class II deficient cells can be engineered to recombinantly express a single chain fusion HLA class I protein in a B2M-/- genetic background. The HLA class I deficient cells or HLA class I/class II deficient cells recombinantly expressing a single chain fusion HLA class I protein are nevertheless deficient in normal B2M function in that the cells do not express wild type B2M protein (SEQ ID NO:2) that can form a non-covalently associated heterodimer with any HLA class I α chain on the cell surface.

[0042] The term "single chain fusion HLA class I protein," "single chain fusion HLA class I molecule" or "single chain fusion HLA class I antigen" refers to a fusion protein comprising at least a portion of the B2M protein covalently linked, either directly or via a linker sequence, to at least a portion of an HLA-I α chain. On the other hand, the term "HLA class I protein," "HLA class I molecule" or "HLA class I antigen" refers to a non-covalently associated heterodimer of B2M and an HLA α chain expressed on the surface of a wild type cell.

[0043] As used herein, the term "HLA class I α chain" or "HLA-I heavy chain" refers to the α chain of the HLA class I heterodimer. HLA class I heavy chain includes without limitation HLA class I α chains HLA-A, HLA-B, HLA-C, HLA-E, HLA-F, and HLA-G. Representative DNA and protein sequences are provided for HLA-A (GenBank No. K02883.1, SEQ ID NO:3; UniProt No. P01892, SEQ ID NO:4), HLA-B (NM_005514, SEQ ID NO:5; NP_005505; SEQ ID NO:6), HLA-C (NM_002117, SEQ ID NO:7; NP_002108, SEQ ID NO:8), HLA-E (NM_005516, SEQ ID NO:9; NP_005507, SEQ ID NO:10), HLA-F (NM_018950, SEQ ID NO:11; NP_061823, SEQ ID NO:12), and HLA-G (NM_002127, SEQ ID NO:13; NP_002118, SEQ ID NO:14).

[0044] In addition, although the term "HLA class I or II protein/molecule" is known to refer to the MHC class I or II protein/molecule in human, the terms HLA and MHC are sometimes used interchangeably throughout this application: for example, the term HLA class I or HLA class II protein can also be used to refer to the primate equivalent to the HLA class I protein or HLA class II protein, respectively, in a primate. One of skill in the art will be able to discern the meaning of the term based on the content.

[0045] Thus, HLA class I deficient cells or HLA class I/class II deficient cells also encompass cells having genetically engineered disruptions in all copies of the *B2M* gene, wherein one *B2M* allele is genetically engineered to express, instead of the wild type B2M protein, a single chain fusion HLA class I protein (*i.e.*, genetically targeted knockin in one *B2M* allele). *B2M*-/- cells with such genetic background express B2M only in the context of the single chain fusion HLA class I protein from a *B2M* genetic locus. In certain advantageous embodiments, the expression of the single chain fusion HLA class I protein is regulated by the endogenous B2M regulatory sequence located at the *B2M* locus.

[0046] In related embodiments, HLA class I deficient cells or HLA class I/class II deficient cells further encompass cells having genetically engineered disruptions in all copies of the *B2M* gene, wherein all *B2M* alleles are genetically engineered to express, instead of the wild type B2M protein, single chain fusion HLA class I proteins (*i.e.*, genetically targeted knockin in all *B2M* alleles). HLA class I deficient cells or HLA class I/class II deficient cells with such genetic disruptions express B2M only in the context of single chain fusion HLA class I proteins from the genetic loci of all the alleles of the *B2M* gene. In certain embodiments, the cells are genetically engineered to express the same type of single chain fusion HLA class I protein from the genetic loci of all alleles of the *B2M* gene; while in other embodiments, the cells are genetically engineered to express different types of single chain fusion HLA class I proteins from different genetic loci of the *B2M* gene.

[0047] In certain embodiments, the single chain fusion HLA class I protein comprises at least a portion of B2M (SEQ ID NO: 2) and at least a portion of HLA-A (SEQ ID NO: 4), HLA-B (SEQ ID NO: 6), HLA-C (SEQ ID NO: 8), HLA-E (SEQ I D NO: 10), HLA-F (SEQ ID NO: 12) or HLA-G (SEQ ID NO: 14) (also referred to as a dimeric construct). In certain preferred embodiments, the HLA α chain contained in the single chain fusion HLA class I protein does not contain the leader sequence (or signal sequence) of the HLA class I α chain (leaderless

HLA α chain). In certain other embodiments, the single chain fusion HLA class I protein comprises at least a portion of B2M (SEQ ID NO: 2) and at least a portion of HLA-C (SEQ ID NO: 8), HLA-E (SEQ ID NO: 10) or HLA-G (SEQ ID NO: 14). In certain further embodiments, the single chain fusion HLA class I protein comprises at least a portion of B2M (SEQ ID NO: 2) and at least a portion of HLA-A (SEQ ID NO: 4), HLA-E (SEQ ID NO: 10) or HLA-G (SEQ ID NO: 14). In certain preferred embodiments, the single chain fusion HLA class I protein comprises a leader sequence (or signal peptide) covalently linked to at least a portion of B2M and at least a portion of an HLA α chain to ensure proper folding of the single chain fusion on the cell surface. The leader sequence can be the leader sequence of the B2M protein, the leader sequence of an HLA α chain protein or the leader sequence of other secretary proteins. In certain particular embodiments, the single chain fusion HLA class I protein comprises a B2M protein with its leader sequence removed. In certain other particular embodiments, the single chain fusion HLA class I protein comprises an HLA α chain protein with its leader sequence removed. Certain HLA class I α chains are highly polymorphic. As will be understood by those of skill in the art, the human cells and methods of the invention are applicable to any such HLA α chains and polymorphism thereof.

[0048] Single chain fusion HLA class I proteins comprising sequence variants and fragments of B2M and/or HLA α chains are contemplated by the instant invention, wherein such single chain fusion constructs nevertheless possess normal HLA class I functions, *e.g.*, forming proper secondary structure of the heterodimer on the cell surface, presenting peptides in the peptide binding cleft and engaging the inhibitory receptors on the surface of NK cells. In certain embodiments, the variants share at least 75%, 80%, 81%, 85%, 88%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or complete sequence homology with the naturally occurring HLA heavy chains and B2M sequences, wherein the variants possess normal HLA class I functions. In certain other embodiments, the variants share at least 75%, 80%, 81%, 85%, 88%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or complete sequence homology with the sequences of B2M or HLA heavy chains as shown in SEQ ID NOs:2, 4, 6, 8, 10, 12 or 14.

[0049] In certain particular embodiments, the HLA-A variants share at least 85%, 88,%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or complete sequence homology with SEQ ID NO:4. In certain other particular embodiments, the HLA-B variants share at

least 81%, 83%, 85%, 88,%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or complete sequence homology with SEQ ID NO:6. In certain further embodiments, the HLA-C variants share at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or complete sequence homology with SEQ ID NO:8. In yet other embodiments, the HLA-E variants share at least 97%, 98%, 99%, or complete sequence homology with SEQ ID NO:10. In certain particular embodiments, the HLA-F variants share at least 99%, or complete sequence homology with SEQ ID NO:12. In certain other embodiments, the HLA-G variants share at least 98%, 99%, or complete sequence homology with SEQ ID NO:14.

[0050] In certain other embodiments, the single chain fusion HLA class I protein comprises full-length B2M (SEQ ID NO: 2) (including its leader sequence) and an HLA α chain without the leader sequence (leaderless HLA α chain); while in certain other embodiments, the single chain fusion HLA class I protein comprises B2M (SEQ ID NO: 2) protein without the leader sequence. It is understood that *B2M*-/- cells expressing two, three or more different types of single chain fusion HLA class I protein in any combination, for example, expressing SC fusion comprising HLA-A (SEQ ID NO: 4)(or a leaderless HLA-A) and SC fusion comprising HLA-C (SEQ ID NO: 8) (or a leaderless HLA-C), expressing SC fusion comprising HLA-A (SEQ ID NO: 4)(or a leaderless HLA-A) and SC fusion comprising HLA-E (SEQ ID NO: 10) (or a leaderless HLA-E), or expressing SC fusion comprising HLA-B (SEQ ID NO: 6)(or a leaderless HLA-B), SC fusion comprising HLA-E (SEQ ID NO: 10)(or a leaderless HLA-E) and SC fusion comprising HLA-G (SEQ ID NO: 14)(or a leaderless HLA-G), etc., are all contemplated by the invention and fall within the scope of the invention.

[0051] Natural killer (NK) cells are part of the innate immune response. Several pathogens can down regulate HLA class I protein expression in infected cells. The NK cells monitor infection by recognizing and inducing apoptosis in cells that do not express HLA class I proteins. The inhibitory receptors on the NK cell surface recognize HLA class I α chain alleles thereby preventing NK-medicated apoptosis in uninfected normal cells. Thus, in certain particular embodiments, the single chain fusion HLA-I protein inhibits NK cell-mediated killing of cells that do not express endogenous HLA class I proteins by binding to the inhibitory receptors on the NK cells. For example, HLA-E is a ligand for the CD94/NKG2 receptor of NK cells that inhibits NK cell-mediated apoptosis. Thus, in certain

particular embodiments, the *B2M*-/- cell expresses the single chain fusion HLA class I protein comprising at least a portion of B2M and at least a portion of HLA-E. In addition, HLA-G is normally expressed on the surface of placental cytotrophoblasts that do not express HLA-A, B or C, and it protects these cells from NK cell-mediated lysis by interacting with the inhibitory ILT2(LIR1) receptor on NK cells (Pazmany *et al.*, 1996, Science *274*, 792-795). Thus, in certain other preferred embodiments, the *B2M*-/- cell expresses the single chain fusion HLA class I protein comprising at least a portion of B2M and at least a portion of HLA-G.

[0052] In certain particular embodiments, the single chain fusion HLA class I protein comprises at least a portion of B2M and at least a portion of HLA-A0201. HLA-A0201 (SEQ ID NO:4) is a common HLA class I allele found in a large percentage of the population in the United States. Thus, in certain advantageous embodiments, the isolated cell expresses the single chain fusion HLA class I protein comprising at least a portion of B2M and at least a portion of HLA-A0201 in a *B2M*-/- genetic background, wherein the isolated cell is immune compatible with a large percentage of the human population in the United States. Other suitable common alleles that can be used include without limitation HLA-A0101, HLA-A0301, HLA-B0702, HLA-B0801, HLA-C0401, HLA-C0701, and HLA-C0702. In certain preferred embodiments, the HLA allele comprises at least a portion of HLA-A0201 (SEQ ID NO:4), HLA-B0702 (SEQ ID NO:6) or HLA-C0401 (SEQ ID NO:8).

[0053] In certain further embodiments, the single chain fusion HLA class I protein also comprises a second target peptide antigen that occupies the peptide binding cleft of the single chain fusion HLA class I protein, wherein the peptide antigen is covalently linked to the single chain fusion HLA class I protein (also referred to as a trimeric construct). An example of the trimeric construct is shown in **Figure 2**. The HLA-bGBE construct of **Figure 2** comprises B2M and HLA-E covalently linked to a peptide antigen (such as, but not limited to, the HLA-G signal peptide as illustrated in the figure) (SEQ ID NO:23) designed to occupy the peptide binding cleft of the single chain fusion HLA class I protein. In certain other embodiments, the covalently linked peptide antigen is cleaved via a built-in protease cleavage site, and the cleaved peptide antigen can bind to the peptide binding cleft of the single chain fusion HLA-I protein for presentation.

[0054] In certain alternative embodiments, the peptide antigen occupying the peptide binding cleft of the single chain fusion HLA class I protein is produced by the intracellular antigen processing pathway, in which the peptide antigen is produced by proteasome, transported to and loaded onto the single chain fusion HLA class I protein in the endoplasmic reticulum. In certain particular embodiments, the peptide antigen comprises a peptide of a tumor antigen. In certain other embodiments, the peptide antigen comprises a peptide of a protein from a pathogen including without limitation a bacterium, a virus, a fungus and a parasite. In further embodiments, the peptide antigen comprises a peptide of a tumor antigen. In certain particular embodiments, the HLA class I deficient cell or HLA class I/class II deficient cell expresses a single chain fusion HLA class I protein that is covalently linked to a peptide that does not comprise an auto-antigen or neo-antigen to the patient. It is within the ability of a skilled person to design the single chain fusion HLA class I protein and the peptide antigen presented thereon to modulate the immune response that may be elicited in a recipient.

[0055] The isolated HLA class II deficient cells, HLA class I deficient cells, or HLA class I/class II deficient cells expressing an HLA class II protein or a single chain fusion HLA class II protein optionally a single chain fusion HLA class I protein comprising a specific peptide antigen either covalently or non-covalently bound to the single chain fusion proteins can be used, for example, for administration to a recipient to elicit an immune response. Accordingly, in a related aspect, the invention provides a vaccine comprising the isolated cell of the invention, wherein the vaccine is capable of eliciting in a recipient an immune response specific for the target peptide antigen. The immune response includes without limitation a cellular immune response and/or a humoral immune response. The vaccine may comprise a stem cell or a differentiated cell; in certain particular embodiments, the cell is a differentiated dendritic cell. In certain other embodiments, the cell further expresses a cytokine. Any suitable cytokine can be used; in certain particular embodiments, the cytokine is IL2 or IFN-γ. In certain preferred embodiments, the cell is a human cell and the recipient is a human. Thus, in a further aspect, the invention provides kits comprising the vaccines of the invention and optionally an immune adjuvant.

[0056] The single chain fusion HLA class I protein, HLA class II protein, or single chain fusion HLA class II protein can be expressed from an expression vector that allows either transient or more preferably, stable expression of the protein in a cell. Exemplary suitable expression vectors are known in the art. One such example is a retroviral vector, which is

capable of integrating into the cellular genome to provide long-term, stable expression of an exogenous gene. In certain particular embodiments, the viral vector is derived from human foamy virus, a type of retrovirus. Other suitable viral vectors include without limitation vectors derived from retrovirus, adenoviral virus, adeno-associated virus, lentivirus, herpes simplex virus, vaccinia virus, and pox virus.

[0057] In certain preferred embodiments, the polynucleotide capable of encoding a single chain fusion HLA class I or class II protein or an HLA class II protein is integrated into the chromosome of the cells, preferably into the *B2M* or the *HLA* class II loci, for stable expression. Thus, in certain preferred embodiments, the *B2M* loci are disrupted by inserting in the *B2M* loci the polynucleotide capable of encoding a single chain fusion HLA class I protein to replace the expression of the endogenous wild type B2M protein. Thus, in certain other preferred embodiments, certain *HLA-II* loci are disrupted by inserting in the *HLA-II* loci the polynucleotide capable of encoding an HLA class II protein or a single chain fusion HLA class II protein to replace the expression of the endogenous wild type HLA-II protein. The result of such gene targeting precludes formation of wild type HLA class I proteins and specific HLA class II proteins but permits expression of a predetermined HLA class II protein or single chain fusion HLA class I or class II protein of choice on the surface of the otherwise HLA class II deficient cells. Other expression vectors are also contemplated and the selection of suitable expression vector is within the ability of one ordinary skill in the art.

[0058] The "isolated cell" can be any suitable cell type for a given purpose. For example, the cell can be a pluripotent stem cell or a differentiated cell. "A stem cell" broadly encompasses any cells that are capable of further differentiation. "A pluripotent stem cell" refers to a stem cell that has the potential to differentiate into any of the three germ layers: endoderm, mesoderm or ectoderm. "An adult stem cell," on the other hand, is multipotent in that it can produce only a limited number of cell types. "An embryonic stem (ES) cell" refers to a pluripotent stem cell derived from the inner cell mass of the blastocyst, an early-stage embryo. "Induced pluripotent stem cells (iPS cells)" are pluripotent stem cell artificially derived from a non-pluripotent cell, typically an adult somatic cell, by artificially inducing expression of certain genes.

[0059] In another aspect, the invention provides a method of transplantation in a patient in need thereof comprising the step of administering to the patient an effective amount of the

cells of the invention for transplantation. Because the HLA class II deficient cells and/or HLA class I deficient cells do not express wild type HLA class II protein (and optionally also HLA class I protein) on the cell surface, the cells when administered to a patient elicit minimal or no immune responses in the patient. Thus, transplantation using the HLA class II deficient cells and/or HLA class I deficient cells limits the need for taking immune suppressant therapies. Thus, in certain preferred embodiments, the patient is immune competent. In certain other embodiments, the cell is an isogeneic cell; while in other embodiments, the cell is an allogeneic cell.

[0060] In certain further embodiments, the cells of the invention are pluripotent stem cells; while in other embodiments, the cells of the invention are differentiated cells. In certain preferred embodiments, the cell is a human cell and the patient is a human patient. In certain particular embodiments, the method of transplantation comprises administering to a human an effective amount of the pluripotent stem cells or differentiated cells. In certain preferred embodiments, the cells of the invention further express one or more engineered single chain fusion HLA class II proteins and optionally also a single chain fusion HLA class I protein. In certain other embodiments, the cells are able to escape NK cell-mediated killing and elicit minimal or no immune response in the recipient after transplantation.

[0061] Transplantation therapy, replacement therapy or regenerative therapy refers to therapies for a disease condition by administering to a patient cells or tissues to replenish or replace defective cellular functions in a target organ. In certain particular embodiments, the need for transplantation arises as a result of physical or pathological injuries to a tissue or organ. In certain other particular embodiments, the need for transplantation arises as a result of one or more genetic defect or mutation in the patient and the transplantation of the cells of the invention replenishes or replaces defective cellular functions in the patient without the need for gene therapy to correct the underlying genetic mutation of the patient. In certain further embodiments, the transplantation includes without limitation hematopoietic stem cell transplantation, or transplantation of cells that are incorporated into an organ such as liver, kidney, pancreas, lung, brain, muscle, heart, gastrointestinal tract, nervous system, skin, bones, bone marrow, fat, connective tissue, immune system, or blood vessels. In certain particular embodiments, the target organ is a solid organ.

[0062] In certain particular embodiments, the cells administered to the recipient may or may not be incorporated into an organ in need of such therapy. In certain embodiments, the cells of the invention are differentiated into the desired cell type, either before or after transplantation, and provide the necessary cellular function without itself being incorporated into the tissue at the site of transplantation. For example, in certain embodiments for treating diabetes, the cells of the invention either as pluripotent stem cells or differentiated pancreatic beta islet cells are transplanted to a diabetic patient. The transplanted cells need not reconstitute a functioning pancreas: they just need to secrete insulin in response to glucose levels. In certain particular embodiments, the cells are transplanted into an ectopic location and are not fully incorporated into the pancreas. Transplantation of pluripotent cells of the invention, differentiated cells of the invention, or a tissue differentiated and developed *ex vivo* from the cells of the invention are all contemplated by the invention. In certain preferred embodiments, the cell is a human cell and the patient is a human patient. In certain other preferred embodiments, the cells of the invention express one or more single chain fusion HLA class II proteins and optionally also single chain fusion HLA class I proteins.

[0063] In a further aspect, the invention provides a method of treating a disease condition in a patient in need thereof comprising the step of administering to the patient an effective amount of the cell of the invention to treat the disease condition, wherein the disease condition is diabetes, an autoimmune disease, cancer, infection, anemia, cytopenia, myocardial infarction, heart failure, skeletal or joint condition, osteogenesis imperfecta or burns. In certain particular embodiments, the disease condition results from pathological or physical injuries to a tissue or organ. In certain embodiments, the cells of the invention are stem cells; while in other embodiments, the cells of the invention are differentiated cells. In certain preferred embodiments, the cell is a human cell and the patient is a human patient. In certain particular embodiments, the human cell is a differentiated cell. Transplantation of a tissue developed *ex vivo* from the cells of the invention is also contemplated by the invention. In certain preferred embodiments, the cells of the invention further express one or more single chain fusion HLA class II proteins and optionally also one or more single chain fusion HLA class I proteins. In certain embodiments, the cell is an isogeneic cell; while in other embodiments, the cell is an allogeneic cell.

[0064] In certain particular embodiments, the cell is a differentiated cell including without limitation a dendritic cell, lymphocyte, red blood cell, platelet, hematopoietic cell, pancreatic

islet cell, liver cell, muscle cell, keratinocyte, cardiomyocyte, neuronal cell, skeletal muscle cell, ocular cell, mesenchymal cell, fibroblast, lung cell, GI tract cell, vascular cell, endocrine cell and adipocyte. In certain other particular embodiments, the invention provides a method of treating a disease condition in a solid organ. In certain embodiments, the cells of the invention used in treating a disease condition express one or more single chain fusion HLA class I proteins and optionally also one or more single chain fusion HLA class I proteins.

[0065] "Treating" a patient having a disease or disorder means accomplishing one or more of the following: (a) reducing the severity of the disease; (b) arresting the development of the disease or disorder; (c) inhibiting worsening of the disease or disorder; (d) limiting or preventing recurrence of the disease or disorder in patients that have previously had the disease or disorder; (e) causing regression of the disease or disorder; (f) improving or eliminating the symptoms of the disease or disorder; and (f) improving survival. In certain preferred embodiments, the disease or disorder is a disease or disorder that can be treated by transplantation of tissues or cells.

[0066] The effective amount of the isolated cells of the invention for transplantation or for treating a disease condition depends on a number of factors, such as the type of tissue, the severity of the disease condition, the transplantation reaction, the reason for transplantation, and the age and general health of the patient. The effective amount can be determined by a skilled researcher or clinician by routine practice. Due to the reduced immunogenicity of the transplanted cells, relative large amount of cells can be tolerated by a patient to achieve the desired therapeutic effects. Alternatively, the cells can be repeatedly transplanted at intervals until a desired therapeutic effect is achieved.

[0067] The route for administration of the cells of the invention is not limited in any particular way. Exemplary delivery routes include without limitation intravenous, intramuscular, subdermal, intraperitoneal, transcutaneous, intracutaneous, and subcutaneous route. The cells of the present invention can also be administered topically by injection. For example, the cells can be injected into an injured joint, a fractured bone, an infarct site, an ischemic site or their periphery.

[0068] In certain particular embodiments, the cells are administered via a delivery device including without limitation a syringe. For example, the cells can be suspended in a solution or a pharmaceutical composition contained in such a delivery device. The "solution" or

"pharmaceutical composition" comprises a physiological compatible buffer and optionally a pharmaceutically acceptable carrier or diluent in which the cells of the invention remain viable. The use of such carriers and diluents is well known in the art. The solution includes without limitation physiologically compatible buffers such as Hank's solution, Ringer' solution, or physiologically buffered saline. The cells can be kept in the solution or pharmaceutical composition for short term storage without losing viability. In certain particular embodiments, the cells are frozen for long term storage without losing viability according to cryopreservation methods well-known in the art.

[0069] Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran, but still fluid to the extent that can be easily delivered by syringe injection. The solution is preferably sterile, stable under the conditions of manufacture and storage and is free of microorganism contamination through the use of, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. The cells contained in the solution can be stem cells or differentiated cells as described herein, in a pharmaceutically acceptable carrier or diluent and, as required, other ingredients indicated above.

[0070] The cells may be administered systemically (*e.g.*, intravenously) or locally (*e.g.*, directly into a myocardial defect under the guidance of echocardiogram, or by direct application to damaged tissues or organs accessible during open surgery). For injections, the cells may be in an injectable liquid suspension preparation or in a biocompatible medium which is injectable in liquid form and becomes semi-solid at the site of damaged tissue. A syringe, a controllable endoscopic delivery device or other similar devises can be used so long as the needle lumen is of sufficient diameter (*e.g.* at least 30 gauge or larger) to avoid physical damages to the cells during delivery.

[0071] In certain other embodiments, the cells can be transplanted via a solid support, *e.g.*, a planar surface or three-dimensional matrix. The matrix or planar surface is surgically implanted into the appropriate site in a patient. For example, a patient needing a pancreatic graft can have differentiated cells on a solid support surgically implanted in the pancreas tissue. Exemplary solid support includes without limitation a patch, a gel matrix (such as GELFOAM® from Pharmacia-Upjohn), polyvinyl alcohol sponge (PVA)–collagen gel implants (such as IVALON, Unipoint Industries, High Point, NC) and other similar or

equivalent devices. A variety of other encapsulation technologies can be used with the cells of the invention, for example, WO 91/10470; WO 91/10425; U.S. Pat. No. 5,837,234; U.S. Pat. No. 5,011,472; U.S. Pat. No. 4,892,538).

[0072] The cells of the invention can be differentiated into various cell types of all three lineages, including without limitation hematopoietic, mesenchymal, pancreatic endoderm, cardiac and keratinocytes cells. In certain embodiments, the differentiated cell further expresses an HLA class II protein or a single chain fusion HLA class II protein and optionally also a single chain fusion HLA class I protein. In general, each cell type can be analyzed for HLA class II and optionally also class I protein expression, reactivity with human T cells and NK cells, appropriate differentiation markers, and xenotransplantation in immunodeficient mice to examine *in vivo* developmental potential. A brief discussion of each differentiated cell type follows.

[0073] In certain embodiments, the cells of the invention can be differentiated to hematopoietic cells for treating various hematopoietic diseases currently treated by bone marrow transplantation. Patients receiving transfusion can become refractory to platelet transfusions due to HLA mismatches. Anemic or cytopenic patients can be treated by delivering the cells of the invention-derived erythrocytes, platelets or neutrophils to treat bleeding or infection.

[0074] Further, stem cells of the invention-derived dendritic cells are antigen-presenting cells that can be used as cellular vaccines when properly engineered. In certain embodiments, the cells of the invention engineered to express an HLA class II protein or a single chain fusion HLA class II protein and optionally also a single chain fusion HLA class I protein and a unique peptide antigen are used to vaccinate against specific pathogen or tumor antigens. In certain other embodiments, differentiated HLA class II deficient, HLA class I deficient, or HLA class I/class II deficient cytotoxic lymphocytes with HLA-restricted reactivity against specific antigens are used to eliminate infected cells or tumor cells.

[0075] To obtain hematopoietic cells, the pluripotent cells are first allowed to form embryoid bodies, thereafter non-adherent cells were cultured in the presence of hematopoietic cytokines to develop into specific cell lineages. The differentiation of hematopoietic cells from the cells of the invention that express an HLA class II protein or a single chain fusion HLA class II protein and optionally also a single chain fusion HLA class I protein can be analyzed by

flow cytometry and colony assays. The different cell populations are sorted based on their surface markers, and used to monitor the expression of HLA genes and reactivity with human NK cells and T cells as measured by Elispot, mixed lymphocyte reactions, and cytotoxicity assays. The effectiveness of the single chain fusion HLA constructs on suppression of NK cell-mediated killing can be examined at different stages of differentiation and transplantation. See Bix *et al.*, 1991, Nature *349*, 329-331. The hematopoietic stem cells can also be assayed using xenotransplantation models in, for example, immunodeficient mice (SCID-repopulating cells or SRCs).

[0076] The cells of the invention can be differentiated into hematopoietic cell either before or after the cells are administered to a patient. In certain preferred embodiments, the cell is a human cell and the patient is a human. *In vitro* hematopoietic differentiation can be performed according to established protocols. See for example, Slukvin *et al.*, 2006, J Immunol *176*:2924-32, and Chang *et al.*, 2006, Blood 108:1515-23.

[0077] In certain other embodiments, the cells of the invention can be differentiated into mesenchymal stem cells. In certain embodiments, the cells of the invention express one or more HLA class II protein or single chain fusion HLA class II proteins and optionally also one or more single chain fusion HLA class I proteins. MSCs have the potential to form several differentiated cell types, including marrow stromal cells, adipocytes, osteoblasts, and chondrocytes. Thus, inducing pluripotent stem cells to form MSCs (iMSCs) is useful in treating skeletal and joint conditions. The iMSCs can be further differentiated into osteoblasts and formed bone *in vivo*. Deyle *et al.*, 2012, Mol Ther. 20(1):204-13. Cellular responses of T cells and NK cells to ESCs, iMSCs, and their more terminally differentiated derivatives such as osteoblasts can be examined.

[0078] In certain particular embodiments, the mesenchymal stem cells are capable of differentiating into non-limiting examples of cell types such as marrow stromal cells, adipocytes, osteoblasts, osteocytes and chondrocytes. The cells of the invention are differentiated into mesenchymal stem cells either before or after the cells are administered to a patient. In certain preferred embodiments, the cell is a human cell and the patient is a human. *In vitro* mesenchymal differentiation can be performed according to established protocols. See for example, Deyle *et al.*, *supra.*

[0079] In yet other particular embodiments, the cells of the invention can be differentiated into insulin-producing pancreatic islet cells. In certain embodiments, the cells of the invention express one or more HLA class II proteins or single chain fusion HLA class II proteins and optionally also one or more single chain fusion HLA class I proteins. The cells of the invention can be used to treat insulin-dependent diabetes mellitus. Advantageously, the transplanted cells do not need to reconstitute a functioning pancreas: they just need to secrete insulin in response to glucose levels. Therefore the treatment can succeed with different cell doses, with cells that are not perfectly differentiated into adult cell types, and when cells are transplanted into an ectopic location. Specific auto-antigens such as those derived from GAD65 or Insulin can cause autoimmune destruction of β cells in diabetes (Di Lorenzo *et al.*, 2007, Clin Exp Immunol *148*, 1-16). Thus, HLA class II deficient, HLA class I deficient, or HLA class I/class II deficient cells expressing single chain fusion HLA protein presenting a predetermined peptide antigen provide additional advantages in that they do not present these auto-antigens and can avoid autoimmune rejection and prevent a relapse of diabetes after transplantation.

[0080] The cells of the invention can be differentiated into pancreatic cells as described previously, which employs exposure of cells to different cytokines and drugs to promote sequential formation of mesendoderm, definitive endoderm, and pancreatic progenitors (Kroon *et al.*, 2008, Nat Biotechnol *26*, 443-452). These cells can be further cultured in implants in immunodeficient mice. The wild-type cells and cells of the invention with or without expressing one or more single chain fusion HLA class II proteins or both one or more single chain fusion HLA class II proteins and optionally also one or more single chain HLA class I proteins can be analyzed at different developmental stages for their reactivity with T cells and NK cells.

[0081] The cells of the invention are differentiated into pancreatic islet cell either before or after patient administration. In certain preferred embodiments, the cell is a human cell and the patient is a human. *In vitro* hematopoietic differentiation can be performed according to established protocols. See for example, Kroon *et al.*, 2008, Nat Biotechnol *26*, 443-452.

[0082] In certain other particular embodiments, the cells of the invention can be differentiated into cardiomyocytes. In certain embodiments, the cells of the invention further express one or more HLA class II proteins or single chain fusion HLA class II proteins and

optionally also one or more single chain fusion HLA class I proteins. The common clinical problems of myocardial infarction and congestive heart failure can be treated by transplanting healthy stem cell-derived cardiomyocytes that engraft and re-establish functional myocardium. The cells of the invention-derived cardiomyocytes allow these treatments to proceed with pre-packaged cells and avoid the immunosuppression currently required for allogeneic heart transplants. Physiologically relevant tests can be performed on the cardiomyocytes derived from the cells of the invention, such as electrical conduction and contraction studies. HLA class II deficient, HLA class I deficient, or HLA class I/class II deficient stem cells or differentiated cardiomyocytes with or without expressing a single chain fusion HLA class I protein can be tested to determine their immunological reactivity when expressing cardiomyocyte genes, and to establish which HLA modifications minimize these immune responses.

[0083] The cells of the invention can be differentiated into cardiomyocytes either before or after the cells are administered to a patient. In certain preferred embodiments, the cell is a human cell and the patient is a human. In certain embodiments, the cells of the invention are differentiated into cardiomyocytes for treating diseases including without limitation myocardial infarction and congestive heart failure. *In vitro* cardiomyocyte differentiation can be performed according to established protocols. See for example, Laflamme *et al.*, 2007, Nat Biotechnol *25*, 1015-1024.

[0084] In yet other particular embodiments, the cells of the invention can be differentiated into keratinocytes. In certain embodiments, the cells of the invention used for differentiation into keratinocytes express one or more single chain fusion HLA class II proteins and optionally also one or more HLA class II proteins or single chain fusion HLA class I proteins. Severe burns and genetic skin conditions require treatment with skin grafts, and this is currently done with a variety of cell sources such as porcine skin grafts and cultured autologous human keratinocytes. Keratinocytes derived from the cells of the invention can provide a major clinical advance, since burns could be treated as an emergency with pre-packaged cells, and genetic diseases such as epidermolysis bullosum can be treated with otherwise normal HLA class II deficient, HLA class I deficient, or HLA class I/class II deficient cells that do not require correction of the responsible genetic mutations. In many cases the cells only need to engraft long enough for neighboring host cells to repopulate the affected area. For *in vivo* differentiation, the cells of the invention can be embedded in

polyvinyl alcohol sponge (PVA)–collagen gel implants for transplantation into a recipient. The cells of the invention can be differentiated into keratinocytes either before or after transplantation. In certain preferred embodiments, the cell is a human cell and the patient is a human.

[0085] In yet another aspect, the invention provides a use of the cells of the invention for the preparation for a medicament for transplantation. In a related aspect, the invention provides a use of the cells of the invention for the preparation for a medicament for treating a disease condition.

[0086] Further, the cells of the invention can serve as a research tool to provide a system for studying the functions of immunoregulatory proteins in a HLA class II deficient, HLA class I deficient, or HLA class I/class II deficient genetic background. In certain embodiments, the cells of the invention further express one or more HLA class II proteins or single chain fusion HLA class II proteins and optionally also one or more single chain fusion HLA class I proteins. Accordingly, in a related aspect, the invention provides a method of determining the function of an immunoregulatory protein comprising the steps of introducing one or more immunoregulatory genes into the cells of the invention of the invention and assaying for the activities of the immunoregulatory genes. In certain preferred embodiments, the cell is a human cell. For example, the cells of the invention can be used to study the function of an immune regulatory gene, or to study an immune response, in the absence of unwanted HLA class II antigens or HLA class I/class II antigens. In a further related aspect, the invention provides a method of identifying a compound or molecule that modulates the function of the immunoregulatory protein comprising the steps of contacting the HLA class II deficient cells, HLA class I deficient cells, or HLA class I/class II deficient cells comprising the one or more immunoregulatory genes with a compound or molecule of interest and assaying for the activities of the immunoregulatory genes. In certain preferred embodiments, the cell is a human cell.

[0087] In a related aspect, the invention provides kits that comprise the HLA class II deficient, HLA class I deficient, or HLA class I/class II deficient cells of the invention and an implant, wherein the implant comprises the cells of the invention.

[0088] In yet another aspect, the invention provides an *in vivo* research tool in a mammal, particular in a non-human primate, that are administered the cells of the invention, for

studying the functions of immunoregulatory genes, or identifying a compound that modulates the function of an immunoregulatory gene in the administered cells in an HLA class II deficient, HLA class I deficient, or HLA class I/class II deficient genetic background. In certain embodiments, the cells of the invention further express one or more HLA class II proteins or single chain fusion HLA class II proteins and optionally also one or more single chain fusion HLA class I proteins.

[0089] Mice, especially immune deficient mice, have been used as a model system for studying human cells *in vivo*. Human stem cells can behave differently in mice. In addition, the mouse and human immune systems have different HLA class II genes, NK cell receptors and non-classical MHC class I genes (e.g. HLA-E, F and G). Therefore, a *Macaca nemestrina* (Mn, pigtailed macaque) model can be developed to study the cells of the invention. The *Macaca mulatta* genome has been sequenced, which is highly homologous to the *nemestrina* genome. Further, the organization of macaque MHC loci is similar to human HLA, including the non-classical genes. Homologs of the human HLA-E and HLA-G genes have been identified in macaques. The macaque MHC loci also contain homologs of many human NK cell receptors. Human and Mn HLA class II deficient, HLA class I deficient, or HLA class I/class II deficient ESCs can be used for transplantation in macaques.

[0090] MHC class II-deficient of MHC class I/class II-deficient macaque ESCs can be developed using the same AAV-mediated gene targeting strategy described for human cells. *Mn* versions of the single chain fusion HLA class II proteins and optionally single chain fusion HLA class I proteins are expressed in the HLA class II or HLA class II/class I deficient macaques ESCs using the analogous viral vectors as described above.

[0091] Cells can be expanded *in vitro* and labeled with a vector expressing GFP for subsequent identification of transplanted cells. The cells can be embedded in polyvinyl alcohol sponge (PVA)–collagen gel implants, and placed subdermally into macaques. The implants can be harvested, sectioned and stained to determine the cell types that are present. Specific antibodies can be used to identify the differentiated cell types formed by the transplanted cells.

[0092] Any and every embodiment described above applies to any and every aspect of the invention, unless the context clearly indicates otherwise. All embodiments within and between different aspects can be combined unless the context clearly dictates otherwise.

EXAMPLES

Example 1 Construction of Human Embryonic Stem Cells with Knockout Mutation in *RFXANK* Gene

[0093] Figure 1 shows the structure of exemplary two adeno-associated virus (AAV) gene targeting vectors, designed to insert either a TKNeo (AAV-RFXANK-ETKNpA) or HyTK (AAV-RFXANK-HyTK) gene controlled by an EF1alpha promoter (EF) into exon 3 of the RFXANK gene, which is also shown below the vectors. Selection of vector-infected cells with G418 or hygromycin (Hygro) allows one to isolate cells targeted by the TKNeo or HyTK vectors respectively. Subsequent expression of Cre recombinase and selection with gancyclovir (GCV) then allows one to isolate clones that have removed the TKNeo or HyTK genes, leaving behind two inactivated RFXANK alleles with stop codons in all 3 reading frames, a loxP site, and a polyadenylation site (StopX3-loxP-pA). LoxP is the recombination site for Cre recombinase. ITR is a vector inverted terminal repeat. Similar vectors could be designed to target other genes.

[0094] The AAV-RFXANK-ETKNpA vector (SEQ ID NO: 56) was used to create a knockout mutation in a first allele of the *RFXANK* gene. Human embryonic stem cells were infected with AAV-RFXANK-ETKNpA and screened for targeting by PCR using a forward primer homologous to the neomycin sequence of the selection cassette and a reverse primer homologous to the RFXANK gene which was outside the targeting homology arm, as indicated by the arrows above. As shown in **Figure 2**, 5 positive clones of the correct size are shown above out of 40 clones screened yielding a targeting frequency of 12.5%.

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CLAIMS

1. An isolated cell comprising a genetically engineered disruption in a human leukocyte antigen (HLA) class II-related gene, wherein the cell is a primate cell wherein:

   (a) the cell further comprises one or more recombinant immunomodulatory genes, each capable of expressing an immunomodulatory polypeptide in the human cell, and wherein the one or more immunomodulatory genes comprise a polynucleotide capable of encoding a single chain fusion HLA class II protein, or an HLA class II protein; and/or

   (b) the cell further comprises genetically engineered disruption in all copies of the β2-microglobulin (*B2M*) gene (SEQ ID NO: 1).

2. The cell of claim 1, wherein the HLA class II-related gene is selected from the group consisting of regulatory factor X-associated ankyrin-containing protein *(RFXANK)*(SEQ ID NO: 24-27), regulatory factor 5 (*RFX5*) (SEQ ID NO: 28-31), regulatory factor X-associated protein (*RFXAP*) (SEQ ID NO: 32-33), class II transactivator (*CIITA*) (SEQ ID NO: 34-35), HLA-DPA (α chain) (SEQ ID NO: 36-37), HLA-DPB (β chain) (SEQ ID NO: 38-39), HLA-DQA (SEQ ID NO: 40-41), HLA-DQB (SEQ ID NO: 42-43), HLA-DRA (SEQ ID NO: 44-45), HLA-DRB (SEQ ID NO: 46-47), HLA-DMA (SEQ ID NO: 48-49), HLA-DMB (SEQ ID NO: 50-51), HLA-DOA (SEQ ID NO: 52-53) and HLA-DOB (SEQ ID NO: 54-55).
3. The cell of claim 2, wherein the cell comprises genetically engineered disruptions in at least two, at least three, or in all four of the HLA class II-related genes.
4. The cell of any one of claims 1 to 3, wherein the HLA class II-related gene is regulatory factor X-associated ankyrin-containing protein *(RFXANK)* (SEQ ID NO: 24-27).
5. The cell of any one of claims 1 to 4, wherein the cell comprises genetically engineered disruptions in all copies of the HLA class II-related gene.
6. The cell of any one of claims 1 to 5, wherein the cell comprises one or more recombinant immunomodulatory genes, each capable of expressing an immunomodulatory polypeptide in the human cell and wherein the one or more immunomodulatory genes comprise a polynucleotide capable of encoding a single chain fusion HLA class II protein, or an HLA class II protein.
7. The cell of any one of claims 1 to 6, wherein the cell comprises genetically engineered disruptions of all copies of the *B2M* gene.

8. The cell of any one of claims 1 to 7, wherein the one or more immunomodulatory genes comprise one or more single chain fusion HLA class II proteins, and wherein the one or more single chain fusion HLA class II proteins comprises at least a portion of an HLA class II gene α chain covalently linked to at least a portion of an HLA class II gene β chain, wherein the HLA class II gene is selected from the group consisting of HLA-DP (SEQ ID NO: 36-39), HLA-DQ (SEQ ID NO: 40-43), HLA-DR (SEQ ID NO: 44-47), HLA-DM (SEQ ID NO: 48-51), and HLA-DO (SEQ ID NO: 52-55).
9. The cell of claim 8, wherein the single chain fusion HLA class II protein comprises a plurality of different single chain fusion HLA class II proteins.
10. The cell of claim 8 or claim 9, wherein the single chain fusion HLA class II protein comprises at least a portion of HLA-DQ α chain (SEQ ID NO: 41) and at least a portion of HLA-DQ β chain (SEQ ID NO: 43).
11. The cell of any one of claims 8 to 10, wherein the single chain fusion HLA class II protein comprises at least a portion of HLA-DQ α chain allele HLA-DQA1*01 (SEQ ID NO: 41) and at least a portion of HLA-DQ β chain allele HLA-DQB1*02 (SEQ ID NO: 43).
12. The cell of any one of claims 8 to 11 wherein the single chain fusion HLA class II protein presents a first target peptide antigen on the cell surface.
13. The cell of claim 12 wherein the first target peptide antigen is covalently linked to the single chain fusion HLA class II protein.
14. The cell of any one of claims 1 to 7 wherein the one or more immunomodulatory genes comprise one or more HLA class II proteins, wherein the one or more HLA class II proteins are selected from the group consisting of an HLA-DM α chain, an HLA-DM β chain, an HLA-DO α chain, an HLA-DO β chain, an HLA-DP α chain, an HLA-DP β chain, an HLA-DQ α chain, an HLA-DQ β chain, an HLA-DR α chain and an HLA-DR β chain.
15. The cell of any one of claims 1 to 7, wherein the cell further comprises a polynucleotide capable of encoding a single chain fusion HLA class I protein and wherein the single chain fusion HLA class I protein comprises at least a portion of B2M (SEQ ID NO: 2) covalently linked to at least a portion of an HLA class I α chain selected from the group consisting of HLA-A (SEQ ID NO: 4), HLA-B (SEQ ID NO: 6), HLA-C (SEQ ID NO: 8), HLA-E (SEQ ID NO: 10), HLA-F (SEQ ID NO: 12) and HLA-G (SEQ ID NO: 14).

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16. The cell of claim 15, wherein the single chain fusion HLA class I protein comprises at least a portion of B2M (SEQ ID NO: 2) covalently linked to at least a portion of HLA-A (SEQ ID NO: 3).
17. The cell of claim 15 or claim 16, wherein the single chain fusion HLA class I protein comprises at least a portion of B2M covalently linked to at least a portion of HLA-A0201(SEQ ID NO: 4).
18. The cell of any one of claims 15 to 17, wherein the cell further expresses a second target peptide antigen that is presented by the single chain fusion HLA class I protein on the cell surface.
19. The cell of claim 18 wherein the second target peptide antigen is covalently linked to the single chain fusion HLA class I protein.
20. The cell of any one of claims 1 to 19, wherein the cell further comprises one or more recombinant genes capable of encoding a suicide gene product.
21. The cell of claim 20 wherein the suicide gene product comprises a protein selected from the group consisting of thymidine kinase and an apoptotic signaling protein.
22. The cell of any one of claims 1 to 21, wherein the cell has a normal karyotype.
23. The cell of any one of claims 1 to 22, wherein the cell is a non-transformed cell.
24. The cell of any one of claims 1 to 23, wherein the cell is a stem cell.
25. The cell of claim 24, wherein the stem cell is selected from the group consisting of a hematopoietic stem cell, an embryonic stem cell, an induced pluripotent stem cell, a liver stem cell, a neural stem cell, a pancreatic stem cell and a mesenchymal stem cell.
26. The cell of claim 24 or claim 25, wherein the stem cell is a pluripotent stem cell.
27. The cell of any one of claims 24 to 26, wherein the stem cell is differentiated.
28. The cell of claim 27, wherein the differentiated cell is selected from the group consisting of a dendritic cell, a pancreatic islet cell, a liver cell, a muscle cell, a keratinocyte, neuronal cell, hematopoietic cell, lymphocyte, red blood cell, platelet, skeletal muscle cell, ocular cell, mesenchymal cell, fibroblast, lung cell, GI tract cell, vascular cell, endocrine cell, adipocyte and a cardiomyocyte.
29. The cell of any one of claims 1 to 28, wherein the cell is a human cell.
30. A vaccine comprising the cell of any one of claims 12 to 29, wherein the vaccine is capable of eliciting in a primate an immune response specific for the first and/or second target peptide antigen.
31. The vaccine of claim 30, wherein the primate is a human and the cell is a human cell.

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32. A method of transplantation in a patient in need thereof comprising the step of administering to the patient an effective amount of the cell of any one of claims 1 to 29 or the vaccine of claim 30 or claim 31.
33. The method of claim 32, wherein the patient is immune competent.
34. The method of claim 32 or claim 33, wherein the cell or vaccine comprises a differentiated cell.
35. The method of any one of claims 32 to 34, wherein the patient is a human and the cell is a human cell.

Date: 8 June 2017

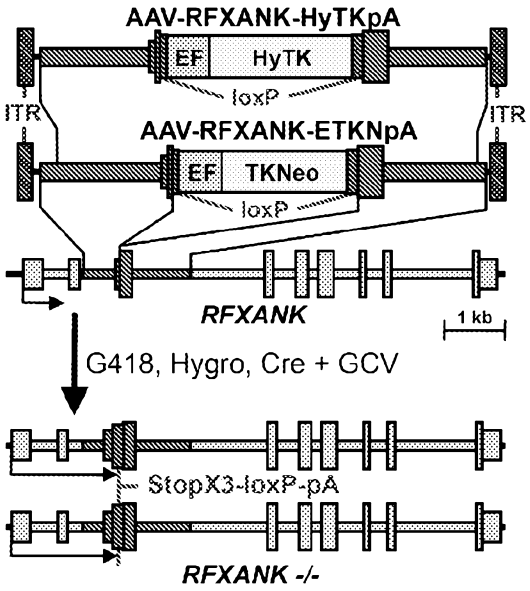

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Figure 1

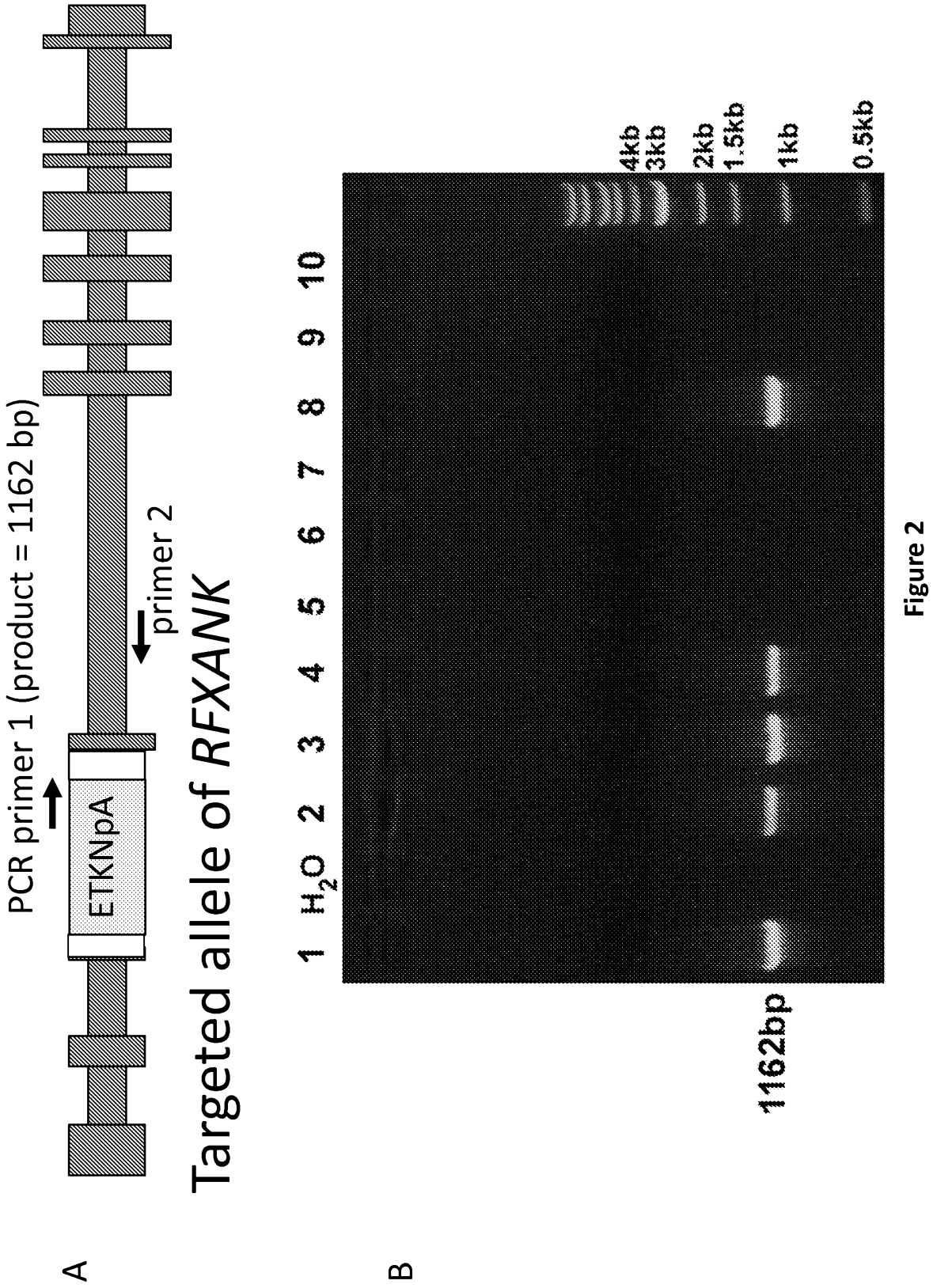

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primer 2
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Figure 2

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acc tgc cat gtg cag cat gag ggt ctg ccc aag ccc ctc acc ctg aga        975
Thr Cys His Val Gln His Glu Gly Leu Pro Lys Pro Leu Thr Leu Arg
            285                 290                 295

tgg gag ctg tct tcc cag ccc acc atc ccc atc gtg ggc atc att gct       1023
Trp Glu Leu Ser Ser Gln Pro Thr Ile Pro Ile Val Gly Ile Ile Ala
        300                 305                 310

ggc ctg gtt ctc ctt gga gct gtg atc act gga gct gtg gtc gct gcc       1071
Gly Leu Val Leu Leu Gly Ala Val Ile Thr Gly Ala Val Val Ala Ala
    315                 320                 325

gtg atg tgg agg agg aag agc tca gat aga aaa gga ggg agt tac act       1119
Val Met Trp Arg Arg Lys Ser Ser Asp Arg Lys Gly Gly Ser Tyr Thr
330                 335                 340                 345

cag gct gca agc agt gac agt gcc cag ggc tct gat gtg tct ctc aca       1167
Gln Ala Ala Ser Ser Asp Ser Ala Gln Gly Ser Asp Val Ser Leu Thr
                350                 355                 360

gct tgt aaa gtg tga gacagctgcc ttgtgtggga ctgagaggca agagttgttc       1222
Ala Cys Lys Val
            365

ctgcccttcc ctttgtgact tgaagaaccc tgactttgtt tctgcaaagg cacctgcatg     1282

tgtctgtgtt cgtgtaggca taatgtgagg aggtggggag agcaccccac ccccatgtcc     1342

accatgaccc tcttcccacg ctgacctgtg ctccctctcc aatcatcttt cctgttccag     1402

agaggtgggg ctgaggtgtc tccatctctg tctcaacttc atggtgcact gagctgtaac     1462

ttcttccttc cctattaaaa ttagaacctg agtataaatt tactttctca aattcttgcc     1522

atgagaggtt gatgagttaa ttaaaggaga agattcctaa aatttgagag acaaaattaa     1582

tggaacgcat gagaaccttc cagagtcca                                       1611
```

<210> 4
<211> 365
<212> PRT
<213> Homo sapiens

<400> 4

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

Leu Ala Leu Thr Gln Thr Trp Ala Gly Ser His Ser Met Arg Tyr Phe
            20                  25                  30

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

Val Gly Tyr Val Asp Asp Thr Gln Phe Val Arg Phe Asp Ser Asp Ala
    50                  55                  60

Ala Ser Gln Lys Met Glu Pro Arg Ala Pro Trp Ile Glu Gln Glu Gly
65                  70                  75                  80

Pro Glu Tyr Trp Asp Gln Glu Thr Arg Asn Met Lys Ala His Ser Gln
                85                  90                  95
```

```
Thr Asp Arg Ala Asn Leu Gly Thr Leu Arg Gly Tyr Tyr Asn Gln Ser
            100                 105                 110

Glu Asp Gly Ser His Thr Ile Gln Ile Met Tyr Gly Cys Asp Val Gly
        115                 120                 125

Pro Asp Gly Arg Phe Leu Arg Gly Tyr Arg Gln Asp Ala Tyr Asp Gly
    130                 135                 140

Lys Asp Tyr Ile Ala Leu Asn Glu Asp Leu Arg Ser Trp Thr Ala Ala
145                 150                 155                 160

Asp Met Ala Ala Gln Ile Thr Lys Arg Lys Trp Glu Ala Val His Ala
                165                 170                 175

Ala Glu Gln Arg Arg Val Tyr Leu Glu Gly Arg Cys Val Asp Gly Leu
            180                 185                 190

Arg Arg Tyr Leu Glu Asn Gly Lys Glu Thr Leu Gln Arg Thr Asp Pro
        195                 200                 205

Pro Lys Thr His Met Thr His His Pro Ile Ser Asp His Glu Ala Thr
    210                 215                 220

Leu Arg Cys Trp Ala Leu Gly Phe Tyr Pro Ala Glu Ile Thr Leu Thr
225                 230                 235                 240

Trp Gln Arg Asp Gly Glu Asp Gln Thr Gln Asp Thr Glu Leu Val Glu
                245                 250                 255

Thr Arg Pro Ala Gly Asp Gly Thr Phe Gln Lys Trp Ala Ala Val Val
            260                 265                 270

Val Pro Ser Gly Glu Glu Gln Arg Tyr Thr Cys His Val Gln His Glu
        275                 280                 285

Gly Leu Pro Lys Pro Leu Thr Leu Arg Trp Glu Leu Ser Ser Gln Pro
    290                 295                 300

Thr Ile Pro Ile Val Gly Ile Ile Ala Gly Leu Val Leu Leu Gly Ala
305                 310                 315                 320

Val Ile Thr Gly Ala Val Val Ala Ala Val Met Trp Arg Arg Lys Ser
                325                 330                 335

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

Ala Gln Gly Ser Asp Val Ser Leu Thr Ala Cys Lys Val
        355                 360                 365
```

<210> 5
<211> 1578
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (55)..(1143)

<400> 5

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agttctaaag tccccacgca cccacccgga ctcagagtct cctcagacgc cgag atg          57
                                                          Met
                                                          1

ctg gtc atg gcg ccc cga acc gtc ctc ctg ctc tcg gcg gcc ctg         105
Leu Val Met Ala Pro Arg Thr Val Leu Leu Leu Ser Ala Ala Leu
            5                  10                  15

gcc ctg acc gag acc tgg gcc ggc tcc cac tcc atg agg tat ttc tac         153
Ala Leu Thr Glu Thr Trp Ala Gly Ser His Ser Met Arg Tyr Phe Tyr
        20                  25                  30

acc tcc gtg tcc cgg ccc ggc cgc ggg gag ccc cgc ttc atc tca gtg         201
Thr Ser Val Ser Arg Pro Gly Arg Gly Glu Pro Arg Phe Ile Ser Val
    35                  40                  45

ggc tac gtg gac gac acc cag ttc gtg agg ttc gac agc gac gcc gcg         249
Gly Tyr Val Asp Asp Thr Gln Phe Val Arg Phe Asp Ser Asp Ala Ala
50                  55                  60                  65

agt ccg aga gag gag ccg cgg gcg ccg tgg ata gag cag gag ggg ccg         297
Ser Pro Arg Glu Glu Pro Arg Ala Pro Trp Ile Glu Gln Glu Gly Pro
                70                  75                  80

gag tat tgg gac cgg aac aca cag atc tac aag gcc cag gca cag act         345
Glu Tyr Trp Asp Arg Asn Thr Gln Ile Tyr Lys Ala Gln Ala Gln Thr
            85                  90                  95

gac cga gag agc ctg cgg aac ctg cgc ggc tac tac aac cag agc gag         393
Asp Arg Glu Ser Leu Arg Asn Leu Arg Gly Tyr Tyr Asn Gln Ser Glu
        100                 105                 110

gcc ggg tct cac acc ctc cag agc atg tac ggc tgc gac gtg ggg ccg         441
Ala Gly Ser His Thr Leu Gln Ser Met Tyr Gly Cys Asp Val Gly Pro
    115                 120                 125

gac ggg cgc ctc ctc cgc ggg cat gac cag tac gcc tac gac ggc aag         489
Asp Gly Arg Leu Leu Arg Gly His Asp Gln Tyr Ala Tyr Asp Gly Lys
130                 135                 140                 145

gat tac atc gcc ctg aac gag gac ctg cgc tcc tgg acc gcc gcg gac         537
Asp Tyr Ile Ala Leu Asn Glu Asp Leu Arg Ser Trp Thr Ala Ala Asp
                150                 155                 160

acg gcg gct cag atc acc cag cgc aag tgg gag gcg gcc cgt gag gcg         585
Thr Ala Ala Gln Ile Thr Gln Arg Lys Trp Glu Ala Ala Arg Glu Ala
            165                 170                 175

gag cag cgg aga gcc tac ctg gag ggc gag tgc gtg gag tgg ctc cgc         633
Glu Gln Arg Arg Ala Tyr Leu Glu Gly Glu Cys Val Glu Trp Leu Arg
        180                 185                 190

aga tac ctg gag aac ggg aag gac aag ctg gag cgc gct gac ccc cca         681
Arg Tyr Leu Glu Asn Gly Lys Asp Lys Leu Glu Arg Ala Asp Pro Pro
    195                 200                 205
```

```
aag aca cac gtg acc cac cac ccc atc tct gac cat gag gcc acc ctg        729
Lys Thr His Val Thr His His Pro Ile Ser Asp His Glu Ala Thr Leu
210                 215                 220                 225

agg tgc tgg gcc ctg ggt ttc tac cct gcg gag atc aca ctg acc tgg        777
Arg Cys Trp Ala Leu Gly Phe Tyr Pro Ala Glu Ile Thr Leu Thr Trp
                230                 235                 240

cag cgg gat ggc gag gac caa act cag gac act gag ctt gtg gag acc        825
Gln Arg Asp Gly Glu Asp Gln Thr Gln Asp Thr Glu Leu Val Glu Thr
            245                 250                 255

aga cca gca gga gat aga acc ttc cag aag tgg gca gct gtg gtg gtg        873
Arg Pro Ala Gly Asp Arg Thr Phe Gln Lys Trp Ala Ala Val Val Val
        260                 265                 270

cct tct gga gaa gag cag aga tac aca tgc cat gta cag cat gag ggg        921
Pro Ser Gly Glu Glu Gln Arg Tyr Thr Cys His Val Gln His Glu Gly
    275                 280                 285

ctg ccg aag ccc ctc acc ctg aga tgg gag ccg tct tcc cag tcc acc        969
Leu Pro Lys Pro Leu Thr Leu Arg Trp Glu Pro Ser Ser Gln Ser Thr
290                 295                 300                 305

gtc ccc atc gtg ggc att gtt gct ggc ctg gct gtc cta gca gtt gtg       1017
Val Pro Ile Val Gly Ile Val Ala Gly Leu Ala Val Leu Ala Val Val
                310                 315                 320

gtc atc gga gct gtg gtc gct gct gtg atg tgt agg agg aag agt tca       1065
Val Ile Gly Ala Val Val Ala Ala Val Met Cys Arg Arg Lys Ser Ser
            325                 330                 335

ggt gga aaa gga ggg agc tac tct cag gct gcg tgc agc gac agt gcc       1113
Gly Gly Lys Gly Gly Ser Tyr Ser Gln Ala Ala Cys Ser Asp Ser Ala
        340                 345                 350

cag ggc tct gat gtg tct ctc aca gct tga aaagcctgag acagctgtct         1163
Gln Gly Ser Asp Val Ser Leu Thr Ala
    355                 360

tgtgagggac tgagatgcag gatttcttca cgcctcccct ttgtgacttc aagagcctct     1223

ggcatctctt tctgcaaagg cacctgaatg tgtctgcgtc cctgttagca taatgtgagg     1283

aggtggagag acagcccacc cttgtgtcca ctgtgacccc tgttcccatg ctgacctgtg     1343

tttcctcccc agtcatcttt cttgttccag agaggtgggg ctggatgtct ccatctctgt     1403

ctcaacttta cgtgcactga gctgcaactt cttacttccc tactgaaaat aagaatctga     1463

atataaattt gttttctcaa atatttgcta tgagaggttg atggattaat taaataagtc     1523

aattcctgga atttgagaga gcaaataaag acctgagaac cttccagaaa aaaaa          1578


<210>  6
<211>  362
<212>  PRT
<213>  Homo sapiens

<400>  6

Met Leu Val Met Ala Pro Arg Thr Val Leu Leu Leu Leu Ser Ala Ala
1               5                   10                  15


Leu Ala Leu Thr Glu Thr Trp Ala Gly Ser His Ser Met Arg Tyr Phe
```

```
            20                  25                  30

Tyr Thr Ser Val Ser Arg Pro Gly Arg Gly Glu Pro Arg Phe Ile Ser
        35                  40                  45

Val Gly Tyr Val Asp Asp Thr Gln Phe Val Arg Phe Asp Ser Asp Ala
    50                  55                  60

Ala Ser Pro Arg Glu Glu Pro Arg Ala Pro Trp Ile Glu Gln Glu Gly
65                  70                  75                  80

Pro Glu Tyr Trp Asp Arg Asn Thr Gln Ile Tyr Lys Ala Gln Ala Gln
                85                  90                  95

Thr Asp Arg Glu Ser Leu Arg Asn Leu Arg Gly Tyr Tyr Asn Gln Ser
            100                 105                 110

Glu Ala Gly Ser His Thr Leu Gln Ser Met Tyr Gly Cys Asp Val Gly
        115                 120                 125

Pro Asp Gly Arg Leu Leu Arg Gly His Asp Gln Tyr Ala Tyr Asp Gly
    130                 135                 140

Lys Asp Tyr Ile Ala Leu Asn Glu Asp Leu Arg Ser Trp Thr Ala Ala
145                 150                 155                 160

Asp Thr Ala Ala Gln Ile Thr Gln Arg Lys Trp Glu Ala Ala Arg Glu
                165                 170                 175

Ala Glu Gln Arg Arg Ala Tyr Leu Glu Gly Glu Cys Val Glu Trp Leu
            180                 185                 190

Arg Arg Tyr Leu Glu Asn Gly Lys Asp Lys Leu Glu Arg Ala Asp Pro
        195                 200                 205

Pro Lys Thr His Val Thr His His Pro Ile Ser Asp His Glu Ala Thr
    210                 215                 220

Leu Arg Cys Trp Ala Leu Gly Phe Tyr Pro Ala Glu Ile Thr Leu Thr
225                 230                 235                 240

Trp Gln Arg Asp Gly Glu Asp Gln Thr Gln Asp Thr Glu Leu Val Glu
                245                 250                 255

Thr Arg Pro Ala Gly Asp Arg Thr Phe Gln Lys Trp Ala Ala Val Val
            260                 265                 270

Val Pro Ser Gly Glu Glu Gln Arg Tyr Thr Cys His Val Gln His Glu
        275                 280                 285

Gly Leu Pro Lys Pro Leu Thr Leu Arg Trp Glu Pro Ser Ser Gln Ser
```

```
    290                 295                 300

Thr Val Pro Ile Val Gly Ile Val Ala Gly Leu Ala Val Leu Ala Val
305                 310                 315                 320

Val Val Ile Gly Ala Val Val Ala Ala Val Met Cys Arg Arg Lys Ser
                325                 330                 335

Ser Gly Gly Lys Gly Gly Ser Tyr Ser Gln Ala Ala Cys Ser Asp Ser
            340                 345                 350

Ala Gln Gly Ser Asp Val Ser Leu Thr Ala
        355                 360
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<210> 7
<211> 1586
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (66)..(1166)

<400> 7

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tccgcagtcc cggttctaaa gtccccagtc acccacccgg actcacattc tccccagagg       60

ccgag atg cgg gtc atg gcg ccc cga gcc ctc ctc ctg ctg ctc tcg gga      110
      Met Arg Val Met Ala Pro Arg Ala Leu Leu Leu Leu Leu Ser Gly
      1               5                   10                  15

ggc ctg gcc ctg acc gag acc tgg gcc tgc tcc cac tcc atg agg tat        158
Gly Leu Ala Leu Thr Glu Thr Trp Ala Cys Ser His Ser Met Arg Tyr
                20                  25                  30

ttc gac acc gcc gtg tcc cgg ccc ggc cgc gga gag ccc cgc ttc atc        206
Phe Asp Thr Ala Val Ser Arg Pro Gly Arg Gly Glu Pro Arg Phe Ile
            35                  40                  45

tca gtg ggc tac gtg gac gac acg cag ttc gtg cgg ttc gac agc gac        254
Ser Val Gly Tyr Val Asp Asp Thr Gln Phe Val Arg Phe Asp Ser Asp
        50                  55                  60

gcc gcg agt ccg aga ggg gag ccg cgg gcg ccg tgg gtg gag cag gag        302
Ala Ala Ser Pro Arg Gly Glu Pro Arg Ala Pro Trp Val Glu Gln Glu
    65                  70                  75

ggg ccg gag tat tgg gac cgg gag aca cag aag tac aag cgc cag gca        350
Gly Pro Glu Tyr Trp Asp Arg Glu Thr Gln Lys Tyr Lys Arg Gln Ala
80                  85                  90                  95

cag gct gac cga gtg agc ctg cgg aac ctg cgc ggc tac tac aac cag        398
Gln Ala Asp Arg Val Ser Leu Arg Asn Leu Arg Gly Tyr Tyr Asn Gln
                100                 105                 110

agc gag gac ggg tct cac acc ctc cag agg atg tct ggc tgc gac ctg        446
Ser Glu Asp Gly Ser His Thr Leu Gln Arg Met Ser Gly Cys Asp Leu
            115                 120                 125

ggg ccc gac ggg cgc ctc ctc cgc ggg tat gac cag tcc gcc tac gac        494
Gly Pro Asp Gly Arg Leu Leu Arg Gly Tyr Asp Gln Ser Ala Tyr Asp
        130                 135                 140
```

```
ggc aag gat tac atc gcc ctg aac gag gac ctg cgc tcc tgg acc gcc        542
Gly Lys Asp Tyr Ile Ala Leu Asn Glu Asp Leu Arg Ser Trp Thr Ala
    145                 150                 155

gcg gac acc gcg gct cag atc acc cag cgc aag ttg gag gcg gcc cgt        590
Ala Asp Thr Ala Ala Gln Ile Thr Gln Arg Lys Leu Glu Ala Ala Arg
160                 165                 170                 175

gcg gcg gag cag ctg aga gcc tac ctg gag ggc acg tgc gtg gag tgg        638
Ala Ala Glu Gln Leu Arg Ala Tyr Leu Glu Gly Thr Cys Val Glu Trp
                180                 185                 190

ctc cgc aga tac ctg gag aac ggg aag gag acg ctg cag cgc gca gaa        686
Leu Arg Arg Tyr Leu Glu Asn Gly Lys Glu Thr Leu Gln Arg Ala Glu
            195                 200                 205

ccc cca aag aca cac gtg acc cac cac ccc ctc tct gac cat gag gcc        734
Pro Pro Lys Thr His Val Thr His His Pro Leu Ser Asp His Glu Ala
        210                 215                 220

acc ctg agg tgc tgg gcc ctg ggc ttc tac cct gcg gag atc aca ctg        782
Thr Leu Arg Cys Trp Ala Leu Gly Phe Tyr Pro Ala Glu Ile Thr Leu
    225                 230                 235

acc tgg cag cgg gat ggg gag gac cag acc cag gac acc gag ctt gtg        830
Thr Trp Gln Arg Asp Gly Glu Asp Gln Thr Gln Asp Thr Glu Leu Val
240                 245                 250                 255

gag acc agg cca gca gga gat gga acc ttc cag aag tgg gca gct gtg        878
Glu Thr Arg Pro Ala Gly Asp Gly Thr Phe Gln Lys Trp Ala Ala Val
                260                 265                 270

gtg gtg cct tct gga caa gag cag aga tac acg tgc cat atg cag cac        926
Val Val Pro Ser Gly Gln Glu Gln Arg Tyr Thr Cys His Met Gln His
            275                 280                 285

gag ggg ctg caa gag ccc ctc acc ctg agc tgg gag cca tct tcc cag        974
Glu Gly Leu Gln Glu Pro Leu Thr Leu Ser Trp Glu Pro Ser Ser Gln
        290                 295                 300

ccc acc atc ccc atc atg ggc atc gtt gct ggc ctg gct gtc ctg gtt       1022
Pro Thr Ile Pro Ile Met Gly Ile Val Ala Gly Leu Ala Val Leu Val
    305                 310                 315

gtc cta gct gtc ctt gga gct gtg gtc acc gct atg atg tgt agg agg       1070
Val Leu Ala Val Leu Gly Ala Val Val Thr Ala Met Met Cys Arg Arg
320                 325                 330                 335

aag agc tca ggt gga aaa gga ggg agc tgc tct cag gct gcg tgc agc       1118
Lys Ser Ser Gly Gly Lys Gly Gly Ser Cys Ser Gln Ala Ala Cys Ser
                340                 345                 350

aac agt gcc cag ggc tct gat gag tct ctc atc act tgt aaa gcc tga       1166
Asn Ser Ala Gln Gly Ser Asp Glu Ser Leu Ile Thr Cys Lys Ala
            355                 360                 365

gacagctgcc tgtgtgggac tgagatgcag gatttcttca cacctctcct ttgtgacttc     1226

aagagcctct ggcatctctt tctgcaaagg cacctgaatg tgtctgcgtt cctgttagca     1286

taatgtgagg aggtggagag acagcccacc cccgtgtcca ccgtgacccc tgtccccaca     1346

ctgacctgtg ttccctcccc gatcatcttt cctgttccag agaggtgggg ctggatgtct     1406

ccatctctgt ctcaaattca tggtgcactg agctgcaact tcttacttcc ctaatgaagt     1466

taagaacctg aatataaatt tgtgttctca aatatttgct atgaagcgtt gatggattaa     1526
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ttaaataagt caattcctag aagttgagag agcaaataaa gacctgagaa ccttccagaa 1586

<210> 8
<211> 366
<212> PRT
<213> Homo sapiens

<400> 8

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

Leu Ala Leu Thr Glu Thr Trp Ala Cys Ser His Ser Met Arg Tyr Phe
20 25 30

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

Val Gly Tyr Val Asp Asp Thr Gln Phe Val Arg Phe Asp Ser Asp Ala
50 55 60

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

Pro Glu Tyr Trp Asp Arg Glu Thr Gln Lys Tyr Lys Arg Gln Ala Gln
85 90 95

Ala Asp Arg Val Ser Leu Arg Asn Leu Arg Gly Tyr Tyr Asn Gln Ser
100 105 110

Glu Asp Gly Ser His Thr Leu Gln Arg Met Ser Gly Cys Asp Leu Gly
115 120 125

Pro Asp Gly Arg Leu Leu Arg Gly Tyr Asp Gln Ser Ala Tyr Asp Gly
130 135 140

Lys Asp Tyr Ile Ala Leu Asn Glu Asp Leu Arg Ser Trp Thr Ala Ala
145 150 155 160

Asp Thr Ala Ala Gln Ile Thr Gln Arg Lys Leu Glu Ala Ala Arg Ala
165 170 175

Ala Glu Gln Leu Arg Ala Tyr Leu Glu Gly Thr Cys Val Glu Trp Leu
180 185 190

Arg Arg Tyr Leu Glu Asn Gly Lys Glu Thr Leu Gln Arg Ala Glu Pro
195 200 205

Pro Lys Thr His Val Thr His His Pro Leu Ser Asp His Glu Ala Thr
210 215 220

Leu Arg Cys Trp Ala Leu Gly Phe Tyr Pro Ala Glu Ile Thr Leu Thr
225 230 235 240

```
Trp Gln Arg Asp Gly Glu Asp Gln Thr Gln Asp Thr Glu Leu Val Glu
                245                 250                 255

Thr Arg Pro Ala Gly Asp Gly Thr Phe Gln Lys Trp Ala Ala Val Val
            260                 265                 270

Val Pro Ser Gly Gln Glu Gln Arg Tyr Thr Cys His Met Gln His Glu
        275                 280                 285

Gly Leu Gln Glu Pro Leu Thr Leu Ser Trp Glu Pro Ser Ser Gln Pro
    290                 295                 300

Thr Ile Pro Ile Met Gly Ile Val Ala Gly Leu Ala Val Leu Val Val
305                 310                 315                 320

Leu Ala Val Leu Gly Ala Val Val Thr Ala Met Met Cys Arg Arg Lys
                325                 330                 335

Ser Ser Gly Gly Lys Gly Gly Ser Cys Ser Gln Ala Ala Cys Ser Asn
            340                 345                 350

Ser Ala Gln Gly Ser Asp Glu Ser Leu Ile Thr Cys Lys Ala
        355                 360                 365


<210>  9
<211>  2679
<212>  DNA
<213>  Homo sapiens


<220>
<221>  CDS
<222>  (127)..(1203)

<400>  9
gcagactcag ttctcattcc caatgggtgt cgggtttcta gagaagccaa tcagcgtcgc       60

cacgactccc gactataaag tccccatccg gactcaagaa gttctcagga ctcagaggct      120

gggatc atg gta gat gga acc ctc ctt tta ctc ctc tcg gag gcc ctg         168
       Met Val Asp Gly Thr Leu Leu Leu Leu Leu Ser Glu Ala Leu
       1               5                   10

gcc ctt acc cag acc tgg gcg ggc tcc cac tcc ttg aag tat ttc cac        216
Ala Leu Thr Gln Thr Trp Ala Gly Ser His Ser Leu Lys Tyr Phe His
15                  20                  25                  30

act tcc gtg tcc cgg ccc ggc cgc ggg gag ccc cgc ttc atc tct gtg        264
Thr Ser Val Ser Arg Pro Gly Arg Gly Glu Pro Arg Phe Ile Ser Val
                35                  40                  45

ggc tac gtg gac gac acc cag ttc gtg cgc ttc gac aac gac gcc gcg        312
Gly Tyr Val Asp Asp Thr Gln Phe Val Arg Phe Asp Asn Asp Ala Ala
            50                  55                  60

agt ccg agg atg gtg ccg cgg gcg ccg tgg atg gag cag gag ggg tca        360
Ser Pro Arg Met Val Pro Arg Ala Pro Trp Met Glu Gln Glu Gly Ser
        65                  70                  75
```

```
gag tat tgg gac cgg gag aca cgg agc gcc agg gac acc gca cag att        408
Glu Tyr Trp Asp Arg Glu Thr Arg Ser Ala Arg Asp Thr Ala Gln Ile
    80                  85                  90

ttc cga gtg aat ctg cgg acg ctg cgc ggc tac tac aat cag agc gag        456
Phe Arg Val Asn Leu Arg Thr Leu Arg Gly Tyr Tyr Asn Gln Ser Glu
95                  100                 105                 110

gcc ggg tct cac acc ctg cag tgg atg cat ggc tgc gag ctg ggg ccc        504
Ala Gly Ser His Thr Leu Gln Trp Met His Gly Cys Glu Leu Gly Pro
                115                 120                 125

gac ggg cgc ttc ctc cgc ggg tat gaa cag ttc gcc tac gac ggc aag        552
Asp Gly Arg Phe Leu Arg Gly Tyr Glu Gln Phe Ala Tyr Asp Gly Lys
            130                 135                 140

gat tat ctc acc ctg aat gag gac ctg cgc tcc tgg acc gcg gtg gac        600
Asp Tyr Leu Thr Leu Asn Glu Asp Leu Arg Ser Trp Thr Ala Val Asp
        145                 150                 155

acg gcg gct cag atc tcc gag caa aag tca aat gat gcc tct gag gcg        648
Thr Ala Ala Gln Ile Ser Glu Gln Lys Ser Asn Asp Ala Ser Glu Ala
    160                 165                 170

gag cac cag aga gcc tac ctg gaa gac aca tgc gtg gag tgg ctc cac        696
Glu His Gln Arg Ala Tyr Leu Glu Asp Thr Cys Val Glu Trp Leu His
175                 180                 185                 190

aaa tac ctg gag aag ggg aag gag acg ctg ctt cac ctg gag ccc cca        744
Lys Tyr Leu Glu Lys Gly Lys Glu Thr Leu Leu His Leu Glu Pro Pro
                195                 200                 205

aag aca cac gtg act cac cac ccc atc tct gac cat gag gcc acc ctg        792
Lys Thr His Val Thr His His Pro Ile Ser Asp His Glu Ala Thr Leu
            210                 215                 220

agg tgc tgg gcc ctg ggc ttc tac cct gcg gag atc aca ctg acc tgg        840
Arg Cys Trp Ala Leu Gly Phe Tyr Pro Ala Glu Ile Thr Leu Thr Trp
        225                 230                 235

cag cag gat ggg gag ggc cat acc cag gac acg gag ctc gtg gag acc        888
Gln Gln Asp Gly Glu Gly His Thr Gln Asp Thr Glu Leu Val Glu Thr
    240                 245                 250

agg cct gca ggg gat gga acc ttc cag aag tgg gca gct gtg gtg gtg        936
Arg Pro Ala Gly Asp Gly Thr Phe Gln Lys Trp Ala Ala Val Val Val
255                 260                 265                 270

cct tct gga gag gag cag aga tac acg tgc cat gtg cag cat gag ggg        984
Pro Ser Gly Glu Glu Gln Arg Tyr Thr Cys His Val Gln His Glu Gly
                275                 280                 285

cta ccc gag ccc gtc acc ctg aga tgg aag ccg gct tcc cag ccc acc       1032
Leu Pro Glu Pro Val Thr Leu Arg Trp Lys Pro Ala Ser Gln Pro Thr
            290                 295                 300

atc ccc atc gtg ggc atc att gct ggc ctg gtt ctc ctt gga tct gtg       1080
Ile Pro Ile Val Gly Ile Ile Ala Gly Leu Val Leu Leu Gly Ser Val
        305                 310                 315

gtc tct gga gct gtg gtt gct gct gtg ata tgg agg aag aag agc tca       1128
Val Ser Gly Ala Val Val Ala Ala Val Ile Trp Arg Lys Lys Ser Ser
    320                 325                 330

ggt gga aaa gga ggg agc tac tct aag gct gag tgg agc gac agt gcc       1176
Gly Gly Lys Gly Gly Ser Tyr Ser Lys Ala Glu Trp Ser Asp Ser Ala
335                 340                 345                 350
```

cag ggg tct gag tct cac agc ttg taa agcctgagac agctgccttg 1223
Gln Gly Ser Glu Ser His Ser Leu
355

tgtgcgactg agatgcacag ctgccttgtg tgcgactgag atgcaggatt tcctcacgcc 1283

tcccctatgt gtcttagggg actctggctt ctctttttgc aagggcctct gaatctgtct 1343

gtgtccctgt tagcacaatg tgaggaggta gagaaacagt ccacctctgt gtctaccatg 1403

acccccttcc tcacactgac ctgtgttcct tccctgttct cttttctatt aaaaataaga 1463

acctgggcag agtgcggcag ctcatgcctg taatcccagc acttagggag gccgaggagg 1523

gcagatcacg aggtcaggag atcgaaacca tcctggctaa cacggtgaaa ccccgtctct 1583

actaaaaaat acaaaaaatt agctgggcgc agaggcacgg gcctgtagtc ccagctactc 1643

aggaggcgga ggcaggagaa tggcgtcaac ccgggaggcg gaggttgcag tgagccagga 1703

ttgtgcgact gcactccagc ctgggtgaca gggtgaaacg ccatctcaaa aaataaaaat 1763

tgaaaaataa aaaaagaacc tggatctcaa tttaattttt catattcttg caatgaaatg 1823

gacttgagga agctaagatc atagctagaa atacagataa ttccacagca catctctagc 1883

aaatttagcc tattcctatt ctctagccta ttccttacca cctgtaatct tgaccatata 1943

ccttggagtt gaatattgtt ttcatactgc tgtggtttga atgttccctc caacactcat 2003

gttgagactt aatccctaat gtggcaatac tgaaaggtgg ggcctttgag atgtgattgg 2063

atcgtaaggc tgtgccttca ttcatgggtt aatggattaa tgggttatca caggaatggg 2123

actggtggct ttataagaag aggaaaagag aactgagcta gcatgcccag cccacagaga 2183

gcctccacta gagtgatgct aagtggaaat gtgaggtgca gctgccacag agggccccca 2243

ccagggaaat gtctagtgtc tagtggatcc aggccacagg agagagtgcc ttgtggagcg 2303

ctgggagcag gacctgacca ccaccaggac cccagaactg tggagtcagt ggcagcatgc 2363

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ccttttctct cccatgaccc tttaacagca tctgcttcat tcccctcacc ttcccaggct 2603

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<211> 358
<212> PRT
<213> Homo sapiens

<400> 10

Met Val Asp Gly Thr Leu Leu Leu Leu Ser Glu Ala Leu Ala Leu
1 5 10 15

Thr Gln Thr Trp Ala Gly Ser His Ser Leu Lys Tyr Phe His Thr Ser

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Val Ser Arg Pro Gly Arg Gly Glu Pro Arg Phe Ile Ser Val Gly Tyr
        35                  40                  45

Val Asp Asp Thr Gln Phe Val Arg Phe Asp Asn Asp Ala Ala Ser Pro
    50                  55                  60

Arg Met Val Pro Arg Ala Pro Trp Met Glu Gln Glu Gly Ser Glu Tyr
65                  70                  75                  80

Trp Asp Arg Glu Thr Arg Ser Ala Arg Asp Thr Ala Gln Ile Phe Arg
                85                  90                  95

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

Ser His Thr Leu Gln Trp Met His Gly Cys Glu Leu Gly Pro Asp Gly
        115                 120                 125

Arg Phe Leu Arg Gly Tyr Glu Gln Phe Ala Tyr Asp Gly Lys Asp Tyr
    130                 135                 140

Leu Thr Leu Asn Glu Asp Leu Arg Ser Trp Thr Ala Val Asp Thr Ala
145                 150                 155                 160

Ala Gln Ile Ser Glu Gln Lys Ser Asn Asp Ala Ser Glu Ala Glu His
                165                 170                 175

Gln Arg Ala Tyr Leu Glu Asp Thr Cys Val Glu Trp Leu His Lys Tyr
            180                 185                 190

Leu Glu Lys Gly Lys Glu Thr Leu Leu His Leu Glu Pro Pro Lys Thr
        195                 200                 205

His Val Thr His His Pro Ile Ser Asp His Glu Ala Thr Leu Arg Cys
    210                 215                 220

Trp Ala Leu Gly Phe Tyr Pro Ala Glu Ile Thr Leu Thr Trp Gln Gln
225                 230                 235                 240

Asp Gly Glu Gly His Thr Gln Asp Thr Glu Leu Val Glu Thr Arg Pro
                245                 250                 255

Ala Gly Asp Gly Thr Phe Gln Lys Trp Ala Ala Val Val Val Pro Ser
            260                 265                 270

Gly Glu Glu Gln Arg Tyr Thr Cys His Val Gln His Glu Gly Leu Pro
        275                 280                 285

Glu Pro Val Thr Leu Arg Trp Lys Pro Ala Ser Gln Pro Thr Ile Pro
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290                 295                 300

Ile Val Gly Ile Ile Ala Gly Leu Val Leu Leu Gly Ser Val Val Ser
305                 310                 315                 320

Gly Ala Val Val Ala Ala Val Ile Trp Arg Lys Lys Ser Ser Gly Gly
                325                 330                 335

Lys Gly Gly Ser Tyr Ser Lys Ala Glu Trp Ser Asp Ser Ala Gln Gly
            340                 345                 350

Ser Glu Ser His Ser Leu
        355
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<210> 11
<211> 1301
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (125)..(1165)

<400> 11

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caggttctaa agtcccacgc accccgcggg actcatattt ttcccagacg cggaggttgg      120

ggtc atg gcg ccc cga agc ctc ctc ctg ctg ctc tca ggg gcc ctg gcc       169
     Met Ala Pro Arg Ser Leu Leu Leu Leu Leu Ser Gly Ala Leu Ala
     1               5                   10                  15

ctg acc gat act tgg gcg ggc tcc cac tcc ttg agg tat ttc agc acc        217
Leu Thr Asp Thr Trp Ala Gly Ser His Ser Leu Arg Tyr Phe Ser Thr
                20                  25                  30

gct gtg tcg cgg ccc ggc cgc ggg gag ccc cgc tac atc gcc gtg gag        265
Ala Val Ser Arg Pro Gly Arg Gly Glu Pro Arg Tyr Ile Ala Val Glu
            35                  40                  45

tac gta gac gac acg caa ttc ctg cgg ttc gac agc gac gcc gcg att        313
Tyr Val Asp Asp Thr Gln Phe Leu Arg Phe Asp Ser Asp Ala Ala Ile
        50                  55                  60

ccg agg atg gag ccg cgg gag ccg tgg gtg gag caa gag ggg ccg cag        361
Pro Arg Met Glu Pro Arg Glu Pro Trp Val Glu Gln Glu Gly Pro Gln
    65                  70                  75

tat tgg gag tgg acc aca ggg tac gcc aag gcc aac gca cag act gac        409
Tyr Trp Glu Trp Thr Thr Gly Tyr Ala Lys Ala Asn Ala Gln Thr Asp
80                  85                  90                  95

cga gtg gcc ctg agg aac ctg ctc cgc cgc tac aac cag agc gag gct        457
Arg Val Ala Leu Arg Asn Leu Leu Arg Arg Tyr Asn Gln Ser Glu Ala
                100                 105                 110

ggg tct cac acc ctc cag gga atg aat ggc tgc gac atg ggg ccc gac        505
Gly Ser His Thr Leu Gln Gly Met Asn Gly Cys Asp Met Gly Pro Asp
            115                 120                 125

gga cgc ctc ctc cgc ggg tat cac cag cac gcg tac gac ggc aag gat        553
Gly Arg Leu Leu Arg Gly Tyr His Gln His Ala Tyr Asp Gly Lys Asp
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        130                 135                 140

tac atc tcc ctg aac gag gac ctg cgc tcc tgg acc gcg gcg gac acc        601
Tyr Ile Ser Leu Asn Glu Asp Leu Arg Ser Trp Thr Ala Ala Asp Thr
    145                 150                 155

gtg gct cag atc acc cag cgc ttc tat gag gca gag gaa tat gca gag        649
Val Ala Gln Ile Thr Gln Arg Phe Tyr Glu Ala Glu Glu Tyr Ala Glu
160                 165                 170                 175

gag ttc agg acc tac ctg gag ggc gag tgc ctg gag ttg ctc cgc aga        697
Glu Phe Arg Thr Tyr Leu Glu Gly Glu Cys Leu Glu Leu Leu Arg Arg
                180                 185                 190

tac ttg gag aat ggg aag gag acg cta cag cgc gca gat cct cca aag        745
Tyr Leu Glu Asn Gly Lys Glu Thr Leu Gln Arg Ala Asp Pro Pro Lys
            195                 200                 205

gca cac gtt gcc cac cac ccc atc tct gac cat gag gcc acc ctg agg        793
Ala His Val Ala His His Pro Ile Ser Asp His Glu Ala Thr Leu Arg
        210                 215                 220

tgc tgg gcc ctg ggc ttc tac cct gcg gag atc acg ctg acc tgg cag        841
Cys Trp Ala Leu Gly Phe Tyr Pro Ala Glu Ile Thr Leu Thr Trp Gln
    225                 230                 235

cgg gat ggg gag gaa cag acc cag gac aca gag ctt gtg gag acc agg        889
Arg Asp Gly Glu Glu Gln Thr Gln Asp Thr Glu Leu Val Glu Thr Arg
240                 245                 250                 255

cct gca ggg gat gga acc ttc cag aag tgg gcc gct gtg gtg gtg cct        937
Pro Ala Gly Asp Gly Thr Phe Gln Lys Trp Ala Ala Val Val Val Pro
                260                 265                 270

cct gga gag gaa cag aga tac aca tgc cat gtg cag cac gag ggg ctg        985
Pro Gly Glu Glu Gln Arg Tyr Thr Cys His Val Gln His Glu Gly Leu
            275                 280                 285

ccc cag ccc ctc atc ctg aga tgg gag cag tct ccc cag ccc acc atc       1033
Pro Gln Pro Leu Ile Leu Arg Trp Glu Gln Ser Pro Gln Pro Thr Ile
        290                 295                 300

ccc atc gtg ggc atc gtt gct ggc ctt gtt gtc ctt gga gct gtg gtc       1081
Pro Ile Val Gly Ile Val Ala Gly Leu Val Val Leu Gly Ala Val Val
    305                 310                 315

act gga gct gtg gtc gct gct gtg atg tgg agg aag aag agc tca gat       1129
Thr Gly Ala Val Val Ala Ala Val Met Trp Arg Lys Lys Ser Ser Asp
320                 325                 330                 335

aga aac aga ggg agc tac tct cag gct gca gtg tga gacagcttcc           1175
Arg Asn Arg Gly Ser Tyr Ser Gln Ala Ala Val
                340                 345

ttgtgtggga ctgagaagca agatatcaat gtagcagaat tgcacttgtg cctcacgaac     1235

atacataaat tttaaaaata aagaataaaa atatatcttt ttatagataa aaaaaaaaaa     1295

aaaaaa                                                               1301


<210>  12
<211>  346
<212>  PRT
<213>  Homo sapiens

<400>  12
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Met Ala Pro Arg Ser Leu Leu Leu Leu Ser Gly Ala Leu Ala Leu
1               5                  10                  15

Thr Asp Thr Trp Ala Gly Ser His Ser Leu Arg Tyr Phe Ser Thr Ala
            20                  25                  30

Val Ser Arg Pro Gly Arg Gly Glu Pro Arg Tyr Ile Ala Val Glu Tyr
        35                  40                  45

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

Arg Met Glu Pro Arg Glu Pro Trp Val Glu Gln Glu Gly Pro Gln Tyr
65                  70                  75                  80

Trp Glu Trp Thr Thr Gly Tyr Ala Lys Ala Asn Ala Gln Thr Asp Arg
                85                  90                  95

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

Ser His Thr Leu Gln Gly Met Asn Gly Cys Asp Met Gly Pro Asp Gly
        115                 120                 125

Arg Leu Leu Arg Gly Tyr His Gln His Ala Tyr Asp Gly Lys Asp Tyr
    130                 135                 140

Ile Ser Leu Asn Glu Asp Leu Arg Ser Trp Thr Ala Ala Asp Thr Val
145                 150                 155                 160

Ala Gln Ile Thr Gln Arg Phe Tyr Glu Ala Glu Glu Tyr Ala Glu Glu
                165                 170                 175

Phe Arg Thr Tyr Leu Glu Gly Glu Cys Leu Glu Leu Leu Arg Arg Tyr
            180                 185                 190

Leu Glu Asn Gly Lys Glu Thr Leu Gln Arg Ala Asp Pro Pro Lys Ala
        195                 200                 205

His Val Ala His His Pro Ile Ser Asp His Glu Ala Thr Leu Arg Cys
    210                 215                 220

Trp Ala Leu Gly Phe Tyr Pro Ala Glu Ile Thr Leu Thr Trp Gln Arg
225                 230                 235                 240

Asp Gly Glu Glu Gln Thr Gln Asp Thr Glu Leu Val Glu Thr Arg Pro
                245                 250                 255

Ala Gly Asp Gly Thr Phe Gln Lys Trp Ala Ala Val Val Val Pro Pro
            260                 265                 270
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Gly Glu Glu Gln Arg Tyr Thr Cys His Val Gln His Glu Gly Leu Pro
        275                 280                 285

Gln Pro Leu Ile Leu Arg Trp Glu Gln Ser Pro Gln Pro Thr Ile Pro
    290                 295                 300

Ile Val Gly Ile Val Ala Gly Leu Val Val Leu Gly Ala Val Val Thr
305                 310                 315                 320

Gly Ala Val Val Ala Ala Val Met Trp Arg Lys Lys Ser Ser Asp Arg
                325                 330                 335

Asn Arg Gly Ser Tyr Ser Gln Ala Ala Val
            340                 345


<210>  13
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<212>  DNA
<213>  Homo sapiens


<220>
<221>  CDS
<222>  (179)..(1195)

<400>  13
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atgaagttct cactcccatt aggtgacagg tttttagaga agccaatcag cgtcgccgcg      120

gtcctggttc taaagtcctc gctcacccac ccggactcat tctccccaga cgccaagg        178

atg gtg gtc atg gcg ccc cga acc ctc ttc ctg ctc tcg ggg gcc        226
Met Val Val Met Ala Pro Arg Thr Leu Phe Leu Leu Ser Gly Ala
1               5                   10                  15

ctg acc ctg acc gag acc tgg gcg ggc tcc cac tcc atg agg tat ttc        274
Leu Thr Leu Thr Glu Thr Trp Ala Gly Ser His Ser Met Arg Tyr Phe
            20                  25                  30

agc gcc gcc gtg tcc cgg ccc ggc cgc ggg gag ccc cgc ttc atc gcc        322
Ser Ala Ala Val Ser Arg Pro Gly Arg Gly Glu Pro Arg Phe Ile Ala
        35                  40                  45

atg ggc tac gtg gac gac acg cag ttc gtg cgg ttc gac agc gac tcg        370
Met Gly Tyr Val Asp Asp Thr Gln Phe Val Arg Phe Asp Ser Asp Ser
    50                  55                  60

gcg tgt ccg agg atg gag ccg cgg gcg ccg tgg gtg gag cag gag ggg        418
Ala Cys Pro Arg Met Glu Pro Arg Ala Pro Trp Val Glu Gln Glu Gly
65                  70                  75                  80

ccg gag tat tgg gaa gag gag aca cgg aac acc aag gcc cac gca cag        466
Pro Glu Tyr Trp Glu Glu Glu Thr Arg Asn Thr Lys Ala His Ala Gln
                85                  90                  95

act gac aga atg aac ctg cag acc ctg cgc ggc tac tac aac cag agc        514
Thr Asp Arg Met Asn Leu Gln Thr Leu Arg Gly Tyr Tyr Asn Gln Ser
            100                 105                 110

gag gcc agt tct cac acc ctc cag tgg atg att ggc tgc gac ctg ggg        562
Glu Ala Ser Ser His Thr Leu Gln Trp Met Ile Gly Cys Asp Leu Gly
        115                 120                 125
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tcc gac gga cgc ctc ctc cgc ggg tat gaa cag tat gcc tac gat ggc        610
Ser Asp Gly Arg Leu Leu Arg Gly Tyr Glu Gln Tyr Ala Tyr Asp Gly
    130                 135                 140

aag gat tac ctc gcc ctg aac gag gac ctg cgc tcc tgg acc gca gcg        658
Lys Asp Tyr Leu Ala Leu Asn Glu Asp Leu Arg Ser Trp Thr Ala Ala
145                 150                 155                 160

gac act gcg gct cag atc tcc aag cgc aag tgt gag gcg gcc aat gtg        706
Asp Thr Ala Ala Gln Ile Ser Lys Arg Lys Cys Glu Ala Ala Asn Val
                165                 170                 175

gct gaa caa agg aga gcc tac ctg gag ggc acg tgc gtg gag tgg ctc        754
Ala Glu Gln Arg Arg Ala Tyr Leu Glu Gly Thr Cys Val Glu Trp Leu
            180                 185                 190

cac aga tac ctg gag aac ggg aag gag atg ctg cag cgc gcg gac ccc        802
His Arg Tyr Leu Glu Asn Gly Lys Glu Met Leu Gln Arg Ala Asp Pro
        195                 200                 205

ccc aag aca cac gtg acc cac cac cct gtc ttt gac tat gag gcc acc        850
Pro Lys Thr His Val Thr His His Pro Val Phe Asp Tyr Glu Ala Thr
    210                 215                 220

ctg agg tgc tgg gcc ctg ggc ttc tac cct gcg gag atc ata ctg acc        898
Leu Arg Cys Trp Ala Leu Gly Phe Tyr Pro Ala Glu Ile Ile Leu Thr
225                 230                 235                 240

tgg cag cgg gat ggg gag gac cag acc cag gac gtg gag ctc gtg gag        946
Trp Gln Arg Asp Gly Glu Asp Gln Thr Gln Asp Val Glu Leu Val Glu
                245                 250                 255

acc agg cct gca ggg gat gga acc ttc cag aag tgg gca gct gtg gtg        994
Thr Arg Pro Ala Gly Asp Gly Thr Phe Gln Lys Trp Ala Ala Val Val
            260                 265                 270

gtg cct tct gga gag gag cag aga tac acg tgc cat gtg cag cat gag       1042
Val Pro Ser Gly Glu Glu Gln Arg Tyr Thr Cys His Val Gln His Glu
        275                 280                 285

ggg ctg ccg gag ccc ctc atg ctg aga tgg aag cag tct tcc ctg ccc       1090
Gly Leu Pro Glu Pro Leu Met Leu Arg Trp Lys Gln Ser Ser Leu Pro
    290                 295                 300

acc atc ccc atc atg ggt atc gtt gct ggc ctg gtt gtc ctt gca gct       1138
Thr Ile Pro Ile Met Gly Ile Val Ala Gly Leu Val Val Leu Ala Ala
305                 310                 315                 320

gta gtc act gga gct gcg gtc gct gct gtg ctg tgg aga aag aag agc       1186
Val Val Thr Gly Ala Ala Val Ala Ala Val Leu Trp Arg Lys Lys Ser
                325                 330                 335

tca gat tga aaaggaggga gctactctca ggctgcaatg tgaaacagct               1235
Ser Asp

gccctgtgtg ggactgagtg gcaagtccct ttgtgacttc aagaaccctg actcctcttt     1295

gtgcagagac cagcccaccc ctgtgcccac catgaccctc ttcctcatgc tgaactgcat     1355

tccttcccca atcacctttc ctgttccaga aaaggggctg ggatgtctcc gtctctgtct     1415

caaatttgtg gtccactgag ctataactta cttctgtatt aaaattagaa tctgagtata     1475

aatttacttt ttcaaattat ttccaagaga gattgatggg ttaattaaag gagaagattc     1535

ctgaaatttg agagacaaaa taaatggaag acatgagaac ttt                       1578
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<210> 14
<211> 338
<212> PRT
<213> Homo sapiens

<400> 14

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


Leu Thr Leu Thr Glu Thr Trp Ala Gly Ser His Ser Met Arg Tyr Phe
            20                  25                  30


Ser Ala Ala Val Ser Arg Pro Gly Arg Gly Glu Pro Arg Phe Ile Ala
        35                  40                  45


Met Gly Tyr Val Asp Asp Thr Gln Phe Val Arg Phe Asp Ser Asp Ser
    50                  55                  60


Ala Cys Pro Arg Met Glu Pro Arg Ala Pro Trp Val Glu Gln Glu Gly
65                  70                  75                  80


Pro Glu Tyr Trp Glu Glu Glu Thr Arg Asn Thr Lys Ala His Ala Gln
                85                  90                  95


Thr Asp Arg Met Asn Leu Gln Thr Leu Arg Gly Tyr Tyr Asn Gln Ser
            100                 105                 110


Glu Ala Ser Ser His Thr Leu Gln Trp Met Ile Gly Cys Asp Leu Gly
        115                 120                 125


Ser Asp Gly Arg Leu Leu Arg Gly Tyr Glu Gln Tyr Ala Tyr Asp Gly
    130                 135                 140


Lys Asp Tyr Leu Ala Leu Asn Glu Asp Leu Arg Ser Trp Thr Ala Ala
145                 150                 155                 160


Asp Thr Ala Ala Gln Ile Ser Lys Arg Lys Cys Glu Ala Ala Asn Val
                165                 170                 175


Ala Glu Gln Arg Arg Ala Tyr Leu Glu Gly Thr Cys Val Glu Trp Leu
            180                 185                 190


His Arg Tyr Leu Glu Asn Gly Lys Glu Met Leu Gln Arg Ala Asp Pro
        195                 200                 205


Pro Lys Thr His Val Thr His His Pro Val Phe Asp Tyr Glu Ala Thr
    210                 215                 220


Leu Arg Cys Trp Ala Leu Gly Phe Tyr Pro Ala Glu Ile Ile Leu Thr
225                 230                 235                 240
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Trp Gln Arg Asp Gly Glu Asp Gln Thr Gln Asp Val Glu Leu Val Glu
245 250 255

Thr Arg Pro Ala Gly Asp Gly Thr Phe Gln Lys Trp Ala Ala Val Val
260 265 270

Val Pro Ser Gly Glu Glu Gln Arg Tyr Thr Cys His Val Gln His Glu
275 280 285

Gly Leu Pro Glu Pro Leu Met Leu Arg Trp Lys Gln Ser Ser Leu Pro
290 295 300

Thr Ile Pro Ile Met Gly Ile Val Ala Gly Leu Val Val Leu Ala Ala
305 310 315 320

Val Val Thr Gly Ala Ala Val Ala Ala Val Leu Trp Arg Lys Lys Ser
325 330 335

Ser Asp

<210> 15
<211> 9232
<212> DNA
<213> Artificial Sequence

<220>
<223> Vector sequence for human B2M-HLA-A0201 fusion protein

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tcaattacgg ggtcattagt tcatagccca tatatggagt tccgcgttac ataacttacg 180

gtaaatggcc cgcctggctg accgcccaac gacccccgcc cattgacgtc aataatgacg 240

tatgttccca tagtaacgcc aatagggact ttccattgac gtcaatgggt ggagtattta 300

cgctaaactg cccacttggc agtacatcaa gtgtatcata tgccaagtac gccccctatt 360

gacgtcaatg acggtaaatg gcccgcctgg cattatgccc agtacatgac cttatgggac 420

tttcctactt ggcagtacat ctacgtatta gtcatcgcta ttaccatggt gatgcggttt 480

tggcagtaca tcaatgggcg tggatagcgg tttgactcac ggggatttcc aagtctccac 540

cccattgacg tcaatgggag tttgttttgg caccaaaatc aacgggactt tccaaaatgt 600

cgtaacaact ccgccccatt gacgcaaatg ggcggtaggc gtgtacggtg ggaggtctat 660

ataagcagag cttctagatt gtacgggagc tcttcactac tcgctgcgtc gagagtgtac 720

gagactctcc aggtttggta agaaatattt tatattgtta taatgttact atgatccatt 780

aacactctgc ttatagattg taagggtgat tgcaatgctt tctgcataaa actttggttt 840

tcttgttaat caataaaccg acttgattcg agaacctact catatattat tgtctctttt 900

atactttatt aagtaaaagg atttgtatat tagccttgct aagggagaca tctagtgata 960

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ttccatgaca attggcgccc aacgtggggc tcgaatataa gtcgggttta tttgtaaatt 1080

atccctaggg acctccgagc aagcgagcat agcgggaggc atataaaagc caatagacaa 1140

tggctagcag gaagtaatgt tgaagaatat gaacttgatg ttgaagctct ggttgtaatt 1200

ttaagagata gaaatatacc aagaaatcct ttacatggag aagttatagg tcttcgcctt 1260

actgaaggat ggtggggaca aattgagaga tttcagatgg tacgttgatc taaggctatg 1320

gatttggcca tgggacaaga aatattagtt tatagtccca ttgtatctat gactaaaata 1380

caaaaaactc cactaccaga aagaaaagct ttacccatta gatggataac atggatgact 1440

tatttagaag atccaagaat ccaatttcat tatgataaaa ccttaccaga acttaagcat 1500

attccagatg tatatacatc tagtcagtct cctgttaaac atccttctca atatgaagga 1560

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ggcatgggaa tagtacatgc cacatacaaa cctgaatatc aagttttgaa tcaatggtca 1680

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aaaaaagctt taaaaatacc tggtcctgta ttagttataa ctgatagttt ctatgtagca 1800

gaaagtgcta ataaagaatt accatactgg aaatctaatg ggtttgttaa taataagaaa 1860

aagcctctta aacatatctc caaatggaaa tctattgctg agtgtttatc tatgaaacca 1920

gacattacta ttcaacatga aaaaggcatc agcctacaaa taccagtatt catactgaaa 1980

ggcaatgccc tagcagataa gcttgccacc caaggaagtt atgtggttaa ttgtaatacc 2040

aaaaaaccaa acctggatgc agagttggat caattattac agggtcatta tataaaagga 2100

tatcccaaac aatatacata ttttttagaa gatggcaaag taaaagtttc cagacctgaa 2160

ggggttaaaa ttattccccc tcagtcagac agacaaaaaa ttgtgcttca agcccacaat 2220

ttggctcaca ccggacgtga agccactctt ttaaaaattg ccaaccttta ttggtggcca 2280

aatatgagaa aggatgtggt taaacaacta ggacgctgtc aacagtgttt aatcacaaat 2340

gcttccaaca aagcctctgg tcctattcta agaccagata ggcctcaaaa acctttttgat 2400

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agcgcaactg ttaaatctct caatgtactc actagtattg caattccaaa ggtgattcac 2580

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aatagtgata taaaacgact tttaactaaa ctgctagtag gaagacccac aaagtggtat 2760

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cttgacttga ccagagaaga agaactttct cttttacagg aaattcgtac ttctttatac 2940

catccatcca cccctccagc ctcctctcgt tcctggtctc ctgttgttgg ccaattggtc 3000

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acaatggatc atttggaaaa aaatgaataa agcgcatgag gcacttcaaa atacaacaac 3240

tgtgactgaa cagcagaagg aacaaattat actggacatt caaaatgaag aagtacaacc 3300

aactaggaga gataaattta gatatctgct ttatacttgt tgtgctacta gctcaagagt 3360

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Glu Tyr Ala Cys Arg Val Asn His Val Thr Leu Ser Gln Pro Lys Ile
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Val Lys Trp Asp Arg Asp Met Gly Gly Gly Gly Ser Gly Gly Gly Gly
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Phe Ile Ser Val Gly Tyr Val Asp Asp Thr Gln Phe Val Arg Phe Asp
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agcggtttcg aataattaac ttatttgttc ccatcacatg tcacttttaa aaaattataa 4200

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aattttgaaa acagttatct tccgccatag ataactacta tggttatctt ctgcctctca 4320

cagatgaaga aactaaggca ccgagatttt aagaaactta attacacagg ggataaatgg 4380

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gccctgatag acggtttttc gccctttgac gttggagtcc acgttcttta atagtggact 4980

cttgttccaa actggaacaa cactcaaccc tatctcgggc tattcttttg atttataagg 5040

gattttgccg atttcggcct attggttaaa aaatgagctg atttaacaaa aatttaacgc 5100

gaattttaac aaaatattaa cgtttacaat tttatggtgc actctcagta caatctgctc 5160

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tccgctcatg agacaataac cctgataaat gcttcaataa tattgaaaaa ggaagagtat 5520

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cctctgactt gagcgtcgat ttttgtgatg ctcgtcaggg gggcggagcc tatggaaaaa 7140

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<211> 29
<212> PRT
<213> Artificial Sequence

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<400> 23

Met Ala Pro Arg Thr Leu Phe Leu Gly Gly Gly Gly Ser Gly Gly Gly
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Gly Ser Gly Gly Gly Gly Ser Ile Gln Arg Thr Pro Lys
20 25

<210> 24
<211> 1369
<212> DNA
<213> Homo sapiens

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<400> 24
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cagtgaggag ggggcgcgac ggccaggagg ctggtggagc gacacccagg caggagaggg 180

ggaagaactc tctccctttc tgaaccccct tttccttgag agacgagttg ggggagtcct 240

ccacgcatta cccactcggg ccgcaaaaac tcccttcttt agccctctgc ccccgccctt 300

gcttataagc ctttgagacc gcagaaggga ccttgttgtg gaacgggacg gccaagagga 360

agccagatcg ctgagggtcc ggtctccagt ttgcctcctg ctatatccat tggaagagaa 420

aagtttgtga cttgggcccc caagttttga gagaactggg ctttcggcgc ggggggacag 480

aggaggctcg tggggagctt tcccc atg gag ctt acc cag cct gca gaa gac 532
Met Glu Leu Thr Gln Pro Ala Glu Asp
1 5

ctc atc cag acc cag cag acc cct gcc tca gaa ctt ggg gac cct gaa 580
Leu Ile Gln Thr Gln Gln Thr Pro Ala Ser Glu Leu Gly Asp Pro Glu
10 15 20 25

gac ccc gga gag gag gct gca gat ggc tca gac act gtg gtc ctc agt 628
Asp Pro Gly Glu Glu Ala Ala Asp Gly Ser Asp Thr Val Val Leu Ser
30 35 40

ctc ttt ccc tgc acc cct gag cct gtg aat cct gaa ccg gat gcc agt 676
Leu Phe Pro Cys Thr Pro Glu Pro Val Asn Pro Glu Pro Asp Ala Ser
45 50 55

gtt tcc tct cca cag ggc agc tcc ctg aag cac tcc acc act ctc acc 724
Val Ser Ser Pro Gln Gly Ser Ser Leu Lys His Ser Thr Thr Leu Thr
60 65 70

aac cgg cag cga ggg aac gag gtg tca gct ctg ccg gcc acc cta gac 772
Asn Arg Gln Arg Gly Asn Glu Val Ser Ala Leu Pro Ala Thr Leu Asp
75 80 85

tgt gac aac ctc gtc aac aag cca gac gag cgc ggc ttc acc ccc ctc 820
Cys Asp Asn Leu Val Asn Lys Pro Asp Glu Arg Gly Phe Thr Pro Leu
90 95 100 105

atc tgg gcc tcc gcc ttt gga gag att gag acc gtt cgc ttc ctg ctg 868
Ile Trp Ala Ser Ala Phe Gly Glu Ile Glu Thr Val Arg Phe Leu Leu
110 115 120

gag tgg ggt gcc gac ccc cac atc ctg gca aaa gag cga gag agc gcc 916
Glu Trp Gly Ala Asp Pro His Ile Leu Ala Lys Glu Arg Glu Ser Ala
125 130 135

ctg tcg ctg gcc agc aca ggc ggc tac aca gac att gtg ggg ctg ctg 964
Leu Ser Leu Ala Ser Thr Gly Gly Tyr Thr Asp Ile Val Gly Leu Leu
140 145 150

ctg gag cgt gac gtg gac atc aac atc tat gat tgg aat gga ggg acg 1012
Leu Glu Arg Asp Val Asp Ile Asn Ile Tyr Asp Trp Asn Gly Gly Thr
155 160 165

cca ctg ctg tac gct gtg cgc ggg aac cac gtg aaa tgc gtt gag gcc 1060

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Pro Leu Leu Tyr Ala Val Arg Gly Asn His Val Lys Cys Val Glu Ala
170                 175                 180                 185

ttg ctg gcc cga ggc gct gac ctc acc acc gaa gcc gac tct ggc tac       1108
Leu Leu Ala Arg Gly Ala Asp Leu Thr Thr Glu Ala Asp Ser Gly Tyr
                190                 195                 200

acc ccg atg gac ctt gcc gtg gcc ctg gga tac cgg aaa gtg caa cag       1156
Thr Pro Met Asp Leu Ala Val Ala Leu Gly Tyr Arg Lys Val Gln Gln
            205                 210                 215

gtg atc gag aac cac atc ctc aag ctc ttc cag agc aac ctg gtg ccc       1204
Val Ile Glu Asn His Ile Leu Lys Leu Phe Gln Ser Asn Leu Val Pro
        220                 225                 230

gct gac cct gag tga aggccgcctg ccggggactc agacactcag ggaacaaaat       1259
Ala Asp Pro Glu
    235

ggtcagccag agctggggaa acccagaact gacttcaaag gcagcttctg gacaggtggt     1319

gggaggggac ccttcccaag aggaaccaat aaaccttctg tgcagaatga               1369


<210>  25
<211>  237
<212>  PRT
<213>  Homo sapiens

<400>  25

Met Glu Leu Thr Gln Pro Ala Glu Asp Leu Ile Gln Thr Gln Gln Thr
1               5                   10                  15


Pro Ala Ser Glu Leu Gly Asp Pro Glu Asp Pro Gly Glu Glu Ala Ala
            20                  25                  30


Asp Gly Ser Asp Thr Val Val Leu Ser Leu Phe Pro Cys Thr Pro Glu
        35                  40                  45


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


Ser Leu Lys His Ser Thr Thr Leu Thr Asn Arg Gln Arg Gly Asn Glu
65                  70                  75                  80


Val Ser Ala Leu Pro Ala Thr Leu Asp Cys Asp Asn Leu Val Asn Lys
                85                  90                  95


Pro Asp Glu Arg Gly Phe Thr Pro Leu Ile Trp Ala Ser Ala Phe Gly
            100                 105                 110


Glu Ile Glu Thr Val Arg Phe Leu Leu Glu Trp Gly Ala Asp Pro His
        115                 120                 125


Ile Leu Ala Lys Glu Arg Glu Ser Ala Leu Ser Leu Ala Ser Thr Gly
    130                 135                 140


Gly Tyr Thr Asp Ile Val Gly Leu Leu Leu Glu Arg Asp Val Asp Ile
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145 150 155 160

Asn Ile Tyr Asp Trp Asn Gly Gly Thr Pro Leu Leu Tyr Ala Val Arg
165 170 175

Gly Asn His Val Lys Cys Val Glu Ala Leu Leu Ala Arg Gly Ala Asp
180 185 190

Leu Thr Thr Glu Ala Asp Ser Gly Tyr Thr Pro Met Asp Leu Ala Val
195 200 205

Ala Leu Gly Tyr Arg Lys Val Gln Gln Val Ile Glu Asn His Ile Leu
210 215 220

Lys Leu Phe Gln Ser Asn Leu Val Pro Ala Asp Pro Glu
225 230 235

<210> 26
<211> 1438
<212> DNA
<213> Homo sapiens

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<222> (506)..(1288)

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cagtgaggag ggggcgcgac ggccaggagg ctggtggagc gacacccagg caggagaggg 180

ggaagaactc tctccctttc tgaaccccct tttccttgag agacgagttg ggggagtcct 240

ccacgcatta cccactcggg ccgcaaaaac tcccttcttt agccctctgc ccccgccctt 300

gcttataagc ctttgagacc gcagaaggga ccttgttgtg gaacgggacg gccaagagga 360

agccagatcg ctgagggtcc ggtctccagt ttgcctcctg ctatatccat tggaagagaa 420

aagtttgtga cttgggcccc caagttttga gagaactggg ctttcggcgc ggggggacag 480

aggaggctcg tggggagctt tcccc atg gag ctt acc cag cct gca gaa gac 532
Met Glu Leu Thr Gln Pro Ala Glu Asp
1 5

ctc atc cag acc cag cag acc cct gcc tca gaa ctt ggg gac cct gaa 580
Leu Ile Gln Thr Gln Gln Thr Pro Ala Ser Glu Leu Gly Asp Pro Glu
10 15 20 25

gac ccc gga gag gag gct gca gat ggc tca gac act gtg gtc ctc agt 628
Asp Pro Gly Glu Glu Ala Ala Asp Gly Ser Asp Thr Val Val Leu Ser
30 35 40

ctc ttt ccc tgc acc cct gag cct gtg aat cct gaa ccg gat gcc agt 676
Leu Phe Pro Cys Thr Pro Glu Pro Val Asn Pro Glu Pro Asp Ala Ser
45 50 55

gtt tcc tct cca cag gca ggc agc tcc ctg aag cac tcc acc act ctc 724

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Val Ser Ser Pro Gln Ala Gly Ser Ser Leu Lys His Ser Thr Thr Leu
        60                  65                  70

acc aac cgg cag cga ggg aac gag gtg tca gct ctg ccg gcc acc cta        772
Thr Asn Arg Gln Arg Gly Asn Glu Val Ser Ala Leu Pro Ala Thr Leu
    75                  80                  85

gac tcc ctg tcc atc cac cag ctc gca gca cag ggg gag ctg gac cag        820
Asp Ser Leu Ser Ile His Gln Leu Ala Ala Gln Gly Glu Leu Asp Gln
90                  95                  100                 105

ctg aag gag cat ttg cgg aaa ggt gac aac ctc gtc aac aag cca gac        868
Leu Lys Glu His Leu Arg Lys Gly Asp Asn Leu Val Asn Lys Pro Asp
                110                 115                 120

gag cgc ggc ttc acc ccc ctc atc tgg gcc tcc gcc ttt gga gag att        916
Glu Arg Gly Phe Thr Pro Leu Ile Trp Ala Ser Ala Phe Gly Glu Ile
            125                 130                 135

gag acc gtt cgc ttc ctg ctg gag tgg ggt gcc gac ccc cac atc ctg        964
Glu Thr Val Arg Phe Leu Leu Glu Trp Gly Ala Asp Pro His Ile Leu
        140                 145                 150

gca aaa gag cga gag agc gcc ctg tcg ctg gcc agc aca ggc ggc tac       1012
Ala Lys Glu Arg Glu Ser Ala Leu Ser Leu Ala Ser Thr Gly Gly Tyr
    155                 160                 165

aca gac att gtg ggg ctg ctg ctg gag cgt gac gtg gac atc aac atc       1060
Thr Asp Ile Val Gly Leu Leu Leu Glu Arg Asp Val Asp Ile Asn Ile
170                 175                 180                 185

tat gat tgg aat gga ggg acg cca ctg ctg tac gct gtg cgc ggg aac       1108
Tyr Asp Trp Asn Gly Gly Thr Pro Leu Leu Tyr Ala Val Arg Gly Asn
                190                 195                 200

cac gtg aaa tgc gtt gag gcc ttg ctg gcc cga ggc gct gac ctc acc       1156
His Val Lys Cys Val Glu Ala Leu Leu Ala Arg Gly Ala Asp Leu Thr
            205                 210                 215

acc gaa gcc gac tct ggc tac acc ccg atg gac ctt gcc gtg gcc ctg       1204
Thr Glu Ala Asp Ser Gly Tyr Thr Pro Met Asp Leu Ala Val Ala Leu
        220                 225                 230

gga tac cgg aaa gtg caa cag gtg atc gag aac cac atc ctc aag ctc       1252
Gly Tyr Arg Lys Val Gln Gln Val Ile Glu Asn His Ile Leu Lys Leu
    235                 240                 245

ttc cag agc aac ctg gtg ccc gct gac cct gag tga aggccgcctg            1298
Phe Gln Ser Asn Leu Val Pro Ala Asp Pro Glu
250                 255                 260

ccggggactc agacactcag ggaacaaaat ggtcagccag agctggggaa acccagaact     1358

gacttcaaag gcagcttctg gacaggtggt gggaggggac ccttcccaag aggaaccaat     1418

aaaccttctg tgcagaatga                                                 1438


<210>  27
<211>  260
<212>  PRT
<213>  Homo sapiens

<400>  27

Met Glu Leu Thr Gln Pro Ala Glu Asp Leu Ile Gln Thr Gln Gln Thr
1               5                   10                  15
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Pro Ala Ser Glu Leu Gly Asp Pro Glu Asp Pro Gly Glu Glu Ala Ala
            20                  25                  30

Asp Gly Ser Asp Thr Val Val Leu Ser Leu Phe Pro Cys Thr Pro Glu
        35                  40                  45

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

Ser Ser Leu Lys His Ser Thr Thr Leu Thr Asn Arg Gln Arg Gly Asn
65                  70                  75                  80

Glu Val Ser Ala Leu Pro Ala Thr Leu Asp Ser Leu Ser Ile His Gln
                85                  90                  95

Leu Ala Ala Gln Gly Glu Leu Asp Gln Leu Lys Glu His Leu Arg Lys
            100                 105                 110

Gly Asp Asn Leu Val Asn Lys Pro Asp Glu Arg Gly Phe Thr Pro Leu
        115                 120                 125

Ile Trp Ala Ser Ala Phe Gly Glu Ile Glu Thr Val Arg Phe Leu Leu
    130                 135                 140

Glu Trp Gly Ala Asp Pro His Ile Leu Ala Lys Glu Arg Glu Ser Ala
145                 150                 155                 160

Leu Ser Leu Ala Ser Thr Gly Gly Tyr Thr Asp Ile Val Gly Leu Leu
                165                 170                 175

Leu Glu Arg Asp Val Asp Ile Asn Ile Tyr Asp Trp Asn Gly Gly Thr
            180                 185                 190

Pro Leu Leu Tyr Ala Val Arg Gly Asn His Val Lys Cys Val Glu Ala
        195                 200                 205

Leu Leu Ala Arg Gly Ala Asp Leu Thr Thr Glu Ala Asp Ser Gly Tyr
    210                 215                 220

Thr Pro Met Asp Leu Ala Val Ala Leu Gly Tyr Arg Lys Val Gln Gln
225                 230                 235                 240

Val Ile Glu Asn His Ile Leu Lys Leu Phe Gln Ser Asn Leu Val Pro
                245                 250                 255

Ala Asp Pro Glu
            260
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<210> 28
<211> 3618
<212> DNA

<213> Homo sapiens

<220>
<221> CDS
<222> (222)..(2072)

<400> 28

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gctggagtga aggtggctac gagttttcca gatttaggag acttcagaaa ggtggggcag       120

atagaatgga gatggcaaag atctctttgg gcatatatgg gcctggcgaa gtaatggaat       180

aatttctaat tttcggagaa ggcaagtgcc ctcatgccgg g atg gca gaa gat gag       236
                                               Met Ala Glu Asp Glu
                                               1               5

cct gat gct aag agc ccc aag act ggg gga agg gcc ccc cca ggt ggt         284
Pro Asp Ala Lys Ser Pro Lys Thr Gly Gly Arg Ala Pro Pro Gly Gly
                10                  15                  20

gct gag gct ggg gaa cct acc acc ctt ctt cag agg ctc cga ggt acc         332
Ala Glu Ala Gly Glu Pro Thr Thr Leu Leu Gln Arg Leu Arg Gly Thr
            25                  30                  35

att tcc aag gcc gtg cag aac aaa gta gag ggg atc ctg caa gat gta         380
Ile Ser Lys Ala Val Gln Asn Lys Val Glu Gly Ile Leu Gln Asp Val
        40                  45                  50

cag aaa ttt tct gac aat gac aag ctg tat ctc tac ctt cag ctc ccc         428
Gln Lys Phe Ser Asp Asn Asp Lys Leu Tyr Leu Tyr Leu Gln Leu Pro
    55                  60                  65

tca gga ccc acc act gga gac aaa agc tca gag cca agt aca ctg agc         476
Ser Gly Pro Thr Thr Gly Asp Lys Ser Ser Glu Pro Ser Thr Leu Ser
70                  75                  80                  85

aat gag gag tac atg tat gcc tat agg tgg atc cgc aac cac ctg gaa         524
Asn Glu Glu Tyr Met Tyr Ala Tyr Arg Trp Ile Arg Asn His Leu Glu
                90                  95                  100

gag cac act gac acc tgt ctg cca aag caa agt gtt tat gat gcc tat         572
Glu His Thr Asp Thr Cys Leu Pro Lys Gln Ser Val Tyr Asp Ala Tyr
            105                 110                 115

cgg aag tac tgt gag agt ctt gcc tgt tgc cgc cca ctc agc aca gcc         620
Arg Lys Tyr Cys Glu Ser Leu Ala Cys Cys Arg Pro Leu Ser Thr Ala
        120                 125                 130

aac ttt ggc aag atc atc aga gag atc ttc cct gac atc aaa gct cga         668
Asn Phe Gly Lys Ile Ile Arg Glu Ile Phe Pro Asp Ile Lys Ala Arg
    135                 140                 145

agg ctt ggt ggc cgg ggc cag tcc aaa tat tgc tac agt ggc ata agg         716
Arg Leu Gly Gly Arg Gly Gln Ser Lys Tyr Cys Tyr Ser Gly Ile Arg
150                 155                 160                 165

agg aag acc ttg gtg tct atg cca ccc ctg cct gga ctt gac cta aag         764
Arg Lys Thr Leu Val Ser Met Pro Pro Leu Pro Gly Leu Asp Leu Lys
                170                 175                 180

ggt tct gag agt cca gaa atg ggc cca gaa gta acc cca gca cct cga         812
Gly Ser Glu Ser Pro Glu Met Gly Pro Glu Val Thr Pro Ala Pro Arg
            185                 190                 195

gat gaa ctg gtg gag gca gcg tgt gcc ctg acc tgt gac tgg gca gag         860
Asp Glu Leu Val Glu Ala Ala Cys Ala Leu Thr Cys Asp Trp Ala Glu
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        200                 205                 210

cgg atc ctg aaa cgg tcc ttc agt tcc atc gtt gag gtc gcc cgc ttc        908
Arg Ile Leu Lys Arg Ser Phe Ser Ser Ile Val Glu Val Ala Arg Phe
    215                 220                 225

ctg cta cag cag cat ctc atc tct gcc cga tct gca cat gcc cat gtg        956
Leu Leu Gln Gln His Leu Ile Ser Ala Arg Ser Ala His Ala His Val
230                 235                 240                 245

ctt aag gcc atg ggg ctt gct gaa gag gac gaa cat gca cct cgg gaa       1004
Leu Lys Ala Met Gly Leu Ala Glu Glu Asp Glu His Ala Pro Arg Glu
                250                 255                 260

cgg tca tct aaa cca aag aat ggt tta gag aac cca gag ggt gga gcc       1052
Arg Ser Ser Lys Pro Lys Asn Gly Leu Glu Asn Pro Glu Gly Gly Ala
            265                 270                 275

cac aag aag cca gag aga ctg gcc cag cct cct aag gat ctg gaa gcc       1100
His Lys Lys Pro Glu Arg Leu Ala Gln Pro Pro Lys Asp Leu Glu Ala
        280                 285                 290

cga act ggg gcc ggt cct ctc gca cgt gga gag cgg aag aag agt gta       1148
Arg Thr Gly Ala Gly Pro Leu Ala Arg Gly Glu Arg Lys Lys Ser Val
    295                 300                 305

gtt gag agc tcg gcc cca gga gcc aat aac ctg cag gtt aat gcc cta       1196
Val Glu Ser Ser Ala Pro Gly Ala Asn Asn Leu Gln Val Asn Ala Leu
310                 315                 320                 325

gtg gct cgg ctg cct ctg ctc ctt ccc cgg gcc cct cgc tca cta att       1244
Val Ala Arg Leu Pro Leu Leu Leu Pro Arg Ala Pro Arg Ser Leu Ile
                330                 335                 340

ccg cca atc cca gtc tct cca cct att ctg gcc ccc agg ctt tct tca       1292
Pro Pro Ile Pro Val Ser Pro Pro Ile Leu Ala Pro Arg Leu Ser Ser
            345                 350                 355

ggt gcc ctg aaa gtg gct aca ctg cct ctg tct agt agg gcc ggg gca       1340
Gly Ala Leu Lys Val Ala Thr Leu Pro Leu Ser Ser Arg Ala Gly Ala
        360                 365                 370

ccc cca gca gct gtg ccc atc att aac atg atc tta cca act gtt cct       1388
Pro Pro Ala Ala Val Pro Ile Ile Asn Met Ile Leu Pro Thr Val Pro
    375                 380                 385

gct ttg cct gga cct gga cct ggg cct ggg cga gct cca cct ggg gga       1436
Ala Leu Pro Gly Pro Gly Pro Gly Pro Gly Arg Ala Pro Pro Gly Gly
390                 395                 400                 405

ctc act cag ccc cgg ggc aca gag aac aga gag gta ggc ata ggt ggt       1484
Leu Thr Gln Pro Arg Gly Thr Glu Asn Arg Glu Val Gly Ile Gly Gly
                410                 415                 420

gac caa gga cca cat gac aag ggt gtc aag agg aca gct gaa gta cct       1532
Asp Gln Gly Pro His Asp Lys Gly Val Lys Arg Thr Ala Glu Val Pro
            425                 430                 435

gtg agt gag gcc agt ggg cag gct cca cca gct aaa gca gca aag cag       1580
Val Ser Glu Ala Ser Gly Gln Ala Pro Pro Ala Lys Ala Ala Lys Gln
        440                 445                 450

gat ata gag gat aca gca agt gat gcc aaa agg aaa cgg ggg cgc cct       1628
Asp Ile Glu Asp Thr Ala Ser Asp Ala Lys Arg Lys Arg Gly Arg Pro
    455                 460                 465

cga aaa aag tca ggt gga agt ggg gaa agg aat tct acc cct ctc aag       1676
Arg Lys Lys Ser Gly Gly Ser Gly Glu Arg Asn Ser Thr Pro Leu Lys
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470                 475                 480                 485

tca gca gct gcc atg gaa tct gcc cag tcc tca agg tta cca tgg gag       1724
Ser Ala Ala Ala Met Glu Ser Ala Gln Ser Ser Arg Leu Pro Trp Glu
                490                 495                 500

aca tgg ggc tca gga ggg gaa ggc aac tca gct gga ggg gca gag agg       1772
Thr Trp Gly Ser Gly Gly Glu Gly Asn Ser Ala Gly Gly Ala Glu Arg
            505                 510                 515

cca ggg cca atg gga gag gct gaa aag ggg gca gta ctt gcc cag ggt       1820
Pro Gly Pro Met Gly Glu Ala Glu Lys Gly Ala Val Leu Ala Gln Gly
        520                 525                 530

cag gga gat ggt act gtt tcc aaa gga gga agg ggc ccc ggt tcc cag       1868
Gln Gly Asp Gly Thr Val Ser Lys Gly Gly Arg Gly Pro Gly Ser Gln
    535                 540                 545

cat acc aaa gaa gca gaa gat aaa att ccc ttg gtc ccc tca aaa gtg       1916
His Thr Lys Glu Ala Glu Asp Lys Ile Pro Leu Val Pro Ser Lys Val
550                 555                 560                 565

agt gtc atc aag ggc agc aga agc caa aag gag gct ttt cct ttg gca       1964
Ser Val Ile Lys Gly Ser Arg Ser Gln Lys Glu Ala Phe Pro Leu Ala
                570                 575                 580

aag gga gag gta gac act gca cca cag ggt aat aaa gac tta aag gag       2012
Lys Gly Glu Val Asp Thr Ala Pro Gln Gly Asn Lys Asp Leu Lys Glu
            585                 590                 595

cat gtg ctt caa agt tcc tta tcc cag gag cat aaa gac cca aaa gca       2060
His Val Leu Gln Ser Ser Leu Ser Gln Glu His Lys Asp Pro Lys Ala
        600                 605                 610

aca ccc cca tga tacaggtctg tggggaagag tgtttatatc cctacgttaa           2112
Thr Pro Pro
    615

ctttgcctag tagaggccct tctttgcact tgcttctcat ttggctattc ttttcctaag     2172

gaagtccatt ctcctctgta cagacagctg agtcacccag tctacttagt acctggttgc     2232

tgcctctgac cttttcagct tgataccctg ggctttagtg taaccaataa atctgtagtg     2292

accttacctg tattccctgt gctatcctgt gggaaggtag gaatgggcta agtatgatga     2352

atatataggt tagggatctt ttggttttaa atcacagaaa acctaattca aactggctta     2412

aaataaaaag gatttattgg ttcatgtaac tagaaagtcc ataggtagtg ctggctccag     2472

gtgaagactt gacccagtag ttcagtatgt ctctaaatac cggactgact tttttctcac     2532

tgttgcatct tctgtaggac catttaagtc tgggccactt aatggctgcc agcattccta     2592

agattacact tttccccatt tatgtccaat cagaaaaaga aggcatcttt gtaccagaaa     2652

tctcagcaaa agccctaata ttcacactga ttaggcctgg gtcacatgtc caccctgacc     2712

aatcactgtg gccaggagga tgatacatgc taatttgctt attctatatc atggacaaca     2772

cctttgggga aaagggtggg ggtcagcctc cccaaaatca catggattcc ccaagtggaa     2832

actaggagca gggagttgct tgggtggccg ctaacaccag gctactctta ttttagcttg     2892

ctaagttgag atcagctaga cctgctttct tttctcctca gtcttgcatt tccctcaata     2952

caagctgtag cctctttcct cgtttctagt ctcagaagga aggagaggga agccattctc     3012
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ctctagggac tcttcagtct catttagatg atagtccctt tttttctacc tccatattag 3072

agatggagct ccttcctttt cctgtttctt aatttttgtc ttctcattcc tgcttccctc 3132

tcaccctatt gccagttcca ccaactagag tgaaagactt cctagccatt tcattaaatc 3192

tattctgtat ccaccaggtg gcagcatctt gtcatacgtg tcaggactta ggactgcggg 3252

gtttaggtta gatgtcacgg aaaaagctag ttctgtggtc aggcggcacc aatgagaaag 3312

gaatgcagac cctccagatg tatccttggg aaaagcagta aaccaactaa tatttattga 3372

agacctactt tgtcctctac atagggtagc ttctgtcagg gaatcttggt tcttcccaag 3432

aaacactgat tttctttcag ggagacttca tgtgttcatt tatttccacc acagcagatt 3492

ttaagaaatt ataatatgta atatttgata tctataaaga gtatatctaa cgtgaataaa 3552

ttatgaagca tactaatgag tacctatgac ccataacaca tatacattaa aacattttaa 3612

atacca 3618

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Ala Pro Pro Gly Gly Ala Glu Ala Gly Glu Pro Thr Thr Leu Leu Gln
20 25 30

Arg Leu Arg Gly Thr Ile Ser Lys Ala Val Gln Asn Lys Val Glu Gly
35 40 45

Ile Leu Gln Asp Val Gln Lys Phe Ser Asp Asn Asp Lys Leu Tyr Leu
50 55 60

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

Pro Ser Thr Leu Ser Asn Glu Glu Tyr Met Tyr Ala Tyr Arg Trp Ile
85 90 95

Arg Asn His Leu Glu Glu His Thr Asp Thr Cys Leu Pro Lys Gln Ser
100 105 110

Val Tyr Asp Ala Tyr Arg Lys Tyr Cys Glu Ser Leu Ala Cys Cys Arg
115 120 125

Pro Leu Ser Thr Ala Asn Phe Gly Lys Ile Ile Arg Glu Ile Phe Pro
130 135 140

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

```
Tyr Ser Gly Ile Arg Arg Lys Thr Leu Val Ser Met Pro Pro Leu Pro
                165                 170                 175

Gly Leu Asp Leu Lys Gly Ser Glu Ser Pro Glu Met Gly Pro Glu Val
            180                 185                 190

Thr Pro Ala Pro Arg Asp Glu Leu Val Glu Ala Ala Cys Ala Leu Thr
        195                 200                 205

Cys Asp Trp Ala Glu Arg Ile Leu Lys Arg Ser Phe Ser Ser Ile Val
    210                 215                 220

Glu Val Ala Arg Phe Leu Leu Gln Gln His Leu Ile Ser Ala Arg Ser
225                 230                 235                 240

Ala His Ala His Val Leu Lys Ala Met Gly Leu Ala Glu Glu Asp Glu
                245                 250                 255

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

Pro Glu Gly Gly Ala His Lys Lys Pro Glu Arg Leu Ala Gln Pro Pro
        275                 280                 285

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

Arg Lys Lys Ser Val Val Glu Ser Ser Ala Pro Gly Ala Asn Asn Leu
305                 310                 315                 320

Gln Val Asn Ala Leu Val Ala Arg Leu Pro Leu Leu Leu Pro Arg Ala
                325                 330                 335

Pro Arg Ser Leu Ile Pro Pro Ile Pro Val Ser Pro Pro Ile Leu Ala
            340                 345                 350

Pro Arg Leu Ser Ser Gly Ala Leu Lys Val Ala Thr Leu Pro Leu Ser
        355                 360                 365

Ser Arg Ala Gly Ala Pro Pro Ala Ala Val Pro Ile Ile Asn Met Ile
    370                 375                 380

Leu Pro Thr Val Pro Ala Leu Pro Gly Pro Gly Pro Gly Pro Gly Arg
385                 390                 395                 400

Ala Pro Pro Gly Gly Leu Thr Gln Pro Arg Gly Thr Glu Asn Arg Glu
                405                 410                 415

Val Gly Ile Gly Gly Asp Gln Gly Pro His Asp Lys Gly Val Lys Arg
            420                 425                 430
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Thr Ala Glu Val Pro Val Ser Glu Ala Ser Gly Gln Ala Pro Pro Ala
        435                 440                 445

Lys Ala Ala Lys Gln Asp Ile Glu Asp Thr Ala Ser Asp Ala Lys Arg
    450                 455                 460

Lys Arg Gly Arg Pro Arg Lys Lys Ser Gly Gly Ser Gly Glu Arg Asn
465                 470                 475                 480

Ser Thr Pro Leu Lys Ser Ala Ala Ala Met Glu Ser Ala Gln Ser Ser
                485                 490                 495

Arg Leu Pro Trp Glu Thr Trp Gly Ser Gly Gly Glu Gly Asn Ser Ala
            500                 505                 510

Gly Gly Ala Glu Arg Pro Gly Pro Met Gly Glu Ala Glu Lys Gly Ala
        515                 520                 525

Val Leu Ala Gln Gly Gln Gly Asp Gly Thr Val Ser Lys Gly Gly Arg
    530                 535                 540

Gly Pro Gly Ser Gln His Thr Lys Glu Ala Glu Asp Lys Ile Pro Leu
545                 550                 555                 560

Val Pro Ser Lys Val Ser Val Ile Lys Gly Ser Arg Ser Gln Lys Glu
                565                 570                 575

Ala Phe Pro Leu Ala Lys Gly Glu Val Asp Thr Ala Pro Gln Gly Asn
            580                 585                 590

Lys Asp Leu Lys Glu His Val Leu Gln Ser Ser Leu Ser Gln Glu His
        595                 600                 605

Lys Asp Pro Lys Ala Thr Pro Pro
    610                 615
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<213> Homo sapiens

<220>
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<222> (215)..(2065)

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gctggagtga aggtggctac gagttttcca gatttaggag acttcagaaa ggtggggcag 120

atagaatgga gatggcaaag atctctttgg gcatatatgg gcctggcgaa gtaatggaat 180

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aatttctaat tttcggagaa gccctcatgc cggg atg gca gaa gat gag cct gat      235
                                       Met Ala Glu Asp Glu Pro Asp
                                       1               5

gct aag agc ccc aag act ggg gga agg gcc ccc cca ggt ggt gct gag        283
Ala Lys Ser Pro Lys Thr Gly Gly Arg Ala Pro Pro Gly Gly Ala Glu
        10                  15                  20

gct ggg gaa cct acc acc ctt ctt cag agg ctc cga ggt acc att tcc        331
Ala Gly Glu Pro Thr Thr Leu Leu Gln Arg Leu Arg Gly Thr Ile Ser
    25                  30                  35

aag gcc gtg cag aac aaa gta gag ggg atc ctg caa gat gta cag aaa        379
Lys Ala Val Gln Asn Lys Val Glu Gly Ile Leu Gln Asp Val Gln Lys
40                  45                  50                  55

ttt tct gac aat gac aag ctg tat ctc tac ctt cag ctc ccc tca gga        427
Phe Ser Asp Asn Asp Lys Leu Tyr Leu Tyr Leu Gln Leu Pro Ser Gly
                60                  65                  70

ccc acc act gga gac aaa agc tca gag cca agt aca ctg agc aat gag        475
Pro Thr Thr Gly Asp Lys Ser Ser Glu Pro Ser Thr Leu Ser Asn Glu
            75                  80                  85

gag tac atg tat gcc tat agg tgg atc cgc aac cac ctg gaa gag cac        523
Glu Tyr Met Tyr Ala Tyr Arg Trp Ile Arg Asn His Leu Glu Glu His
        90                  95                  100

act gac acc tgt ctg cca aag caa agt gtt tat gat gcc tat cgg aag        571
Thr Asp Thr Cys Leu Pro Lys Gln Ser Val Tyr Asp Ala Tyr Arg Lys
    105                 110                 115

tac tgt gag agt ctt gcc tgt tgc cgc cca ctc agc aca gcc aac ttt        619
Tyr Cys Glu Ser Leu Ala Cys Cys Arg Pro Leu Ser Thr Ala Asn Phe
120                 125                 130                 135

ggc aag atc atc aga gag atc ttc cct gac atc aaa gct cga agg ctt        667
Gly Lys Ile Ile Arg Glu Ile Phe Pro Asp Ile Lys Ala Arg Arg Leu
                140                 145                 150

ggt ggc cgg ggc cag tcc aaa tat tgc tac agt ggc ata agg agg aag        715
Gly Gly Arg Gly Gln Ser Lys Tyr Cys Tyr Ser Gly Ile Arg Arg Lys
            155                 160                 165

acc ttg gtg tct atg cca ccc ctg cct gga ctt gac cta aag ggt tct        763
Thr Leu Val Ser Met Pro Pro Leu Pro Gly Leu Asp Leu Lys Gly Ser
        170                 175                 180

gag agt cca gaa atg ggc cca gaa gta acc cca gca cct cga gat gaa        811
Glu Ser Pro Glu Met Gly Pro Glu Val Thr Pro Ala Pro Arg Asp Glu
    185                 190                 195

ctg gtg gag gca gcg tgt gcc ctg acc tgt gac tgg gca gag cgg atc        859
Leu Val Glu Ala Ala Cys Ala Leu Thr Cys Asp Trp Ala Glu Arg Ile
200                 205                 210                 215

ctg aaa cgg tcc ttc agt tcc atc gtt gag gtc gcc cgc ttc ctg cta        907
Leu Lys Arg Ser Phe Ser Ser Ile Val Glu Val Ala Arg Phe Leu Leu
                220                 225                 230

cag cag cat ctc atc tct gcc cga tct gca cat gcc cat gtg ctt aag        955
Gln Gln His Leu Ile Ser Ala Arg Ser Ala His Ala His Val Leu Lys
            235                 240                 245

gcc atg ggg ctt gct gaa gag gac gaa cat gca cct cgg gaa cgg tca       1003
Ala Met Gly Leu Ala Glu Glu Asp Glu His Ala Pro Arg Glu Arg Ser
        250                 255                 260
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tct aaa cca aag aat ggt tta gag aac cca gag ggt gga gcc cac aag       1051
Ser Lys Pro Lys Asn Gly Leu Glu Asn Pro Glu Gly Gly Ala His Lys
    265                 270                 275

aag cca gag aga ctg gcc cag cct cct aag gat ctg gaa gcc cga act       1099
Lys Pro Glu Arg Leu Ala Gln Pro Pro Lys Asp Leu Glu Ala Arg Thr
280                 285                 290                 295

ggg gcc ggt cct ctc gca cgt gga gag cgg aag aag agt gta gtt gag       1147
Gly Ala Gly Pro Leu Ala Arg Gly Glu Arg Lys Lys Ser Val Val Glu
                300                 305                 310

agc tcg gcc cca gga gcc aat aac ctg cag gtt aat gcc cta gtg gct       1195
Ser Ser Ala Pro Gly Ala Asn Asn Leu Gln Val Asn Ala Leu Val Ala
            315                 320                 325

cgg ctg cct ctg ctc ctt ccc cgg gcc cct cgc tca cta att ccg cca       1243
Arg Leu Pro Leu Leu Leu Pro Arg Ala Pro Arg Ser Leu Ile Pro Pro
        330                 335                 340

atc cca gtc tct cca cct att ctg gcc ccc agg ctt tct tca ggt gcc       1291
Ile Pro Val Ser Pro Pro Ile Leu Ala Pro Arg Leu Ser Ser Gly Ala
    345                 350                 355

ctg aaa gtg gct aca ctg cct ctg tct agt agg gcc ggg gca ccc cca       1339
Leu Lys Val Ala Thr Leu Pro Leu Ser Ser Arg Ala Gly Ala Pro Pro
360                 365                 370                 375

gca gct gtg ccc atc att aac atg atc tta cca act gtt cct gct ttg       1387
Ala Ala Val Pro Ile Ile Asn Met Ile Leu Pro Thr Val Pro Ala Leu
                380                 385                 390

cct gga cct gga cct ggg cct ggg cga gct cca cct ggg gga ctc act       1435
Pro Gly Pro Gly Pro Gly Pro Gly Arg Ala Pro Pro Gly Gly Leu Thr
            395                 400                 405

cag ccc cgg ggc aca gag aac aga gag gta ggc ata ggt ggt gac caa       1483
Gln Pro Arg Gly Thr Glu Asn Arg Glu Val Gly Ile Gly Gly Asp Gln
        410                 415                 420

gga cca cat gac aag ggt gtc aag agg aca gct gaa gta cct gtg agt       1531
Gly Pro His Asp Lys Gly Val Lys Arg Thr Ala Glu Val Pro Val Ser
    425                 430                 435

gag gcc agt ggg cag gct cca cca gct aaa gca gca aag cag gat ata       1579
Glu Ala Ser Gly Gln Ala Pro Pro Ala Lys Ala Ala Lys Gln Asp Ile
440                 445                 450                 455

gag gat aca gca agt gat gcc aaa agg aaa cgg ggg cgc cct cga aaa       1627
Glu Asp Thr Ala Ser Asp Ala Lys Arg Lys Arg Gly Arg Pro Arg Lys
                460                 465                 470

aag tca ggt gga agt ggg gaa agg aat tct acc cct ctc aag tca gca       1675
Lys Ser Gly Gly Ser Gly Glu Arg Asn Ser Thr Pro Leu Lys Ser Ala
            475                 480                 485

gct gcc atg gaa tct gcc cag tcc tca agg tta cca tgg gag aca tgg       1723
Ala Ala Met Glu Ser Ala Gln Ser Ser Arg Leu Pro Trp Glu Thr Trp
        490                 495                 500

ggc tca gga ggg gaa ggc aac tca gct gga ggg gca gag agg cca ggg       1771
Gly Ser Gly Gly Glu Gly Asn Ser Ala Gly Gly Ala Glu Arg Pro Gly
    505                 510                 515

cca atg gga gag gct gaa aag ggg gca gta ctt gcc cag ggt cag gga       1819
Pro Met Gly Glu Ala Glu Lys Gly Ala Val Leu Ala Gln Gly Gln Gly
520                 525                 530                 535
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gat ggt act gtt tcc aaa gga gga agg ggc ccc ggt tcc cag cat acc       1867
Asp Gly Thr Val Ser Lys Gly Gly Arg Gly Pro Gly Ser Gln His Thr
                540                 545                 550

aaa gaa gca gaa gat aaa att ccc ttg gtc ccc tca aaa gtg agt gtc       1915
Lys Glu Ala Glu Asp Lys Ile Pro Leu Val Pro Ser Lys Val Ser Val
            555                 560                 565

atc aag ggc agc aga agc caa aag gag gct ttt cct ttg gca aag gga       1963
Ile Lys Gly Ser Arg Ser Gln Lys Glu Ala Phe Pro Leu Ala Lys Gly
        570                 575                 580

gag gta gac act gca cca cag ggt aat aaa gac tta aag gag cat gtg       2011
Glu Val Asp Thr Ala Pro Gln Gly Asn Lys Asp Leu Lys Glu His Val
    585                 590                 595

ctt caa agt tcc tta tcc cag gag cat aaa gac cca aaa gca aca ccc       2059
Leu Gln Ser Ser Leu Ser Gln Glu His Lys Asp Pro Lys Ala Thr Pro
600                 605                 610                 615

cca tga tacaggtctg tggggaagag tgtttatatc cctacgttaa ctttgcctag       2115
Pro
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tagaggccct tctttgcact tgcttctcat ttggctattc ttttcctaag gaagtccatt     2175

ctcctctgta cagacagctg agtcacccag tctacttagt acctggttgc tgcctctgac     2235

cttttcagct tgataccctg ggctttagtg taaccaataa atctgtagtg accttacctg     2295

tattccctgt gctatcctgt gggaaggtag gaatgggcta agtatgatga atatataggt     2355

tagggatctt ttggttttaa atcacagaaa acctaattca aactggctta aaataaaaag     2415

gatttattgg ttcatgtaac tagaaagtcc ataggtagtg ctggctccag gtgaagactt     2475

gacccagtag ttcagtatgt ctctaaatac cggactgact tttttctcac tgttgcatct     2535

tctgtaggac catttaagtc tgggccactt aatggctgcc agcattccta agattacact     2595

tttccccatt tatgtccaat cagaaaaaga aggcatcttt gtaccagaaa tctcagcaaa     2655

agccctaata ttcacactga ttaggcctgg gtcacatgtc caccctgacc aatcactgtg     2715

gccaggagga tgatacatgc taatttgctt attctatatc atggacaaca cctttgggga     2775

aaagggtggg ggtcagcctc cccaaaatca catggattcc ccaagtggaa actaggagca     2835

gggagttgct tgggtggccg ctaacaccag gctactctta ttttagcttg ctaagttgag     2895

atcagctaga cctgctttct tttctcctca gtcttgcatt tccctcaata caagctgtag     2955

cctctttcct cgtttctagt ctcagaagga aggagaggga agccattctc ctctagggac     3015

tcttcagtct catttagatg atagtccctt tttttctacc tccatattag agatggagct     3075

ccttcctttt cctgtttctt aatttttgtc ttctcattcc tgcttccctc tcaccctatt     3135

gccagttcca ccaactagag tgaaagactt cctagccatt tcattaaatc tattctgtat     3195

ccaccaggtg gcagcatctt gtcatacgtg tcaggactta ggactgcggg gtttaggtta     3255

gatgtcacgg aaaaagctag ttctgtggtc aggcggcacc aatgagaaag gaatgcagac     3315

cctccagatg tatccttggg aaaagcagta aaccaactaa tatttattga agacctactt     3375

tgtcctctac atagggtagc ttctgtcagg gaatcttggt tcttcccaag aaacactgat     3435
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tttctttcag ggagacttca tgtgttcatt tatttccacc acagcagatt ttaagaaatt 3495

ataatatgta atatttgata tctataaaga gtatatctaa cgtgaataaa ttatgaagca 3555

tactaatgag tacctatgac ccataacaca tatacattaa aacattttaa atacca 3611

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<212> PRT
<213> Homo sapiens

<400> 31

Met Ala Glu Asp Glu Pro Asp Ala Lys Ser Pro Lys Thr Gly Gly Arg
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Ala Pro Pro Gly Gly Ala Glu Ala Gly Glu Pro Thr Thr Leu Leu Gln
20 25 30

Arg Leu Arg Gly Thr Ile Ser Lys Ala Val Gln Asn Lys Val Glu Gly
35 40 45

Ile Leu Gln Asp Val Gln Lys Phe Ser Asp Asn Asp Lys Leu Tyr Leu
50 55 60

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

Pro Ser Thr Leu Ser Asn Glu Glu Tyr Met Tyr Ala Tyr Arg Trp Ile
85 90 95

Arg Asn His Leu Glu Glu His Thr Asp Thr Cys Leu Pro Lys Gln Ser
100 105 110

Val Tyr Asp Ala Tyr Arg Lys Tyr Cys Glu Ser Leu Ala Cys Cys Arg
115 120 125

Pro Leu Ser Thr Ala Asn Phe Gly Lys Ile Ile Arg Glu Ile Phe Pro
130 135 140

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

Tyr Ser Gly Ile Arg Arg Lys Thr Leu Val Ser Met Pro Pro Leu Pro
165 170 175

Gly Leu Asp Leu Lys Gly Ser Glu Ser Pro Glu Met Gly Pro Glu Val
180 185 190

Thr Pro Ala Pro Arg Asp Glu Leu Val Glu Ala Ala Cys Ala Leu Thr
195 200 205

Cys Asp Trp Ala Glu Arg Ile Leu Lys Arg Ser Phe Ser Ser Ile Val
210 215 220

```
Glu Val Ala Arg Phe Leu Leu Gln Gln His Leu Ile Ser Ala Arg Ser
225                 230                 235                 240

Ala His Ala His Val Leu Lys Ala Met Gly Leu Ala Glu Glu Asp Glu
                245                 250                 255

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

Pro Glu Gly Gly Ala His Lys Lys Pro Glu Arg Leu Ala Gln Pro Pro
        275                 280                 285

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

Arg Lys Lys Ser Val Val Glu Ser Ser Ala Pro Gly Ala Asn Asn Leu
305                 310                 315                 320

Gln Val Asn Ala Leu Val Ala Arg Leu Pro Leu Leu Leu Pro Arg Ala
                325                 330                 335

Pro Arg Ser Leu Ile Pro Pro Ile Pro Val Ser Pro Pro Ile Leu Ala
            340                 345                 350

Pro Arg Leu Ser Ser Gly Ala Leu Lys Val Ala Thr Leu Pro Leu Ser
        355                 360                 365

Ser Arg Ala Gly Ala Pro Pro Ala Ala Val Pro Ile Ile Asn Met Ile
    370                 375                 380

Leu Pro Thr Val Pro Ala Leu Pro Gly Pro Gly Pro Gly Pro Gly Arg
385                 390                 395                 400

Ala Pro Pro Gly Gly Leu Thr Gln Pro Arg Gly Thr Glu Asn Arg Glu
                405                 410                 415

Val Gly Ile Gly Gly Asp Gln Gly Pro His Asp Lys Gly Val Lys Arg
            420                 425                 430

Thr Ala Glu Val Pro Val Ser Glu Ala Ser Gly Gln Ala Pro Pro Ala
        435                 440                 445

Lys Ala Ala Lys Gln Asp Ile Glu Asp Thr Ala Ser Asp Ala Lys Arg
    450                 455                 460

Lys Arg Gly Arg Pro Arg Lys Lys Ser Gly Gly Ser Gly Glu Arg Asn
465                 470                 475                 480

Ser Thr Pro Leu Lys Ser Ala Ala Ala Met Glu Ser Ala Gln Ser Ser
                485                 490                 495
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Arg Leu Pro Trp Glu Thr Trp Gly Ser Gly Gly Glu Gly Asn Ser Ala
            500                 505                 510

Gly Gly Ala Glu Arg Pro Gly Pro Met Gly Glu Ala Glu Lys Gly Ala
        515                 520                 525

Val Leu Ala Gln Gly Gln Gly Asp Gly Thr Val Ser Lys Gly Gly Arg
    530                 535                 540

Gly Pro Gly Ser Gln His Thr Lys Glu Ala Glu Asp Lys Ile Pro Leu
545                 550                 555                 560

Val Pro Ser Lys Val Ser Val Ile Lys Gly Ser Arg Ser Gln Lys Glu
                565                 570                 575

Ala Phe Pro Leu Ala Lys Gly Glu Val Asp Thr Ala Pro Gln Gly Asn
            580                 585                 590

Lys Asp Leu Lys Glu His Val Leu Gln Ser Ser Leu Ser Gln Glu His
        595                 600                 605

Lys Asp Pro Lys Ala Thr Pro Pro
    610                 615



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<222>  (157)..(975)

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ccccagcgtg tcctgagtct ttggttcgcg aagtgccgtt aggccaagca ggtgctaaaa      120

gcccggggtc gtggaccccg gccaggtctt agcagc atg gag gcg cag ggt gta        174
                                        Met Glu Ala Gln Gly Val
                                        1               5

gcg gag ggc gcg ggg ccg ggc gcc gcc agc ggc gtg ccc cac ccc gcg        222
Ala Glu Gly Ala Gly Pro Gly Ala Ala Ser Gly Val Pro His Pro Ala
            10                  15                  20

gcc cta gcc ccg gct gcg gct ccc acc ttg gcg cca gcc tcg gtg gcg        270
Ala Leu Ala Pro Ala Ala Ala Pro Thr Leu Ala Pro Ala Ser Val Ala
        25                  30                  35

gcc gcg gcc tct caa ttc acc ctg cta gtg atg caa ccc tgt gct ggg        318
Ala Ala Ala Ser Gln Phe Thr Leu Leu Val Met Gln Pro Cys Ala Gly
    40                  45                  50

cag gac gag gct gcg gcc ccc ggg ggc agc gtt ggg gcg ggc aag ccc        366
Gln Asp Glu Ala Ala Ala Pro Gly Gly Ser Val Gly Ala Gly Lys Pro
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```
55                  60                  65                  70

gtt agg tac ctg tgc gaa ggg gcc ggg gat ggc gaa gag gag gct ggg        414
Val Arg Tyr Leu Cys Glu Gly Ala Gly Asp Gly Glu Glu Glu Ala Gly
                75                  80                  85

gag gac gag gcg gac ctg tta gac act tcg gac cct ccg ggg gga ggc        462
Glu Asp Glu Ala Asp Leu Leu Asp Thr Ser Asp Pro Pro Gly Gly Gly
            90                  95                  100

gag agc gcg gct agt ttg gag gat cta gag gac gag gag act cac tcg        510
Glu Ser Ala Ala Ser Leu Glu Asp Leu Glu Asp Glu Glu Thr His Ser
        105                 110                 115

ggg ggc gag ggc agc agc ggg ggc gcc cgg agg cgg ggc agc ggt ggg        558
Gly Gly Glu Gly Ser Ser Gly Gly Ala Arg Arg Arg Gly Ser Gly Gly
    120                 125                 130

ggc agc atg agc aag acc tgc acc tac gaa ggc tgc agc gag acc acg        606
Gly Ser Met Ser Lys Thr Cys Thr Tyr Glu Gly Cys Ser Glu Thr Thr
135                 140                 145                 150

agc cag gtg gcc aag cag cgc aaa ccg tgg atg tgc aag aaa cac cgc        654
Ser Gln Val Ala Lys Gln Arg Lys Pro Trp Met Cys Lys Lys His Arg
                155                 160                 165

aac aag atg tac aag gac aag tat aaa aag aag aag agc gac cag gcc        702
Asn Lys Met Tyr Lys Asp Lys Tyr Lys Lys Lys Lys Ser Asp Gln Ala
            170                 175                 180

ctg aac tgc ggt ggg act gcc tcg act ggc agc gcg gga aac gtc aaa        750
Leu Asn Cys Gly Gly Thr Ala Ser Thr Gly Ser Ala Gly Asn Val Lys
        185                 190                 195

ctc gag gaa agt gca gat aac ata ctc tcc att gtt aaa caa aga aca        798
Leu Glu Glu Ser Ala Asp Asn Ile Leu Ser Ile Val Lys Gln Arg Thr
    200                 205                 210

gga tct ttt ggg gat cgt cct gca aga cct act ctt tta gaa caa gtg        846
Gly Ser Phe Gly Asp Arg Pro Ala Arg Pro Thr Leu Leu Glu Gln Val
215                 220                 225                 230

tta aat caa aaa aga ctg tcg tta cta aga agt cca gaa gta gtg caa        894
Leu Asn Gln Lys Arg Leu Ser Leu Leu Arg Ser Pro Glu Val Val Gln
                235                 240                 245

ttt tta cag aaa cag caa cag cta tta aat cag caa gtt ttg gag caa        942
Phe Leu Gln Lys Gln Gln Gln Leu Leu Asn Gln Gln Val Leu Glu Gln
            250                 255                 260

aga caa cag cag ttt cca gga aca tca atg tga gggaacttac caagaacatc      995
Arg Gln Gln Gln Phe Pro Gly Thr Ser Met
        265                 270

tacatggttt tttatcttat tgtaatagat gagcatattt ttttaccaga cataaatggg     1055

gtaataatct atgcctgtag aacataaaca ttttcctgta aatgtatgtg tgcatttggg     1115

gataagtaag tattgcactt tgtgcatcta atctttcaga ttactgtgag tttgaagaag     1175

tcagcttatc tttccaaata acatttaatt ataatgtttt ttaaaaaata tattcctctt     1235

cagtcattgt tactgaaggt aatgaagcag ttactttctg tggaagtcat aaagttaata     1295

gatattaatc ttgactcatc tagctcagtg gttctcatca agggtcaatt tgattgtcat     1355

agtgaccttg aaaaccactg gcttttagtg agtggccagg aatgctaaat gttctgcagt     1415
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gtcaggggta gtcccacata ctaaagattg tctcacccgc agtgccaata acactcctaa 1475

gaaatgttga tggctatttt gtggtgctaa catgtagttg gggcacctat aattgggttc 1535

tcttaataac ctttctttgc agttaagact gaagctgtca aagaggtaag cacattttat 1595

atagacgtaa ggaaagtgat tattgtttaa tatctgtgaa tttaggatgt gcatctcttt 1655

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agttggcttc tctctttgat gttacctgtt agtgctgatc tcttaaagca gacatttctt 1775

gtttgttgaa tttgtgaaca gtatagatct cagcccacca atgccaagac aaaattattt 1835

ttcttatact tatttttat taaacaaaat gaaaaagatc cttttcaaaa aggtgatcct 1895

gaaaataaaa ctaacactcc agtattttgt cattgttttt cgcaattgag ctatctgaaa 1955

actgttattc ctaagtaatg ttcaaaaatg ataagtaatc tggatacctt tttcttatac 2015

tttctcctag gaaaacttta aaactttaaa aaggcaaacc taccaatagg aataacaaat 2075

taaatgtcaa gagagtatat ccaatattag gatataaatg tatgtgtctc aagtttaact 2135

ctacaaaaat ttgttacttg ttttttaaac tctatatata aagttcgact taatcatggc 2195

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gatggaataa tgggaaagga gggaaatggg aaatggatgg aaatgggaaa ggagggaaaa 2555

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tgatgatgag taattgtcag acgtgggata gataactgag aggctcagaa tctttaccaa 2675

ggatattttt taggataagg tagctgcctg ttcatgaatt tggataagaa tagtaggaca 2735

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atcaataaag caataaggtt tattttgggt 2825

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Gly Val Pro His Pro Ala Ala Leu Ala Pro Ala Ala Ala Pro Thr Leu
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Ala Pro Ala Ser Val Ala Ala Ala Ala Ser Gln Phe Thr Leu Leu Val
35 40 45

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Met Gln Pro Cys Ala Gly Gln Asp Glu Ala Ala Pro Gly Gly Ser
    50                  55                  60

Val Gly Ala Gly Lys Pro Val Arg Tyr Leu Cys Glu Gly Ala Gly Asp
65                  70                  75                  80

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

Asp Pro Pro Gly Gly Gly Glu Ser Ala Ala Ser Leu Glu Asp Leu Glu
            100                 105                 110

Asp Glu Glu Thr His Ser Gly Gly Glu Gly Ser Ser Gly Gly Ala Arg
        115                 120                 125

Arg Arg Gly Ser Gly Gly Gly Ser Met Ser Lys Thr Cys Thr Tyr Glu
    130                 135                 140

Gly Cys Ser Glu Thr Thr Ser Gln Val Ala Lys Gln Arg Lys Pro Trp
145                 150                 155                 160

Met Cys Lys Lys His Arg Asn Lys Met Tyr Lys Asp Lys Tyr Lys Lys
                165                 170                 175

Lys Lys Ser Asp Gln Ala Leu Asn Cys Gly Gly Thr Ala Ser Thr Gly
            180                 185                 190

Ser Ala Gly Asn Val Lys Leu Glu Glu Ser Ala Asp Asn Ile Leu Ser
        195                 200                 205

Ile Val Lys Gln Arg Thr Gly Ser Phe Gly Asp Arg Pro Ala Arg Pro
    210                 215                 220

Thr Leu Leu Glu Gln Val Leu Asn Gln Lys Arg Leu Ser Leu Leu Arg
225                 230                 235                 240

Ser Pro Glu Val Val Gln Phe Leu Gln Lys Gln Gln Gln Leu Leu Asn
                245                 250                 255

Gln Gln Val Leu Glu Gln Arg Gln Gln Gln Phe Pro Gly Thr Ser Met
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ggattcctac aca atg cgt tgc ctg gct cca cgc cct gct ggg tcc tac          169
              Met Arg Cys Leu Ala Pro Arg Pro Ala Gly Ser Tyr
              1               5                   10

ctg tca gag ccc caa ggc agc tca cag tgt gcc acc atg gag ttg ggg        217
Leu Ser Glu Pro Gln Gly Ser Ser Gln Cys Ala Thr Met Glu Leu Gly
        15                  20                  25

ccc cta gaa ggt ggc tac ctg gag ctt ctt aac agc gat gct gac ccc        265
Pro Leu Glu Gly Gly Tyr Leu Glu Leu Leu Asn Ser Asp Ala Asp Pro
    30                  35                  40

ctg tgc ctc tac cac ttc tat gac cag atg gac ctg gct gga gaa gaa        313
Leu Cys Leu Tyr His Phe Tyr Asp Gln Met Asp Leu Ala Gly Glu Glu
45                  50                  55                  60

gag att gag ctc tac tca gaa ccc gac aca gac acc atc aac tgc gac        361
Glu Ile Glu Leu Tyr Ser Glu Pro Asp Thr Asp Thr Ile Asn Cys Asp
                65                  70                  75

cag ttc agc agg ctg ttg tgt gac atg gaa ggt gat gaa gag acc agg        409
Gln Phe Ser Arg Leu Leu Cys Asp Met Glu Gly Asp Glu Glu Thr Arg
            80                  85                  90

gag gct tat gcc aat atc gcg gaa ctg gac cag tat gtc ttc cag gac        457
Glu Ala Tyr Ala Asn Ile Ala Glu Leu Asp Gln Tyr Val Phe Gln Asp
        95                  100                 105

tcc cag ctg gag ggc ctg agc aag gac att ttc aag cac ata gga cca        505
Ser Gln Leu Glu Gly Leu Ser Lys Asp Ile Phe Lys His Ile Gly Pro
    110                 115                 120

gat gaa gtg atc ggt gag agt atg gag atg cca gca gaa gtt ggg cag        553
Asp Glu Val Ile Gly Glu Ser Met Glu Met Pro Ala Glu Val Gly Gln
125                 130                 135                 140

aaa agt cag aaa aga ccc ttc cca gag gag ctt ccg gca gac ctg aag        601
Lys Ser Gln Lys Arg Pro Phe Pro Glu Glu Leu Pro Ala Asp Leu Lys
                145                 150                 155

cac tgg aag cca gct gag ccc ccc act gtg gtg act ggc agt ctc cta        649
His Trp Lys Pro Ala Glu Pro Pro Thr Val Val Thr Gly Ser Leu Leu
            160                 165                 170

gtg gga cca gtg agc gac tgc tcc acc ctg ccc tgc ctg cca ctg cct        697
Val Gly Pro Val Ser Asp Cys Ser Thr Leu Pro Cys Leu Pro Leu Pro
        175                 180                 185

gcg ctg ttc aac cag gag cca gcc tcc ggc cag atg cgc ctg gag aaa        745
Ala Leu Phe Asn Gln Glu Pro Ala Ser Gly Gln Met Arg Leu Glu Lys
    190                 195                 200

acc gac cag att ccc atg cct ttc tcc agt tcc tcg ttg agc tgc ctg        793
Thr Asp Gln Ile Pro Met Pro Phe Ser Ser Ser Ser Leu Ser Cys Leu
205                 210                 215                 220

aat ctc cct gag gga ccc atc cag ttt gtc ccc acc atc tcc act ctg        841
Asn Leu Pro Glu Gly Pro Ile Gln Phe Val Pro Thr Ile Ser Thr Leu
                225                 230                 235

ccc cat ggg ctc tgg caa atc tct gag gct gga aca ggg gtc tcc agt        889
Pro His Gly Leu Trp Gln Ile Ser Glu Ala Gly Thr Gly Val Ser Ser
            240                 245                 250
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ata ttc atc tac cat ggt gag gtg ccc cag gcc agc caa gta ccc cct        937
Ile Phe Ile Tyr His Gly Glu Val Pro Gln Ala Ser Gln Val Pro Pro
        255                 260                 265

ccc agt gga ttc act gtc cac ggc ctc cca aca tct cca gac cgg cca        985
Pro Ser Gly Phe Thr Val His Gly Leu Pro Thr Ser Pro Asp Arg Pro
    270                 275                 280

ggc tcc acc agc ccc ttc gct cca tca gcc act gac ctg ccc agc atg       1033
Gly Ser Thr Ser Pro Phe Ala Pro Ser Ala Thr Asp Leu Pro Ser Met
285                 290                 295                 300

cct gaa cct gcc ctg acc tcc cga gca aac atg aca gag cac aag acg       1081
Pro Glu Pro Ala Leu Thr Ser Arg Ala Asn Met Thr Glu His Lys Thr
                305                 310                 315

tcc ccc acc caa tgc ccg gca gct gga gag gtc tcc aac aag ctt cca       1129
Ser Pro Thr Gln Cys Pro Ala Ala Gly Glu Val Ser Asn Lys Leu Pro
            320                 325                 330

aaa tgg cct gag ccg gtg gag cag ttc tac cgc tca ctg cag gac acg       1177
Lys Trp Pro Glu Pro Val Glu Gln Phe Tyr Arg Ser Leu Gln Asp Thr
        335                 340                 345

tat ggt gcc gag ccc gca ggc ccg gat ggc atc cta gtg gag gtg gat       1225
Tyr Gly Ala Glu Pro Ala Gly Pro Asp Gly Ile Leu Val Glu Val Asp
    350                 355                 360

ctg gtg cag gcc agg ctg gag agg agc agc agc aag agc ctg gag cgg       1273
Leu Val Gln Ala Arg Leu Glu Arg Ser Ser Ser Lys Ser Leu Glu Arg
365                 370                 375                 380

gaa ctg gcc acc ccg gac tgg gca gaa cgg cag ctg gcc caa gga ggc       1321
Glu Leu Ala Thr Pro Asp Trp Ala Glu Arg Gln Leu Ala Gln Gly Gly
                385                 390                 395

ctg gct gag gtg ctg ttg gct gcc aag gag cac cgg cgg ccg cgt gag       1369
Leu Ala Glu Val Leu Leu Ala Ala Lys Glu His Arg Arg Pro Arg Glu
            400                 405                 410

aca cga gtg att gct gtg ctg ggc aaa gct ggt cag ggc aag agc tat       1417
Thr Arg Val Ile Ala Val Leu Gly Lys Ala Gly Gln Gly Lys Ser Tyr
        415                 420                 425

tgg gct ggg gca gtg agc cgg gcc tgg gct tgt ggc cgg ctt ccc cag       1465
Trp Ala Gly Ala Val Ser Arg Ala Trp Ala Cys Gly Arg Leu Pro Gln
    430                 435                 440

tac gac ttt gtc ttc tct gtc ccc tgc cat tgc ttg aac cgt ccg ggg       1513
Tyr Asp Phe Val Phe Ser Val Pro Cys His Cys Leu Asn Arg Pro Gly
445                 450                 455                 460

gat gcc tat ggc ctg cag gat ctg ctc ttc tcc ctg ggc cca cag cca       1561
Asp Ala Tyr Gly Leu Gln Asp Leu Leu Phe Ser Leu Gly Pro Gln Pro
                465                 470                 475

ctc gtg gcg gcc gat gag gtt ttc agc cac atc ttg aag aga cct gac       1609
Leu Val Ala Ala Asp Glu Val Phe Ser His Ile Leu Lys Arg Pro Asp
            480                 485                 490

cgc gtt ctg ctc atc cta gac ggc ttc gag gag ctg gaa gcg caa gat       1657
Arg Val Leu Leu Ile Leu Asp Gly Phe Glu Glu Leu Glu Ala Gln Asp
        495                 500                 505

ggc ttc ctg cac agc acg tgc gga ccg gca ccg gcg gag ccc tgc tcc       1705
Gly Phe Leu His Ser Thr Cys Gly Pro Ala Pro Ala Glu Pro Cys Ser
    510                 515                 520
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ctc cgg ggg ctg ctg gcc ggc ctt ttc cag aag aag ctg ctc cga ggt       1753
Leu Arg Gly Leu Leu Ala Gly Leu Phe Gln Lys Lys Leu Leu Arg Gly
525                 530                 535                 540

tgc acc ctc ctc ctc aca gcc cgg ccc cgg ggc cgc ctg gtc cag agc       1801
Cys Thr Leu Leu Leu Thr Ala Arg Pro Arg Gly Arg Leu Val Gln Ser
                545                 550                 555

ctg agc aag gcc gac gcc cta ttt gag ctg tcc ggc ttc tcc atg gag       1849
Leu Ser Lys Ala Asp Ala Leu Phe Glu Leu Ser Gly Phe Ser Met Glu
            560                 565                 570

cag gcc cag gca tac gtg atg cgc tac ttt gag agc tca ggg atg aca       1897
Gln Ala Gln Ala Tyr Val Met Arg Tyr Phe Glu Ser Ser Gly Met Thr
        575                 580                 585

gag cac caa gac aga gcc ctg acg ctc ctc cgg gac cgg cca ctt ctt       1945
Glu His Gln Asp Arg Ala Leu Thr Leu Leu Arg Asp Arg Pro Leu Leu
    590                 595                 600

ctc agt cac agc cac agc cct act ttg tgc cgg gca gtg tgc cag ctc       1993
Leu Ser His Ser His Ser Pro Thr Leu Cys Arg Ala Val Cys Gln Leu
605                 610                 615                 620

tca gag gcc ctg ctg gag ctt ggg gag gac gcc aag ctg ccc tcc acg       2041
Ser Glu Ala Leu Leu Glu Leu Gly Glu Asp Ala Lys Leu Pro Ser Thr
                625                 630                 635

ctc acg gga ctc tat gtc ggc ctg ctg ggc cgt gca gcc ctc gac agc       2089
Leu Thr Gly Leu Tyr Val Gly Leu Leu Gly Arg Ala Ala Leu Asp Ser
            640                 645                 650

ccc ccc ggg gcc ctg gca gag ctg gcc aag ctg gcc tgg gag ctg ggc       2137
Pro Pro Gly Ala Leu Ala Glu Leu Ala Lys Leu Ala Trp Glu Leu Gly
        655                 660                 665

cgc aga cat caa agt acc cta cag gag gac cag ttc cca tcc gca gac       2185
Arg Arg His Gln Ser Thr Leu Gln Glu Asp Gln Phe Pro Ser Ala Asp
    670                 675                 680

gtg agg acc tgg gcg atg gcc aaa ggc tta gtc caa cac cca ccg cgg       2233
Val Arg Thr Trp Ala Met Ala Lys Gly Leu Val Gln His Pro Pro Arg
685                 690                 695                 700

gcc gca gag tcc gag ctg gcc ttc ccc agc ttc ctc ctg caa tgc ttc       2281
Ala Ala Glu Ser Glu Leu Ala Phe Pro Ser Phe Leu Leu Gln Cys Phe
                705                 710                 715

ctg ggg gcc ctg tgg ctg gct ctg agt ggc gaa atc aag gac aag gag       2329
Leu Gly Ala Leu Trp Leu Ala Leu Ser Gly Glu Ile Lys Asp Lys Glu
            720                 725                 730

ctc ccg cag tac cta gca ttg acc cca agg aag aag agg ccc tat gac       2377
Leu Pro Gln Tyr Leu Ala Leu Thr Pro Arg Lys Lys Arg Pro Tyr Asp
        735                 740                 745

aac tgg ctg gag ggc gtg cca cgc ttt ctg gct ggg ctg atc ttc cag       2425
Asn Trp Leu Glu Gly Val Pro Arg Phe Leu Ala Gly Leu Ile Phe Gln
    750                 755                 760

cct ccc gcc cgc tgc ctg gga gcc cta ctc ggg cca tcg gcg gct gcc       2473
Pro Pro Ala Arg Cys Leu Gly Ala Leu Leu Gly Pro Ser Ala Ala Ala
765                 770                 775                 780

tcg gtg gac agg aag cag aag gtg ctt gcg agg tac ctg aag cgg ctg       2521
Ser Val Asp Arg Lys Gln Lys Val Leu Ala Arg Tyr Leu Lys Arg Leu
                785                 790                 795
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cag ccg ggg aca ctg cgg gcg cgg cag ctg ctg gag ctg ctg cac tgc       2569
Gln Pro Gly Thr Leu Arg Ala Arg Gln Leu Leu Glu Leu Leu His Cys
            800                 805                 810

gcc cac gag gcc gag gag gct gga att tgg cag cac gtg gta cag gag       2617
Ala His Glu Ala Glu Glu Ala Gly Ile Trp Gln His Val Val Gln Glu
        815                 820                 825

ctc ccc ggc cgc ctc tct ttt ctg ggc acc cgc ctc acg cct cct gat       2665
Leu Pro Gly Arg Leu Ser Phe Leu Gly Thr Arg Leu Thr Pro Pro Asp
    830                 835                 840

gca cat gta ctg ggc aag gcc ttg gag gcg gcg ggc caa gac ttc tcc       2713
Ala His Val Leu Gly Lys Ala Leu Glu Ala Ala Gly Gln Asp Phe Ser
845                 850                 855                 860

ctg gac ctc cgc agc act ggc att tgc ccc tct gga ttg ggg agc ctc       2761
Leu Asp Leu Arg Ser Thr Gly Ile Cys Pro Ser Gly Leu Gly Ser Leu
                865                 870                 875

gtg gga ctc agc tgt gtc acc cgt ttc agg gct gcc ttg agc gac acg       2809
Val Gly Leu Ser Cys Val Thr Arg Phe Arg Ala Ala Leu Ser Asp Thr
            880                 885                 890

gtg gcg ctg tgg gag tcc ctg cag cag cat ggg gag acc aag cta ctt       2857
Val Ala Leu Trp Glu Ser Leu Gln Gln His Gly Glu Thr Lys Leu Leu
        895                 900                 905

cag gca gca gag gag aag ttc acc atc gag cct ttc aaa gcc aag tcc       2905
Gln Ala Ala Glu Glu Lys Phe Thr Ile Glu Pro Phe Lys Ala Lys Ser
    910                 915                 920

ctg aag gat gtg gaa gac ctg gga aag ctt gtg cag act cag agg acg       2953
Leu Lys Asp Val Glu Asp Leu Gly Lys Leu Val Gln Thr Gln Arg Thr
925                 930                 935                 940

aga agt tcc tcg gaa gac aca gct ggg gag ctc cct gct gtt cgg gac       3001
Arg Ser Ser Ser Glu Asp Thr Ala Gly Glu Leu Pro Ala Val Arg Asp
                945                 950                 955

cta aag aaa ctg gag ttt gcg ctg ggc cct gtc tca ggc ccc cag gct       3049
Leu Lys Lys Leu Glu Phe Ala Leu Gly Pro Val Ser Gly Pro Gln Ala
            960                 965                 970

ttc ccc aaa ctg gtg cgg atc ctc acg gcc ttt tcc tcc ctg cag cat       3097
Phe Pro Lys Leu Val Arg Ile Leu Thr Ala Phe Ser Ser Leu Gln His
        975                 980                 985

ctg gac ctg gat gcg ctg agt gag aac aag atc ggg  gac gag ggt gtc       3145
Leu Asp Leu Asp Ala Leu Ser Glu Asn Lys Ile Gly  Asp Glu Gly Val
    990                 995                 1000

tcg  cag ctc tca gcc acc  ttc ccc cag ctg aag  tcc ttg gaa acc       3190
Ser  Gln Leu Ser Ala Thr  Phe Pro Gln Leu Lys  Ser Leu Glu Thr
1005                1010                1015

ctc  aat ctg tcc cag aac  aac atc act gac ctg  ggt gcc tac aaa       3235
Leu  Asn Leu Ser Gln Asn  Asn Ile Thr Asp Leu  Gly Ala Tyr Lys
1020                1025                1030

ctc  gcc gag gcc ctg cct  tcg ctc gct gca tcc  ctg ctc agg cta       3280
Leu  Ala Glu Ala Leu Pro  Ser Leu Ala Ala Ser  Leu Leu Arg Leu
1035                1040                1045

agc  ttg tac aat aac tgc  atc tgc gac gtg gga  gcc gag agc ttg       3325
Ser  Leu Tyr Asn Asn Cys  Ile Cys Asp Val Gly  Ala Glu Ser Leu
1050                1055                1060
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gct  cgt gtg ctt ccg gac  atg gtg tcc ctc cgg  gtg atg gac gtc        3370
Ala  Arg Val Leu Pro Asp  Met Val Ser Leu Arg  Val Met Asp Val
1065                 1070                 1075

cag  tac aac aag ttc acg  gct gcc ggg gcc cag  cag ctc gct gcc        3415
Gln  Tyr Asn Lys Phe Thr  Ala Ala Gly Ala Gln  Gln Leu Ala Ala
1080                 1085                 1090

agc  ctt cgg agg tgt cct  cat gtg gag acg ctg  gcg atg tgg acg        3460
Ser  Leu Arg Arg Cys Pro  His Val Glu Thr Leu  Ala Met Trp Thr
1095                 1100                 1105

ccc  acc atc cca ttc agt  gtc cag gaa cac ctg  caa caa cag gat        3505
Pro  Thr Ile Pro Phe Ser  Val Gln Glu His Leu  Gln Gln Gln Asp
1110                 1115                 1120

tca  cgg atc agc ctg aga  tga tcccagctgt gctctggaca ggcatgttct        3556
Ser  Arg Ile Ser Leu Arg
1125                 1130

ctgaggacac taaccacgct ggaccttgaa ctgggtactt gtggacacag ctcttctcca     3616

ggctgtatcc catgagcctc agcatcctgg cacccggccc ctgctggttc agggttggcc     3676

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ggctccttta gcgcccagtt gggtggatgc ctggtggcag ctgcggtcca cccaggagcc     3796

ccgaggcctt ctctgaagga cattgcggac agccacggcc aggccagagg gagtgacaga     3856

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aaacaacact cacattta                                                   4654


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Met Arg Cys Leu Ala Pro Arg Pro Ala Gly Ser Tyr Leu Ser Glu Pro
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Gln Gly Ser Ser Gln Cys Ala Thr Met Glu Leu Gly Pro Leu Glu Gly
            20                  25                  30

Gly Tyr Leu Glu Leu Leu Asn Ser Asp Ala Asp Pro Leu Cys Leu Tyr
        35                  40                  45

His Phe Tyr Asp Gln Met Asp Leu Ala Gly Glu Glu Glu Ile Glu Leu
    50                  55                  60

Tyr Ser Glu Pro Asp Thr Asp Thr Ile Asn Cys Asp Gln Phe Ser Arg
65                  70                  75                  80

Leu Leu Cys Asp Met Glu Gly Asp Glu Glu Thr Arg Glu Ala Tyr Ala
                85                  90                  95

Asn Ile Ala Glu Leu Asp Gln Tyr Val Phe Gln Asp Ser Gln Leu Glu
            100                 105                 110

Gly Leu Ser Lys Asp Ile Phe Lys His Ile Gly Pro Asp Glu Val Ile
        115                 120                 125

Gly Glu Ser Met Glu Met Pro Ala Glu Val Gly Gln Lys Ser Gln Lys
    130                 135                 140

Arg Pro Phe Pro Glu Glu Leu Pro Ala Asp Leu Lys His Trp Lys Pro
145                 150                 155                 160

Ala Glu Pro Pro Thr Val Val Thr Gly Ser Leu Leu Val Gly Pro Val
                165                 170                 175

Ser Asp Cys Ser Thr Leu Pro Cys Leu Pro Leu Pro Ala Leu Phe Asn
            180                 185                 190

Gln Glu Pro Ala Ser Gly Gln Met Arg Leu Glu Lys Thr Asp Gln Ile
        195                 200                 205

Pro Met Pro Phe Ser Ser Ser Ser Leu Ser Cys Leu Asn Leu Pro Glu
    210                 215                 220

Gly Pro Ile Gln Phe Val Pro Thr Ile Ser Thr Leu Pro His Gly Leu
225                 230                 235                 240

Trp Gln Ile Ser Glu Ala Gly Thr Gly Val Ser Ser Ile Phe Ile Tyr
                245                 250                 255

His Gly Glu Val Pro Gln Ala Ser Gln Val Pro Pro Pro Ser Gly Phe
            260                 265                 270

Thr Val His Gly Leu Pro Thr Ser Pro Asp Arg Pro Gly Ser Thr Ser
        275                 280                 285
```

```
Pro Phe Ala Pro Ser Ala Thr Asp Leu Pro Ser Met Pro Glu Pro Ala
    290                 295                 300

Leu Thr Ser Arg Ala Asn Met Thr Glu His Lys Thr Ser Pro Thr Gln
305                 310                 315                 320

Cys Pro Ala Ala Gly Glu Val Ser Asn Lys Leu Pro Lys Trp Pro Glu
                325                 330                 335

Pro Val Glu Gln Phe Tyr Arg Ser Leu Gln Asp Thr Tyr Gly Ala Glu
            340                 345                 350

Pro Ala Gly Pro Asp Gly Ile Leu Val Glu Val Asp Leu Val Gln Ala
        355                 360                 365

Arg Leu Glu Arg Ser Ser Ser Lys Ser Leu Glu Arg Glu Leu Ala Thr
    370                 375                 380

Pro Asp Trp Ala Glu Arg Gln Leu Ala Gln Gly Gly Leu Ala Glu Val
385                 390                 395                 400

Leu Leu Ala Ala Lys Glu His Arg Arg Pro Arg Glu Thr Arg Val Ile
                405                 410                 415

Ala Val Leu Gly Lys Ala Gly Gln Gly Lys Ser Tyr Trp Ala Gly Ala
            420                 425                 430

Val Ser Arg Ala Trp Ala Cys Gly Arg Leu Pro Gln Tyr Asp Phe Val
        435                 440                 445

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

Leu Gln Asp Leu Leu Phe Ser Leu Gly Pro Gln Pro Leu Val Ala Ala
465                 470                 475                 480

Asp Glu Val Phe Ser His Ile Leu Lys Arg Pro Asp Arg Val Leu Leu
                485                 490                 495

Ile Leu Asp Gly Phe Glu Glu Leu Glu Ala Gln Asp Gly Phe Leu His
            500                 505                 510

Ser Thr Cys Gly Pro Ala Pro Ala Glu Pro Cys Ser Leu Arg Gly Leu
        515                 520                 525

Leu Ala Gly Leu Phe Gln Lys Lys Leu Leu Arg Gly Cys Thr Leu Leu
    530                 535                 540

Leu Thr Ala Arg Pro Arg Gly Arg Leu Val Gln Ser Leu Ser Lys Ala
545                 550                 555                 560
```

```
Asp Ala Leu Phe Glu Leu Ser Gly Phe Ser Met Glu Gln Ala Gln Ala
                565                 570                 575

Tyr Val Met Arg Tyr Phe Glu Ser Ser Gly Met Thr Glu His Gln Asp
            580                 585                 590

Arg Ala Leu Thr Leu Leu Arg Asp Arg Pro Leu Leu Leu Ser His Ser
        595                 600                 605

His Ser Pro Thr Leu Cys Arg Ala Val Cys Gln Leu Ser Glu Ala Leu
    610                 615                 620

Leu Glu Leu Gly Glu Asp Ala Lys Leu Pro Ser Thr Leu Thr Gly Leu
625                 630                 635                 640

Tyr Val Gly Leu Leu Gly Arg Ala Ala Leu Asp Ser Pro Pro Gly Ala
                645                 650                 655

Leu Ala Glu Leu Ala Lys Leu Ala Trp Glu Leu Gly Arg Arg His Gln
            660                 665                 670

Ser Thr Leu Gln Glu Asp Gln Phe Pro Ser Ala Asp Val Arg Thr Trp
        675                 680                 685

Ala Met Ala Lys Gly Leu Val Gln His Pro Pro Arg Ala Ala Glu Ser
    690                 695                 700

Glu Leu Ala Phe Pro Ser Phe Leu Leu Gln Cys Phe Leu Gly Ala Leu
705                 710                 715                 720

Trp Leu Ala Leu Ser Gly Glu Ile Lys Asp Lys Glu Leu Pro Gln Tyr
                725                 730                 735

Leu Ala Leu Thr Pro Arg Lys Lys Arg Pro Tyr Asp Asn Trp Leu Glu
            740                 745                 750

Gly Val Pro Arg Phe Leu Ala Gly Leu Ile Phe Gln Pro Pro Ala Arg
        755                 760                 765

Cys Leu Gly Ala Leu Leu Gly Pro Ser Ala Ala Ala Ser Val Asp Arg
    770                 775                 780

Lys Gln Lys Val Leu Ala Arg Tyr Leu Lys Arg Leu Gln Pro Gly Thr
785                 790                 795                 800

Leu Arg Ala Arg Gln Leu Leu Glu Leu Leu His Cys Ala His Glu Ala
                805                 810                 815

Glu Glu Ala Gly Ile Trp Gln His Val Val Gln Glu Leu Pro Gly Arg
            820                 825                 830
```

```
Leu Ser Phe Leu Gly Thr Arg Leu Thr Pro Pro Asp Ala His Val Leu
        835                 840                 845

Gly Lys Ala Leu Glu Ala Ala Gly Gln Asp Phe Ser Leu Asp Leu Arg
    850                 855                 860

Ser Thr Gly Ile Cys Pro Ser Gly Leu Gly Ser Leu Val Gly Leu Ser
865                 870                 875                 880

Cys Val Thr Arg Phe Arg Ala Ala Leu Ser Asp Thr Val Ala Leu Trp
                885                 890                 895

Glu Ser Leu Gln Gln His Gly Glu Thr Lys Leu Leu Gln Ala Ala Glu
            900                 905                 910

Glu Lys Phe Thr Ile Glu Pro Phe Lys Ala Lys Ser Leu Lys Asp Val
        915                 920                 925

Glu Asp Leu Gly Lys Leu Val Gln Thr Gln Arg Thr Arg Ser Ser Ser
    930                 935                 940

Glu Asp Thr Ala Gly Glu Leu Pro Ala Val Arg Asp Leu Lys Lys Leu
945                 950                 955                 960

Glu Phe Ala Leu Gly Pro Val Ser Gly Pro Gln Ala Phe Pro Lys Leu
                965                 970                 975

Val Arg Ile Leu Thr Ala Phe Ser Ser Leu Gln His Leu Asp Leu Asp
            980                 985                 990

Ala Leu Ser Glu Asn Lys Ile Gly  Asp Glu Gly Val Ser  Gln Leu Ser
        995                 1000                1005

Ala Thr  Phe Pro Gln Leu Lys  Ser Leu Glu Thr Leu  Asn Leu Ser
    1010                1015                1020

Gln Asn  Asn Ile Thr Asp Leu  Gly Ala Tyr Lys Leu  Ala Glu Ala
    1025                1030                1035

Leu Pro  Ser Leu Ala Ala Ser  Leu Leu Arg Leu Ser  Leu Tyr Asn
    1040                1045                1050

Asn Cys  Ile Cys Asp Val Gly  Ala Glu Ser Leu Ala  Arg Val Leu
    1055                1060                1065

Pro Asp  Met Val Ser Leu Arg  Val Met Asp Val Gln  Tyr Asn Lys
    1070                1075                1080

Phe Thr  Ala Ala Gly Ala Gln  Gln Leu Ala Ala Ser  Leu Arg Arg
    1085                1090                1095
```

```
Cys Pro  His Val Glu Thr Leu  Ala Met Trp Thr Pro  Thr Ile Pro
    1100                1105                1110


Phe Ser  Val Gln Glu His Leu  Gln Gln Gln Asp Ser  Arg Ile Ser
    1115                1120                1125


Leu Arg
    1130


<210>  36
<211>  1697
<212>  DNA
<213>  Homo sapiens


<220>
<221>  CDS
<222>  (108)..(890)

<400>  36
atttccagtg ctagaggccc acagtttcag tctcatctgc ctccactcgg cctcagttcc       60

tcatcactgt tcctgtgctc acagtcatca attatagacc ccacaac atg cgc cct        116
                                                 Met Arg Pro
                                                 1

gaa gac aga atg ttc cat atc aga gct gtg atc ttg aga gcc ctc tcc        164
Glu Asp Arg Met Phe His Ile Arg Ala Val Ile Leu Arg Ala Leu Ser
    5                   10                  15

ttg gct ttc ctg ctg agt ctc cga gga gct ggg gcc atc aag gcg gac        212
Leu Ala Phe Leu Leu Ser Leu Arg Gly Ala Gly Ala Ile Lys Ala Asp
20                  25                  30                  35

cat gtg tca act tat gcc gcg ttt gta cag acg cat aga cca aca ggg        260
His Val Ser Thr Tyr Ala Ala Phe Val Gln Thr His Arg Pro Thr Gly
                40                  45                  50

gag ttt atg ttt gaa ttt gat gaa gat gag atg ttc tat gtg gat ctg        308
Glu Phe Met Phe Glu Phe Asp Glu Asp Glu Met Phe Tyr Val Asp Leu
            55                  60                  65

gac aag aag gag acc gtc tgg cat ctg gag gag ttt ggc caa gcc ttt        356
Asp Lys Lys Glu Thr Val Trp His Leu Glu Glu Phe Gly Gln Ala Phe
        70                  75                  80

tcc ttt gag gct cag ggc ggg ctg gct aac att gct ata ttg aac aac        404
Ser Phe Glu Ala Gln Gly Gly Leu Ala Asn Ile Ala Ile Leu Asn Asn
    85                  90                  95

aac ttg aat acc ttg atc cag cgt tcc aac cac act cag gcc acc aac        452
Asn Leu Asn Thr Leu Ile Gln Arg Ser Asn His Thr Gln Ala Thr Asn
100                 105                 110                 115

gat ccc cct gag gtg acc gtg ttt ccc aag gag cct gtg gag ctg ggc        500
Asp Pro Pro Glu Val Thr Val Phe Pro Lys Glu Pro Val Glu Leu Gly
                120                 125                 130

cag ccc aac acc ctc atc tgc cac att gac aag ttc ttc cca cca gtg        548
Gln Pro Asn Thr Leu Ile Cys His Ile Asp Lys Phe Phe Pro Pro Val
            135                 140                 145

ctc aac gtc acg tgg ctg tgc aac ggg gag ctg gtc act gag ggt gtc        596
```

```
Leu Asn Val Thr Trp Leu Cys Asn Gly Glu Leu Val Thr Glu Gly Val
        150                 155                 160

gct gag agc ctc ttc ctg ccc aga aca gat tac agc ttc cac aag ttc        644
Ala Glu Ser Leu Phe Leu Pro Arg Thr Asp Tyr Ser Phe His Lys Phe
    165                 170                 175

cat tac ctg acc ttt gtg ccc tca gca gag gac ttc tat gac tgc agg        692
His Tyr Leu Thr Phe Val Pro Ser Ala Glu Asp Phe Tyr Asp Cys Arg
180                 185                 190                 195

gtg gag cac tgg ggc ttg gac cag ccg ctc ctc aag cac tgg gag gcc        740
Val Glu His Trp Gly Leu Asp Gln Pro Leu Leu Lys His Trp Glu Ala
                200                 205                 210

caa gag cca atc cag atg cct gag aca acg gag act gtg ctc tgt gcc        788
Gln Glu Pro Ile Gln Met Pro Glu Thr Thr Glu Thr Val Leu Cys Ala
            215                 220                 225

ctg ggc ctg gtg ctg ggc cta gtc ggc atc atc gtg ggc acc gtc ctc        836
Leu Gly Leu Val Leu Gly Leu Val Gly Ile Ile Val Gly Thr Val Leu
        230                 235                 240

atc ata aag tct ctg cgt tct ggc cat gac ccc cgg gcc cag ggg acc        884
Ile Ile Lys Ser Leu Arg Ser Gly His Asp Pro Arg Ala Gln Gly Thr
    245                 250                 255

ctg tga aatactgtaa aggtgacaaa atatctgaac agaagaggac ttaggagaga        940
Leu
260

tctgaactcc agctgcccta caaactccat ctcagctttt cttctcactt catgtgaaaa    1000

ctactccagt ggctgactga attgctgacc cttcaagctc tgtccttatc cattacctca    1060

aagcagtcat tccttagtaa agtttccaac aaatagaaat taatgacact ttggtagcac    1120

taatatggag attatccttt cattgagcct tttatcctct gttctccttt gaagaacccc    1180

tcactgtcac cttcccgaga ataccctaag accaataaat acttcagtat ttcagagcgg    1240

ggagactctg agtcattctt actggaagtc taggaccagg tcacatgtga atactatttc    1300

ttgaaggtgt ggtttcaacc tctgttgccg atgtggttac taaaggttct gatcccactt    1360

gaacggaaag gtctgaggat attgattcag tcctgggttt ttccctaact acaggatagg    1420

gtggggtaga gaaaggatat ttgggggaaa ttttacttgg atgaagattt tcttggatgt    1480

agtttgaaga ctgcagtgtt tgaagtctct gagggaagag atttggtctg tctggatcaa    1540

gatttcaggc agattaggat tccattcaca gcccctgagc ttccttccca aggctgtatt    1600

gtaattatag caatatttca tggaggattt ttctacatga taaactaaga gccaagaaat    1660

aaaattttta aaatgcccta aaaaaaaaaa aaaaaaa                             1697


<210>  37
<211>  260
<212>  PRT
<213>  Homo sapiens

<400>  37

Met Arg Pro Glu Asp Arg Met Phe His Ile Arg Ala Val Ile Leu Arg
1               5                   10                  15
```

```
Ala Leu Ser Leu Ala Phe Leu Leu Ser Leu Arg Gly Ala Gly Ala Ile
            20                  25                  30

Lys Ala Asp His Val Ser Thr Tyr Ala Ala Phe Val Gln Thr His Arg
        35                  40                  45

Pro Thr Gly Glu Phe Met Phe Glu Phe Asp Glu Asp Glu Met Phe Tyr
    50                  55                  60

Val Asp Leu Asp Lys Lys Glu Thr Val Trp His Leu Glu Glu Phe Gly
65                  70                  75                  80

Gln Ala Phe Ser Phe Glu Ala Gln Gly Gly Leu Ala Asn Ile Ala Ile
                85                  90                  95

Leu Asn Asn Asn Leu Asn Thr Leu Ile Gln Arg Ser Asn His Thr Gln
            100                 105                 110

Ala Thr Asn Asp Pro Pro Glu Val Thr Val Phe Pro Lys Glu Pro Val
        115                 120                 125

Glu Leu Gly Gln Pro Asn Thr Leu Ile Cys His Ile Asp Lys Phe Phe
    130                 135                 140

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

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

His Lys Phe His Tyr Leu Thr Phe Val Pro Ser Ala Glu Asp Phe Tyr
            180                 185                 190

Asp Cys Arg Val Glu His Trp Gly Leu Asp Gln Pro Leu Leu Lys His
        195                 200                 205

Trp Glu Ala Gln Glu Pro Ile Gln Met Pro Glu Thr Thr Glu Thr Val
    210                 215                 220

Leu Cys Ala Leu Gly Leu Val Leu Gly Leu Val Gly Ile Ile Val Gly
225                 230                 235                 240

Thr Val Leu Ile Ile Lys Ser Leu Arg Ser Gly His Asp Pro Arg Ala
                245                 250                 255

Gln Gly Thr Leu
            260
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<210> 38

<211> 777
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)..(777)

<400> 38

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atg atg gtt ctg cag gtt tct gcg gcc ccc cgg aca gtg gct ctg acg          48
Met Met Val Leu Gln Val Ser Ala Ala Pro Arg Thr Val Ala Leu Thr
1               5                   10                  15

gcg tta ctg atg gtg ctg ctc aca tct gtg gtc cag ggc agg gcc act          96
Ala Leu Leu Met Val Leu Leu Thr Ser Val Val Gln Gly Arg Ala Thr
            20                  25                  30

cca gag aat tac gtg tac cag gga cgg cag gaa tgc tac gcg ttt aat         144
Pro Glu Asn Tyr Val Tyr Gln Gly Arg Gln Glu Cys Tyr Ala Phe Asn
        35                  40                  45

ggg aca cag cgc ttc ctg gag aga tac atc tac aac cgg gag gag tac         192
Gly Thr Gln Arg Phe Leu Glu Arg Tyr Ile Tyr Asn Arg Glu Glu Tyr
    50                  55                  60

gcg cgc ttc gac agc gac gtg ggg gag ttc cgg gcg gtg acg gag ctg         240
Ala Arg Phe Asp Ser Asp Val Gly Glu Phe Arg Ala Val Thr Glu Leu
65                  70                  75                  80

ggg cgg cct gct gcg gag tac tgg aac agc cag aag gac atc ctg gag         288
Gly Arg Pro Ala Ala Glu Tyr Trp Asn Ser Gln Lys Asp Ile Leu Glu
                85                  90                  95

gag aag cgg gca gtg ccg gac agg gta tgc aga cac aac tac gag ctg         336
Glu Lys Arg Ala Val Pro Asp Arg Val Cys Arg His Asn Tyr Glu Leu
            100                 105                 110

gac gag gcc gtg acc ctg cag cgc cga gtc cag cct aag gtg aac gtt         384
Asp Glu Ala Val Thr Leu Gln Arg Arg Val Gln Pro Lys Val Asn Val
        115                 120                 125

tcc ccc tcc aag aag ggg ccc ctg cag cac cac aac ctg ctt gtc tgc         432
Ser Pro Ser Lys Lys Gly Pro Leu Gln His His Asn Leu Leu Val Cys
    130                 135                 140

cac gtg aca gat ttc tac cca ggc agc att caa gtc cga tgg ttc ctg         480
His Val Thr Asp Phe Tyr Pro Gly Ser Ile Gln Val Arg Trp Phe Leu
145                 150                 155                 160

aat gga cag gag gaa aca gct ggg gtc gtg tcc acc aac ctg atc cgt         528
Asn Gly Gln Glu Glu Thr Ala Gly Val Val Ser Thr Asn Leu Ile Arg
                165                 170                 175

aat gga gac tgg acc ttc cag atc ctg gtg atg ctg gaa atg acc ccc         576
Asn Gly Asp Trp Thr Phe Gln Ile Leu Val Met Leu Glu Met Thr Pro
            180                 185                 190

cag cag gga gac gtc tac atc tgc caa gtg gag cac acc agc ctg gac         624
Gln Gln Gly Asp Val Tyr Ile Cys Gln Val Glu His Thr Ser Leu Asp
        195                 200                 205

agt cct gtc acc gtg gag tgg aag gca cag tct gat tct gcc cag agt         672
Ser Pro Val Thr Val Glu Trp Lys Ala Gln Ser Asp Ser Ala Gln Ser
    210                 215                 220

aag aca ttg acg gga gct ggg ggc ttc gtg ctg ggg ctc atc atc tgt         720
Lys Thr Leu Thr Gly Ala Gly Gly Phe Val Leu Gly Leu Ile Ile Cys
```

225 230 235 240

gga gtg ggc atc ttc atg cac agg agg agc aag aaa gtt caa cga gga 768
Gly Val Gly Ile Phe Met His Arg Arg Ser Lys Lys Val Gln Arg Gly
245 250 255

tct gca taa 777
Ser Ala

<210> 39
<211> 258
<212> PRT
<213> Homo sapiens

<400> 39

Met Met Val Leu Gln Val Ser Ala Ala Pro Arg Thr Val Ala Leu Thr
1 5 10 15

Ala Leu Leu Met Val Leu Leu Thr Ser Val Val Gln Gly Arg Ala Thr
20 25 30

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

Gly Thr Gln Arg Phe Leu Glu Arg Tyr Ile Tyr Asn Arg Glu Glu Tyr
50 55 60

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

Gly Arg Pro Ala Ala Glu Tyr Trp Asn Ser Gln Lys Asp Ile Leu Glu
85 90 95

Glu Lys Arg Ala Val Pro Asp Arg Val Cys Arg His Asn Tyr Glu Leu
100 105 110

Asp Glu Ala Val Thr Leu Gln Arg Arg Val Gln Pro Lys Val Asn Val
115 120 125

Ser Pro Ser Lys Lys Gly Pro Leu Gln His His Asn Leu Leu Val Cys
130 135 140

His Val Thr Asp Phe Tyr Pro Gly Ser Ile Gln Val Arg Trp Phe Leu
145 150 155 160

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

Asn Gly Asp Trp Thr Phe Gln Ile Leu Val Met Leu Glu Met Thr Pro
180 185 190

Gln Gln Gly Asp Val Tyr Ile Cys Gln Val Glu His Thr Ser Leu Asp
195 200 205

```
Ser Pro Val Thr Val Glu Trp Lys Ala Gln Ser Asp Ser Ala Gln Ser
    210                 215                 220

Lys Thr Leu Thr Gly Ala Gly Gly Phe Val Leu Gly Leu Ile Ile Cys
225                 230                 235                 240

Gly Val Gly Ile Phe Met His Arg Arg Ser Lys Lys Val Gln Arg Gly
                245                 250                 255

Ser Ala
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<210> 40
<211> 768
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)..(768)

<400> 40

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atg atc cta aac aaa gct ctg ctg ctg ggg gcc ctc gct ctg acc acc          48
Met Ile Leu Asn Lys Ala Leu Leu Leu Gly Ala Leu Ala Leu Thr Thr
1               5                   10                  15

gtg atg agc ccc tgt gga ggt gaa gac att gtg gct gac cac gtt gcc          96
Val Met Ser Pro Cys Gly Gly Glu Asp Ile Val Ala Asp His Val Ala
            20                  25                  30

tct tgt ggt gta aac ttg tac cag ttt tac ggt ccc tct ggc cag tac         144
Ser Cys Gly Val Asn Leu Tyr Gln Phe Tyr Gly Pro Ser Gly Gln Tyr
        35                  40                  45

acc cat gaa ttt gat gga gat gag gag ttc tac gtg gac ctg gag agg         192
Thr His Glu Phe Asp Gly Asp Glu Glu Phe Tyr Val Asp Leu Glu Arg
    50                  55                  60

aag gag act gcc tgg cgg tgg cct gag ttc agc aaa ttt gga ggt ttt         240
Lys Glu Thr Ala Trp Arg Trp Pro Glu Phe Ser Lys Phe Gly Gly Phe
65                  70                  75                  80

gac ccg cag ggt gca ctg aga aac atg gct gtg gca aaa cac aac ttg         288
Asp Pro Gln Gly Ala Leu Arg Asn Met Ala Val Ala Lys His Asn Leu
                85                  90                  95

aac atc atg att aaa cgc tac aac tct acc gct gct acc aat gag gtt         336
Asn Ile Met Ile Lys Arg Tyr Asn Ser Thr Ala Ala Thr Asn Glu Val
            100                 105                 110

cct gag gtc aca gtg ttt tcc aag tct ccc gtg aca ctg ggt cag ccc         384
Pro Glu Val Thr Val Phe Ser Lys Ser Pro Val Thr Leu Gly Gln Pro
        115                 120                 125

aac acc ctc att tgt ctt gtg gac aac atc ttt cct cct gtg gtc aac         432
Asn Thr Leu Ile Cys Leu Val Asp Asn Ile Phe Pro Pro Val Val Asn
    130                 135                 140

atc aca tgg ctg agc aat ggg cag tca gtc aca gaa ggt gtt tct gag         480
```

```
Ile Thr Trp Leu Ser Asn Gly Gln Ser Val Thr Glu Gly Val Ser Glu
145                 150                 155                 160

acc agc ttc ctc tcc aag agt gat cat tcc ttc ttc aag atc agt tac        528
Thr Ser Phe Leu Ser Lys Ser Asp His Ser Phe Phe Lys Ile Ser Tyr
                165                 170                 175

ctc acc ttc ctc cct tct gct gat gag att tat gac tgc aag gtg gag        576
Leu Thr Phe Leu Pro Ser Ala Asp Glu Ile Tyr Asp Cys Lys Val Glu
            180                 185                 190

cac tgg ggc ctg gac cag cct ctt ctg aaa cac tgg gag cct gag att        624
His Trp Gly Leu Asp Gln Pro Leu Leu Lys His Trp Glu Pro Glu Ile
        195                 200                 205

cca gcc cct atg tca gag ctc aca gag act gtg gtc tgc gcc ctg ggg        672
Pro Ala Pro Met Ser Glu Leu Thr Glu Thr Val Val Cys Ala Leu Gly
    210                 215                 220

ttg tct gtg ggc ctc gtg ggc att gtg gtg ggc act gtc ttc atc atc        720
Leu Ser Val Gly Leu Val Gly Ile Val Val Gly Thr Val Phe Ile Ile
225                 230                 235                 240

caa ggc ctg cgt tca gtt ggt gct tcc aga cac caa ggg cca ttg tga        768
Gln Gly Leu Arg Ser Val Gly Ala Ser Arg His Gln Gly Pro Leu
                245                 250                 255


<210>  41
<211>  255
<212>  PRT
<213>  Homo sapiens

<400>  41

Met Ile Leu Asn Lys Ala Leu Leu Leu Gly Ala Leu Ala Leu Thr Thr
1               5                   10                  15


Val Met Ser Pro Cys Gly Gly Glu Asp Ile Val Ala Asp His Val Ala
            20                  25                  30


Ser Cys Gly Val Asn Leu Tyr Gln Phe Tyr Gly Pro Ser Gly Gln Tyr
        35                  40                  45


Thr His Glu Phe Asp Gly Asp Glu Glu Phe Tyr Val Asp Leu Glu Arg
    50                  55                  60


Lys Glu Thr Ala Trp Arg Trp Pro Glu Phe Ser Lys Phe Gly Gly Phe
65                  70                  75                  80


Asp Pro Gln Gly Ala Leu Arg Asn Met Ala Val Ala Lys His Asn Leu
                85                  90                  95


Asn Ile Met Ile Lys Arg Tyr Asn Ser Thr Ala Ala Thr Asn Glu Val
            100                 105                 110


Pro Glu Val Thr Val Phe Ser Lys Ser Pro Val Thr Leu Gly Gln Pro
        115                 120                 125


Asn Thr Leu Ile Cys Leu Val Asp Asn Ile Phe Pro Pro Val Val Asn
```

```
    130                 135                 140

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

Thr Ser Phe Leu Ser Lys Ser Asp His Ser Phe Phe Lys Ile Ser Tyr
                165                 170                 175

Leu Thr Phe Leu Pro Ser Ala Asp Glu Ile Tyr Asp Cys Lys Val Glu
            180                 185                 190

His Trp Gly Leu Asp Gln Pro Leu Leu Lys His Trp Glu Pro Glu Ile
        195                 200                 205

Pro Ala Pro Met Ser Glu Leu Thr Glu Thr Val Val Cys Ala Leu Gly
    210                 215                 220

Leu Ser Val Gly Leu Val Gly Ile Val Val Gly Thr Val Phe Ile Ile
225                 230                 235                 240

Gln Gly Leu Arg Ser Val Gly Ala Ser Arg His Gln Gly Pro Leu
                245                 250                 255



<210>  42
<211>  786
<212>  DNA
<213>  Homo sapiens


<220>
<221>  CDS
<222>  (1)..(786)

<400>  42
atg tct tgg aaa aag gct ttg cgg atc ccc gga ggc ctt cgg gca gca          48
Met Ser Trp Lys Lys Ala Leu Arg Ile Pro Gly Gly Leu Arg Ala Ala
1               5                   10                  15

act gtg acc ttg atg ctg tcg atg ctg agc acc cca gtg gct gag ggc          96
Thr Val Thr Leu Met Leu Ser Met Leu Ser Thr Pro Val Ala Glu Gly
            20                  25                  30

aga gac tct ccc gag gat ttc gtg tac cag ttt aag ggc atg tgc tac         144
Arg Asp Ser Pro Glu Asp Phe Val Tyr Gln Phe Lys Gly Met Cys Tyr
        35                  40                  45

ttc acc aac ggg aca gag cgc gtg cgt ctt gtg agc aga agc atc tat         192
Phe Thr Asn Gly Thr Glu Arg Val Arg Leu Val Ser Arg Ser Ile Tyr
    50                  55                  60

aac cga gaa gag atc gtg cgc ttc gac agc gac gtg ggg gag ttc cgg         240
Asn Arg Glu Glu Ile Val Arg Phe Asp Ser Asp Val Gly Glu Phe Arg
65                  70                  75                  80

gcg gtg acg ctg ctg ggg ctg cct gcc gcc gag tac tgg aac agc cag         288
Ala Val Thr Leu Leu Gly Leu Pro Ala Ala Glu Tyr Trp Asn Ser Gln
                85                  90                  95

aag gac atc ctg gag agg aaa cgg gcg gcg gtg gac agg gtg tgc aga         336
```

```
Lys Asp Ile Leu Glu Arg Lys Arg Ala Ala Val Asp Arg Val Cys Arg
            100                 105                 110

cac aac tac cag ttg gag ctc cgc acg acc ttg cag cgg cga gtg gag        384
His Asn Tyr Gln Leu Glu Leu Arg Thr Thr Leu Gln Arg Arg Val Glu
        115                 120                 125

ccc aca gtg acc atc tcc cca tcc agg aca gag gcc ctc aac cac cac        432
Pro Thr Val Thr Ile Ser Pro Ser Arg Thr Glu Ala Leu Asn His His
    130                 135                 140

aac ctg ctg gtc tgc tcg gtg aca gat ttc tat cca gcc cag atc aaa        480
Asn Leu Leu Val Cys Ser Val Thr Asp Phe Tyr Pro Ala Gln Ile Lys
145                 150                 155                 160

gtc cgg tgg ttt cgg aat gac cag gag gag aca gct ggc gtt gtg tcc        528
Val Arg Trp Phe Arg Asn Asp Gln Glu Glu Thr Ala Gly Val Val Ser
                165                 170                 175

acc ccc ctt att agg aat ggt gac tgg acc ttc cag atc ctg gtg atg        576
Thr Pro Leu Ile Arg Asn Gly Asp Trp Thr Phe Gln Ile Leu Val Met
            180                 185                 190

ctg gaa atg act ccc cag cgt gga gac gtc tac acc tgc cac gtg gag        624
Leu Glu Met Thr Pro Gln Arg Gly Asp Val Tyr Thr Cys His Val Glu
        195                 200                 205

cac ccc agc ctc cag agc ccc atc acc gtg gag tgg cgg gct caa tct        672
His Pro Ser Leu Gln Ser Pro Ile Thr Val Glu Trp Arg Ala Gln Ser
    210                 215                 220

gaa tct gcc cag agc aag atg ctg agt ggc att gga ggc ttc gtg ctg        720
Glu Ser Ala Gln Ser Lys Met Leu Ser Gly Ile Gly Gly Phe Val Leu
225                 230                 235                 240

ggg ctg atc ttc ctc ggg ctg ggc ctt atc atc cat cac agg agt cag        768
Gly Leu Ile Phe Leu Gly Leu Gly Leu Ile Ile His His Arg Ser Gln
                245                 250                 255

aaa ggg ctc ctg cac tga                                               786
Lys Gly Leu Leu His
            260


<210>  43
<211>  261
<212>  PRT
<213>  Homo sapiens

<400>  43

Met Ser Trp Lys Lys Ala Leu Arg Ile Pro Gly Gly Leu Arg Ala Ala
1               5                   10                  15


Thr Val Thr Leu Met Leu Ser Met Leu Ser Thr Pro Val Ala Glu Gly
            20                  25                  30


Arg Asp Ser Pro Glu Asp Phe Val Tyr Gln Phe Lys Gly Met Cys Tyr
        35                  40                  45


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


Asn Arg Glu Glu Ile Val Arg Phe Asp Ser Asp Val Gly Glu Phe Arg
```

65 70 75 80

Ala Val Thr Leu Leu Gly Leu Pro Ala Ala Glu Tyr Trp Asn Ser Gln
85 90 95

Lys Asp Ile Leu Glu Arg Lys Arg Ala Ala Val Asp Arg Val Cys Arg
100 105 110

His Asn Tyr Gln Leu Glu Leu Arg Thr Thr Leu Gln Arg Arg Val Glu
115 120 125

Pro Thr Val Thr Ile Ser Pro Ser Arg Thr Glu Ala Leu Asn His His
130 135 140

Asn Leu Leu Val Cys Ser Val Thr Asp Phe Tyr Pro Ala Gln Ile Lys
145 150 155 160

Val Arg Trp Phe Arg Asn Asp Gln Glu Glu Thr Ala Gly Val Val Ser
165 170 175

Thr Pro Leu Ile Arg Asn Gly Asp Trp Thr Phe Gln Ile Leu Val Met
180 185 190

Leu Glu Met Thr Pro Gln Arg Gly Asp Val Tyr Thr Cys His Val Glu
195 200 205

His Pro Ser Leu Gln Ser Pro Ile Thr Val Glu Trp Arg Ala Gln Ser
210 215 220

Glu Ser Ala Gln Ser Lys Met Leu Ser Gly Ile Gly Gly Phe Val Leu
225 230 235 240

Gly Leu Ile Phe Leu Gly Leu Gly Leu Ile Ile His His Arg Ser Gln
245 250 255

Lys Gly Leu Leu His
260

<210> 44
<211> 1312
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (110)..(874)

<400> 44
ttttaatggt cagactctat tacaccccac attctctttt cttttattct tgtctgttct 60

gcctcactcc cgagctctac tgactcccaa cagagcgccc aagaagaaa atg gcc ata 118
Met Ala Ile
1

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agt gga gtc cct gtg cta gga ttt ttc atc ata gct gtg ctg atg agc        166
Ser Gly Val Pro Val Leu Gly Phe Phe Ile Ile Ala Val Leu Met Ser
    5                   10                  15

gct cag gaa tca tgg gct atc aaa gaa gaa cat gtg atc atc cag gcc        214
Ala Gln Glu Ser Trp Ala Ile Lys Glu Glu His Val Ile Ile Gln Ala
20                  25                  30                  35

gag ttc tat ctg aat cct gac caa tca ggc gag ttt atg ttt gac ttt        262
Glu Phe Tyr Leu Asn Pro Asp Gln Ser Gly Glu Phe Met Phe Asp Phe
                40                  45                  50

gat ggt gat gag att ttc cat gtg gat atg gca aag aag gag acg gtc        310
Asp Gly Asp Glu Ile Phe His Val Asp Met Ala Lys Lys Glu Thr Val
            55                  60                  65

tgg cgg ctt gaa gaa ttt gga cga ttt gcc agc ttt gag gct caa ggt        358
Trp Arg Leu Glu Glu Phe Gly Arg Phe Ala Ser Phe Glu Ala Gln Gly
        70                  75                  80

gca ttg gcc aac ata gct gtg gac aaa gcc aac ctg gaa atc atg aca        406
Ala Leu Ala Asn Ile Ala Val Asp Lys Ala Asn Leu Glu Ile Met Thr
    85                  90                  95

aag cgc tcc aac tat act ccg atc acc aat gta cct cca gag gta act        454
Lys Arg Ser Asn Tyr Thr Pro Ile Thr Asn Val Pro Pro Glu Val Thr
100                 105                 110                 115

gtg ctc aca aac agc cct gtg gaa ctg aga gag ccc aac gtc ctc atc        502
Val Leu Thr Asn Ser Pro Val Glu Leu Arg Glu Pro Asn Val Leu Ile
                120                 125                 130

tgt ttc ata gac aag ttc acc cca cca gtg gtc aat gtc acg tgg ctt        550
Cys Phe Ile Asp Lys Phe Thr Pro Pro Val Val Asn Val Thr Trp Leu
            135                 140                 145

cga aat gga aaa cct gtc acc aca gga gtg tca gag aca gtc ttc ctg        598
Arg Asn Gly Lys Pro Val Thr Thr Gly Val Ser Glu Thr Val Phe Leu
        150                 155                 160

ccc agg gaa gac cac ctt ttc cgc aag ttc cac tat ctc ccc ttc ctg        646
Pro Arg Glu Asp His Leu Phe Arg Lys Phe His Tyr Leu Pro Phe Leu
    165                 170                 175

ccc tca act gag gac gtt tac gac tgc agg gtg gag cac tgg ggc ttg        694
Pro Ser Thr Glu Asp Val Tyr Asp Cys Arg Val Glu His Trp Gly Leu
180                 185                 190                 195

gat gag cct ctt ctc aag cac tgg gag ttt gat gct cca agc cct ctc        742
Asp Glu Pro Leu Leu Lys His Trp Glu Phe Asp Ala Pro Ser Pro Leu
                200                 205                 210

cca gag act aca gag aac gtg gtg tgt gcc ctg ggc ctg act gtg ggt        790
Pro Glu Thr Thr Glu Asn Val Val Cys Ala Leu Gly Leu Thr Val Gly
            215                 220                 225

ctg gtg ggc atc att att ggg acc atc ttc atc atc aag gga ttg cgc        838
Leu Val Gly Ile Ile Ile Gly Thr Ile Phe Ile Ile Lys Gly Leu Arg
        230                 235                 240

aaa agc aat gca gca gaa cgc agg ggg cct ctg taa ggcacatgga             884
Lys Ser Asn Ala Ala Glu Arg Arg Gly Pro Leu
    245                 250

ggtgatggtg tttcttagag agaagatcac tgaagaaact tctgctttaa tggctttaca      944

aagctggcaa tattacaatc cttgacctca gtgaaagcag tcatcttcag cattttccag     1004
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ccctatagcc accccaagtg tggatatgcc tcttcgattg ctccgtactc taacatctag 1064

ctggcttccc tgtctattgc cttttcctgt atctattttc ctctatttcc tatcatttta 1124

ttatcaccat gcaatgcctc tggaataaaa catacaggag tctgtctctg ctatggaatg 1184

ccccatgggg catctcttgt gtacttattg tttaaggttt cctcaaactg tgatttttct 1244

gaacacaata aactattttg atgatcttgg gtggaaaaaa aaaaaaaaaa aaaaaaaaaa 1304

aaaaaaaa 1312

<210> 45
<211> 254
<212> PRT
<213> Homo sapiens

<400> 45

Met Ala Ile Ser Gly Val Pro Val Leu Gly Phe Phe Ile Ile Ala Val
1 5 10 15

Leu Met Ser Ala Gln Glu Ser Trp Ala Ile Lys Glu Glu His Val Ile
20 25 30

Ile Gln Ala Glu Phe Tyr Leu Asn Pro Asp Gln Ser Gly Glu Phe Met
35 40 45

Phe Asp Phe Asp Gly Asp Glu Ile Phe His Val Asp Met Ala Lys Lys
50 55 60

Glu Thr Val Trp Arg Leu Glu Glu Phe Gly Arg Phe Ala Ser Phe Glu
65 70 75 80

Ala Gln Gly Ala Leu Ala Asn Ile Ala Val Asp Lys Ala Asn Leu Glu
85 90 95

Ile Met Thr Lys Arg Ser Asn Tyr Thr Pro Ile Thr Asn Val Pro Pro
100 105 110

Glu Val Thr Val Leu Thr Asn Ser Pro Val Glu Leu Arg Glu Pro Asn
115 120 125

Val Leu Ile Cys Phe Ile Asp Lys Phe Thr Pro Pro Val Val Asn Val
130 135 140

Thr Trp Leu Arg Asn Gly Lys Pro Val Thr Thr Gly Val Ser Glu Thr
145 150 155 160

Val Phe Leu Pro Arg Glu Asp His Leu Phe Arg Lys Phe His Tyr Leu
165 170 175

Pro Phe Leu Pro Ser Thr Glu Asp Val Tyr Asp Cys Arg Val Glu His
180 185 190

```
Trp Gly Leu Asp Glu Pro Leu Leu Lys His Trp Glu Phe Asp Ala Pro
        195                 200                 205

Ser Pro Leu Pro Glu Thr Thr Glu Asn Val Val Cys Ala Leu Gly Leu
    210                 215                 220

Thr Val Gly Leu Val Gly Ile Ile Ile Gly Thr Ile Phe Ile Ile Lys
225                 230                 235                 240

Gly Leu Arg Lys Ser Asn Ala Ala Glu Arg Arg Gly Pro Leu
                245                 250
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<210> 46
<211> 801
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)..(801)

<400> 46

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atg gtg tgt ctg aag ctc cct gga ggc tcc tgc atg aca gcg ctg aca          48
Met Val Cys Leu Lys Leu Pro Gly Gly Ser Cys Met Thr Ala Leu Thr
1               5                   10                  15

gtg aca ctg atg gtg ctg agc tcc cca ctg gct ttg gct ggg gac acc          96
Val Thr Leu Met Val Leu Ser Ser Pro Leu Ala Leu Ala Gly Asp Thr
            20                  25                  30

cga cca cgt ttc ttg tgg cag ctt aag ttt gaa tgt cat ttc ttc aat         144
Arg Pro Arg Phe Leu Trp Gln Leu Lys Phe Glu Cys His Phe Phe Asn
        35                  40                  45

ggg acg gag cgg gtg cgg ttg ctg gaa aga tgc atc tat aac caa gag         192
Gly Thr Glu Arg Val Arg Leu Leu Glu Arg Cys Ile Tyr Asn Gln Glu
    50                  55                  60

gag tcc gtg cgc ttc gac agc gac gtg ggg gag tac cgg gcg gtg acg         240
Glu Ser Val Arg Phe Asp Ser Asp Val Gly Glu Tyr Arg Ala Val Thr
65                  70                  75                  80

gag ctg ggg cgg cct gat gcc gag tac tgg aac agc cag aag gac ctc         288
Glu Leu Gly Arg Pro Asp Ala Glu Tyr Trp Asn Ser Gln Lys Asp Leu
                85                  90                  95

ctg gag cag agg cgg gcc gcg gtg gac acc tac tgc aga cac aac tac         336
Leu Glu Gln Arg Arg Ala Ala Val Asp Thr Tyr Cys Arg His Asn Tyr
            100                 105                 110

ggg gtt ggt gag agc ttc aca gtg cag cgg cga gtt gag cct aag gtg         384
Gly Val Gly Glu Ser Phe Thr Val Gln Arg Arg Val Glu Pro Lys Val
        115                 120                 125

act gtg tat cct tca aag acc cag ccc ctg cag cac cac aac ctc ctg         432
Thr Val Tyr Pro Ser Lys Thr Gln Pro Leu Gln His His Asn Leu Leu
    130                 135                 140

gtc tgc tct gtg agt ggt ttc tat cca ggc agc att gaa gtc agg tgg         480
Val Cys Ser Val Ser Gly Phe Tyr Pro Gly Ser Ile Glu Val Arg Trp
145                 150                 155                 160
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ttc cgg aac ggc cag gaa gag aag gct ggg gtg gtg tcc aca ggc ctg        528
Phe Arg Asn Gly Gln Glu Glu Lys Ala Gly Val Val Ser Thr Gly Leu
                165                 170                 175

atc cag aat gga gat tgg acc ttc cag acc ctg gtg atg ctg gaa aca        576
Ile Gln Asn Gly Asp Trp Thr Phe Gln Thr Leu Val Met Leu Glu Thr
            180                 185                 190

gtt cct cgg agt gga gag gtt tac acc tgc caa gtg gag cac cca agt        624
Val Pro Arg Ser Gly Glu Val Tyr Thr Cys Gln Val Glu His Pro Ser
        195                 200                 205

gtg acg agc cct ctc aca gtg gaa tgg aga gca cgg tct gaa tct gca        672
Val Thr Ser Pro Leu Thr Val Glu Trp Arg Ala Arg Ser Glu Ser Ala
    210                 215                 220

cag agc aag atg ctg agt gga gtc ggg ggc ttc gtg ctg ggc ctg ctc        720
Gln Ser Lys Met Leu Ser Gly Val Gly Gly Phe Val Leu Gly Leu Leu
225                 230                 235                 240

ttc ctt ggg gcc ggg ctg ttc atc tac ttc agg aat cag aaa gga cac        768
Phe Leu Gly Ala Gly Leu Phe Ile Tyr Phe Arg Asn Gln Lys Gly His
                245                 250                 255

tct gga ctt cag cca aca gga ttc ctg agc tga                            801
Ser Gly Leu Gln Pro Thr Gly Phe Leu Ser
            260                 265


<210>  47
<211>  266
<212>  PRT
<213>  Homo sapiens

<400>  47

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


Val Thr Leu Met Val Leu Ser Ser Pro Leu Ala Leu Ala Gly Asp Thr
            20                  25                  30


Arg Pro Arg Phe Leu Trp Gln Leu Lys Phe Glu Cys His Phe Phe Asn
        35                  40                  45


Gly Thr Glu Arg Val Arg Leu Leu Glu Arg Cys Ile Tyr Asn Gln Glu
    50                  55                  60


Glu Ser Val Arg Phe Asp Ser Asp Val Gly Glu Tyr Arg Ala Val Thr
65                  70                  75                  80


Glu Leu Gly Arg Pro Asp Ala Glu Tyr Trp Asn Ser Gln Lys Asp Leu
                85                  90                  95


Leu Glu Gln Arg Arg Ala Ala Val Asp Thr Tyr Cys Arg His Asn Tyr
            100                 105                 110


Gly Val Gly Glu Ser Phe Thr Val Gln Arg Arg Val Glu Pro Lys Val
        115                 120                 125
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Thr Val Tyr Pro Ser Lys Thr Gln Pro Leu Gln His His Asn Leu Leu
    130                 135                 140

Val Cys Ser Val Ser Gly Phe Tyr Pro Gly Ser Ile Glu Val Arg Trp
145                 150                 155                 160

Phe Arg Asn Gly Gln Glu Glu Lys Ala Gly Val Val Ser Thr Gly Leu
                165                 170                 175

Ile Gln Asn Gly Asp Trp Thr Phe Gln Thr Leu Val Met Leu Glu Thr
            180                 185                 190

Val Pro Arg Ser Gly Glu Val Tyr Thr Cys Gln Val Glu His Pro Ser
        195                 200                 205

Val Thr Ser Pro Leu Thr Val Glu Trp Arg Ala Arg Ser Glu Ser Ala
    210                 215                 220

Gln Ser Lys Met Leu Ser Gly Val Gly Gly Phe Val Leu Gly Leu Leu
225                 230                 235                 240

Phe Leu Gly Ala Gly Leu Phe Ile Tyr Phe Arg Asn Gln Lys Gly His
                245                 250                 255

Ser Gly Leu Gln Pro Thr Gly Phe Leu Ser
            260                 265



<210>  48
<211>  1122
<212>  DNA
<213>  Homo sapiens


<220>
<221>  CDS
<222>  (87)..(872)

<400>  48
gatctaaggc caccctctcg gggagggagt tggggaagct gggttggctg ggttggtagc       60

tcctacctac tgtgtggcaa gaaggt atg ggt cat gaa cag aac caa gga gct       113
                               Met Gly His Glu Gln Asn Gln Gly Ala
                               1               5

gcg ctg cta cag atg tta cca ctt ctg tgg ctg cta ccc cac tcc tgg       161
Ala Leu Leu Gln Met Leu Pro Leu Leu Trp Leu Leu Pro His Ser Trp
10                  15                  20                  25

gcc gtc cct gaa gct cct act cca atg tgg cca gat gac ctg caa aac       209
Ala Val Pro Glu Ala Pro Thr Pro Met Trp Pro Asp Asp Leu Gln Asn
                30                  35                  40

cac aca ttc ctg cac aca gtg tac tgc cag gat ggg agt ccc agt gtg       257
His Thr Phe Leu His Thr Val Tyr Cys Gln Asp Gly Ser Pro Ser Val
            45                  50                  55

gga ctc tct gag gcc tac gac gag gac cag ctt ttc ttc ttc gac ttt       305
Gly Leu Ser Glu Ala Tyr Asp Glu Asp Gln Leu Phe Phe Phe Asp Phe
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        60                  65                  70

tcc cag aac act cgg gtg cct cgc ctg ccc gaa ttt gct gac tgg gct        353
Ser Gln Asn Thr Arg Val Pro Arg Leu Pro Glu Phe Ala Asp Trp Ala
    75                  80                  85

cag gaa cag gga gat gct cct gcc att tta ttt gac aaa gag ttc tgc        401
Gln Glu Gln Gly Asp Ala Pro Ala Ile Leu Phe Asp Lys Glu Phe Cys
90                  95                  100                 105

gag tgg atg atc cag caa ata ggg cca aaa ctt gat ggg aaa atc ccg        449
Glu Trp Met Ile Gln Gln Ile Gly Pro Lys Leu Asp Gly Lys Ile Pro
                110                 115                 120

gtg tcc aga ggg ttt cct atc gct gaa gtg ttc acg ctg aag ccc ctg        497
Val Ser Arg Gly Phe Pro Ile Ala Glu Val Phe Thr Leu Lys Pro Leu
            125                 130                 135

gag ttt ggc aag ccc aac act ttg gtc tgt ttt gtc agt aat ctc ttc        545
Glu Phe Gly Lys Pro Asn Thr Leu Val Cys Phe Val Ser Asn Leu Phe
        140                 145                 150

cca ccc atg ctg aca gtg aac tgg cag cat cat tcc gtc cct gtg gaa        593
Pro Pro Met Leu Thr Val Asn Trp Gln His His Ser Val Pro Val Glu
    155                 160                 165

gga ttt ggg cct act ttt gtc tca gct gtc gat gga ctc agc ttc cag        641
Gly Phe Gly Pro Thr Phe Val Ser Ala Val Asp Gly Leu Ser Phe Gln
170                 175                 180                 185

gcc ttt tct tac tta aac ttc aca cca gaa cct tct gac att ttc tcc        689
Ala Phe Ser Tyr Leu Asn Phe Thr Pro Glu Pro Ser Asp Ile Phe Ser
                190                 195                 200

tgc att gtg act cac gaa att gac cgc tac aca gca att gcc tat tgg        737
Cys Ile Val Thr His Glu Ile Asp Arg Tyr Thr Ala Ile Ala Tyr Trp
            205                 210                 215

gta ccc cgg aac gca ctg ccc tca gat ctg ctg gag aat gtg ctg tgt        785
Val Pro Arg Asn Ala Leu Pro Ser Asp Leu Leu Glu Asn Val Leu Cys
        220                 225                 230

ggc gtg gcc ttt ggc ctg ggt gtg ctg ggc atc atc gtg ggc att gtt        833
Gly Val Ala Phe Gly Leu Gly Val Leu Gly Ile Ile Val Gly Ile Val
    235                 240                 245

ctc atc atc tac ttc cgg aag cct tgc tca ggt gac tga ttcttccaga        882
Leu Ile Ile Tyr Phe Arg Lys Pro Cys Ser Gly Asp
250                 255                 260

ccagagtttg atgccagcag cttcggccat ccaaacagag gatgctcaga tttctcacat      942

cctgcccagg atctcctctt agggtagaag tctctgggac atccctgggg tgtgtgtgta     1002

gatttcccac ctggggactc tgctgtccct gggcttgcat cccagggatc ccagagtggc     1062

ctgcctatca caaccacatc ccttcccccc acaaggcaat aaatctcatt tctttatatc     1122


<210>  49
<211>  261
<212>  PRT
<213>  Homo sapiens

<400>  49

Met Gly His Glu Gln Asn Gln Gly Ala Ala Leu Leu Gln Met Leu Pro
1               5                   10                  15
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Leu Leu Trp Leu Leu Pro His Ser Trp Ala Val Pro Glu Ala Pro Thr
            20                  25                  30

Pro Met Trp Pro Asp Asp Leu Gln Asn His Thr Phe Leu His Thr Val
        35                  40                  45

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

Glu Asp Gln Leu Phe Phe Phe Asp Phe Ser Gln Asn Thr Arg Val Pro
65                  70                  75                  80

Arg Leu Pro Glu Phe Ala Asp Trp Ala Gln Glu Gln Gly Asp Ala Pro
                85                  90                  95

Ala Ile Leu Phe Asp Lys Glu Phe Cys Glu Trp Met Ile Gln Gln Ile
            100                 105                 110

Gly Pro Lys Leu Asp Gly Lys Ile Pro Val Ser Arg Gly Phe Pro Ile
        115                 120                 125

Ala Glu Val Phe Thr Leu Lys Pro Leu Glu Phe Gly Lys Pro Asn Thr
    130                 135                 140

Leu Val Cys Phe Val Ser Asn Leu Phe Pro Pro Met Leu Thr Val Asn
145                 150                 155                 160

Trp Gln His His Ser Val Pro Val Glu Gly Phe Gly Pro Thr Phe Val
                165                 170                 175

Ser Ala Val Asp Gly Leu Ser Phe Gln Ala Phe Ser Tyr Leu Asn Phe
            180                 185                 190

Thr Pro Glu Pro Ser Asp Ile Phe Ser Cys Ile Val Thr His Glu Ile
        195                 200                 205

Asp Arg Tyr Thr Ala Ile Ala Tyr Trp Val Pro Arg Asn Ala Leu Pro
    210                 215                 220

Ser Asp Leu Leu Glu Asn Val Leu Cys Gly Val Ala Phe Gly Leu Gly
225                 230                 235                 240

Val Leu Gly Ile Ile Val Gly Ile Val Leu Ile Ile Tyr Phe Arg Lys
                245                 250                 255

Pro Cys Ser Gly Asp
            260
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<210> 50

<211> 1412
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (264)..(1055)

<400> 50
atttgtccct gcctacctag ccaatctgtc cctgtttggg acactggact cccgtgagct 60

ggaaggaaca gatttaatat ctaggggctg ggtatcccca catcactcat ttgggggtc 120

aagggacccg ggcaatatag tattctgctc agtgtctgga gatcatctac ccaggctggg 180

gcttctggga caggcgagga cccacggacc ctggaagagc tggtccaggg gactgaactc 240

ccggcatctt tacagagcag agc atg atc aca ttc ctg ccg ctg ctg ctg ggg 293
Met Ile Thr Phe Leu Pro Leu Leu Leu Gly
1 5 10

ctc agc ctg ggc tgc aca gga gca ggt ggc ttc gtg gcc cat gtg gaa 341
Leu Ser Leu Gly Cys Thr Gly Ala Gly Gly Phe Val Ala His Val Glu
15 20 25

agc acc tgt ctg ttg gat gat gct ggg act cca aag gat ttc aca tac 389
Ser Thr Cys Leu Leu Asp Asp Ala Gly Thr Pro Lys Asp Phe Thr Tyr
30 35 40

tgc atc tcc ttc aac aag gat ctg ctg acc tgc tgg gat cca gag gag 437
Cys Ile Ser Phe Asn Lys Asp Leu Leu Thr Cys Trp Asp Pro Glu Glu
45 50 55

aat aag atg gcc cct tgc gaa ttt ggg gtg ctg aat agc ttg gcg aat 485
Asn Lys Met Ala Pro Cys Glu Phe Gly Val Leu Asn Ser Leu Ala Asn
60 65 70

gtc ctc tca cag cac ctc aac caa aaa gac acc ctg atg cag cgc ttg 533
Val Leu Ser Gln His Leu Asn Gln Lys Asp Thr Leu Met Gln Arg Leu
75 80 85 90

cgc aat ggg ctt cag aat tgt gcc aca cac acc cag ccc ttc tgg gga 581
Arg Asn Gly Leu Gln Asn Cys Ala Thr His Thr Gln Pro Phe Trp Gly
95 100 105

tca ctg acc aac agg aca cgg cca cca tct gtg caa gta gcc aaa acc 629
Ser Leu Thr Asn Arg Thr Arg Pro Pro Ser Val Gln Val Ala Lys Thr
110 115 120

act cct ttt aac acg agg gag cct gtg atg ctg gcc tgc tat gtg tgg 677
Thr Pro Phe Asn Thr Arg Glu Pro Val Met Leu Ala Cys Tyr Val Trp
125 130 135

ggc ttc tat cca gca gaa gtg act atc acg tgg agg aag aac ggg aag 725
Gly Phe Tyr Pro Ala Glu Val Thr Ile Thr Trp Arg Lys Asn Gly Lys
140 145 150

ctt gtc atg cct cac agc agt gcg cac aag act gcc cag ccc aat gga 773
Leu Val Met Pro His Ser Ser Ala His Lys Thr Ala Gln Pro Asn Gly
155 160 165 170

gac tgg aca tac cag acc ctc tcc cat tta gcc tta acc ccc tct tac 821
Asp Trp Thr Tyr Gln Thr Leu Ser His Leu Ala Leu Thr Pro Ser Tyr
175 180 185

ggg gac act tac acc tgt gtg gta gag cac act ggg gct cct gag ccc 869
Gly Asp Thr Tyr Thr Cys Val Val Glu His Thr Gly Ala Pro Glu Pro

```
            190                 195                 200

atc ctt cgg gac tgg aca cct ggg ctg tcc ccc atg cag acc ctg aag        917
Ile Leu Arg Asp Trp Thr Pro Gly Leu Ser Pro Met Gln Thr Leu Lys
        205                 210                 215

gtt tct gtg tct gca gtg act ctg ggc ctg ggc ctc atc atc ttc tct        965
Val Ser Val Ser Ala Val Thr Leu Gly Leu Gly Leu Ile Ile Phe Ser
    220                 225                 230

ctt ggt gtg atc agc tgg cgg aga gct ggc cac tct agt tac act cct       1013
Leu Gly Val Ile Ser Trp Arg Arg Ala Gly His Ser Ser Tyr Thr Pro
235                 240                 245                 250

ctt cct ggg tcc aat tat tca gaa gga tgg cac att tcc tag               1055
Leu Pro Gly Ser Asn Tyr Ser Glu Gly Trp His Ile Ser
                255                 260

aggcagaatc ctacaacttc cactccaagt gagaaggaga ttcaaactca atgatgctac     1115

catgcctctc caacatcttc aacccccctga cattatcttg gatcctatgg tttctccatc     1175

caattctttg aatttcccag tctcccctat gtaaaactta gcaacttggg ggacctcatt     1235

cctgggacta tgctgtaacc aaattattgt ccaaggctat atttctggga tgaatataat     1295

ctgaggaagg gagttaaaga ccctcctggg gctctcagtg tgccatagag gacagcaact     1355

ggtgattgtt tcagagaaat aaactttggt ggaaatattg ttaaaaaaaa aaaaaaa        1412


<210>  51
<211>  263
<212>  PRT
<213>  Homo sapiens

<400>  51

Met Ile Thr Phe Leu Pro Leu Leu Leu Gly Leu Ser Leu Gly Cys Thr
1               5                   10                  15


Gly Ala Gly Gly Phe Val Ala His Val Glu Ser Thr Cys Leu Leu Asp
            20                  25                  30


Asp Ala Gly Thr Pro Lys Asp Phe Thr Tyr Cys Ile Ser Phe Asn Lys
        35                  40                  45


Asp Leu Leu Thr Cys Trp Asp Pro Glu Glu Asn Lys Met Ala Pro Cys
    50                  55                  60


Glu Phe Gly Val Leu Asn Ser Leu Ala Asn Val Leu Ser Gln His Leu
65                  70                  75                  80


Asn Gln Lys Asp Thr Leu Met Gln Arg Leu Arg Asn Gly Leu Gln Asn
                85                  90                  95


Cys Ala Thr His Thr Gln Pro Phe Trp Gly Ser Leu Thr Asn Arg Thr
            100                 105                 110


Arg Pro Pro Ser Val Gln Val Ala Lys Thr Thr Pro Phe Asn Thr Arg
        115                 120                 125
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Glu Pro Val Met Leu Ala Cys Tyr Val Trp Gly Phe Tyr Pro Ala Glu
    130                 135                 140

Val Thr Ile Thr Trp Arg Lys Asn Gly Lys Leu Val Met Pro His Ser
145                 150                 155                 160

Ser Ala His Lys Thr Ala Gln Pro Asn Gly Asp Trp Thr Tyr Gln Thr
                165                 170                 175

Leu Ser His Leu Ala Leu Thr Pro Ser Tyr Gly Asp Thr Tyr Thr Cys
            180                 185                 190

Val Val Glu His Thr Gly Ala Pro Glu Pro Ile Leu Arg Asp Trp Thr
        195                 200                 205

Pro Gly Leu Ser Pro Met Gln Thr Leu Lys Val Ser Val Ser Ala Val
    210                 215                 220

Thr Leu Gly Leu Gly Leu Ile Ile Phe Ser Leu Gly Val Ile Ser Trp
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                  Met Ala Leu Arg Ala Gly Leu Val Leu Gly Phe His
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acc ctg atg acc ctc ctg agc ccg cag gag gca ggg gcc acc aag gct       160
Thr Leu Met Thr Leu Leu Ser Pro Gln Glu Ala Gly Ala Thr Lys Ala
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gac cac atg ggc tcc tac gga ccc gcc ttc tac cag tct tac ggc gcc       208
Asp His Met Gly Ser Tyr Gly Pro Ala Phe Tyr Gln Ser Tyr Gly Ala
    30                  35                  40

tcg ggc cag ttc acc cat gaa ttt gat gag gaa cag ctg ttc tct gtg       256
Ser Gly Gln Phe Thr His Glu Phe Asp Glu Glu Gln Leu Phe Ser Val
45                  50                  55                  60
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Asp Leu Lys Lys Ser Glu Ala Val Trp Arg Leu Pro Glu Phe Gly Asp
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ttt gcc cgc ttt gac ccg cag ggc ggg ctg gcc ggc atc gcc gca atc        352
Phe Ala Arg Phe Asp Pro Gln Gly Gly Leu Ala Gly Ile Ala Ala Ile
            80                  85                  90

aaa gcc cat ctg gac atc ctg gtg gag cgc tcc aac cgc agc aga gcc        400
Lys Ala His Leu Asp Ile Leu Val Glu Arg Ser Asn Arg Ser Arg Ala
        95                  100                 105

atc aac gtg cct cca cgg gtg acc gtg ctc ccc aag tct cgg gtg gag        448
Ile Asn Val Pro Pro Arg Val Thr Val Leu Pro Lys Ser Arg Val Glu
    110                 115                 120

ctg ggc cag ccc aac atc ctc atc tgc atc gtg gac aac atc ttc ccc        496
Leu Gly Gln Pro Asn Ile Leu Ile Cys Ile Val Asp Asn Ile Phe Pro
125                 130                 135                 140

cct gtg atc aat atc acc tgg ctg cgc aac ggc caa act gtc act gag        544
Pro Val Ile Asn Ile Thr Trp Leu Arg Asn Gly Gln Thr Val Thr Glu
                145                 150                 155

gga gtg gcc cag acc agc ttc tat tcc cag cct gac cat ttg ttc cgc        592
Gly Val Ala Gln Thr Ser Phe Tyr Ser Gln Pro Asp His Leu Phe Arg
            160                 165                 170

aag ttc cac tac ctg ccc ttc gtg ccc tca gcc gag gac gtc tat gac        640
Lys Phe His Tyr Leu Pro Phe Val Pro Ser Ala Glu Asp Val Tyr Asp
        175                 180                 185

tgc cag gtg gag cac tgg ggc ctg gat gcg cca ctc ctc agg cat tgg        688
Cys Gln Val Glu His Trp Gly Leu Asp Ala Pro Leu Leu Arg His Trp
    190                 195                 200

gag ctc cag gtg cct att cca cca cca gat gcc atg gag acc ctg gtc        736
Glu Leu Gln Val Pro Ile Pro Pro Pro Asp Ala Met Glu Thr Leu Val
205                 210                 215                 220

tgt gcc ctg ggc ctg gcc atc ggc ctg gtg ggc ttc ctc gtg ggc acc        784
Cys Ala Leu Gly Leu Ala Ile Gly Leu Val Gly Phe Leu Val Gly Thr
                225                 230                 235

gtc ctc atc atc atg ggc aca tat gtg tcc agt gtc ccc agg taa             829
Val Leu Ile Ile Met Gly Thr Tyr Val Ser Ser Val Pro Arg
            240                 245                 250

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caacatctgt cctacgggtc ccctcttttt tggccccagt attcatggca gggtttgttg     1009

gacacctact agcttccctt cccattcaac acacacacac attcttgctc tacccaaagc     1069

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Ser Tyr Gly Pro Ala Phe Tyr Gln Ser Tyr Gly Ala Ser Gly Gln Phe
35 40 45

Thr His Glu Phe Asp Glu Glu Gln Leu Phe Ser Val Asp Leu Lys Lys
50 55 60

Ser Glu Ala Val Trp Arg Leu Pro Glu Phe Gly Asp Phe Ala Arg Phe
65 70 75 80

Asp Pro Gln Gly Gly Leu Ala Gly Ile Ala Ala Ile Lys Ala His Leu
85 90 95

Asp Ile Leu Val Glu Arg Ser Asn Arg Ser Arg Ala Ile Asn Val Pro
100 105 110

Pro Arg Val Thr Val Leu Pro Lys Ser Arg Val Glu Leu Gly Gln Pro
115 120 125

Asn Ile Leu Ile Cys Ile Val Asp Asn Ile Phe Pro Pro Val Ile Asn
130 135 140

Ile Thr Trp Leu Arg Asn Gly Gln Thr Val Thr Glu Gly Val Ala Gln
145 150 155 160

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

Leu Pro Phe Val Pro Ser Ala Glu Asp Val Tyr Asp Cys Gln Val Glu
180 185 190

His Trp Gly Leu Asp Ala Pro Leu Leu Arg His Trp Glu Leu Gln Val
195 200 205

Pro Ile Pro Pro Pro Asp Ala Met Glu Thr Leu Val Cys Ala Leu Gly
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ccc tgg gtg gtg gct ctg cta gtg aat ctg acc cga ctg gat tcc tcc        163
Pro Trp Val Val Ala Leu Leu Val Asn Leu Thr Arg Leu Asp Ser Ser
            10                  15                  20

atg act caa ggc aca gac tct cca gaa gat ttt gtg att cag gca aag        211
Met Thr Gln Gly Thr Asp Ser Pro Glu Asp Phe Val Ile Gln Ala Lys
        25                  30                  35

gct gac tgt tac ttc acc aac ggg aca gaa aag gtg cag ttt gtg gtc        259
Ala Asp Cys Tyr Phe Thr Asn Gly Thr Glu Lys Val Gln Phe Val Val
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aga ttc atc ttt aac ttg gag gag tat gta cgt ttc gac agt gat gtg        307
Arg Phe Ile Phe Asn Leu Glu Glu Tyr Val Arg Phe Asp Ser Asp Val
55                  60                  65                  70

ggg atg ttt gtg gca ttg acc aag ctg ggg cag cca gat gct gag cag        355
Gly Met Phe Val Ala Leu Thr Lys Leu Gly Gln Pro Asp Ala Glu Gln
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tgg aac agc cgg ctg gat ctc ttg gag agg agc aga cag gcc gtg gat        403
Trp Asn Ser Arg Leu Asp Leu Leu Glu Arg Ser Arg Gln Ala Val Asp
            90                  95                  100

ggg gtc tgt aga cac aac tac agg ctg ggc gca ccc ttc act gtg ggg        451
Gly Val Cys Arg His Asn Tyr Arg Leu Gly Ala Pro Phe Thr Val Gly
        105                 110                 115

aga aaa gtg caa cca gag gtg aca gtg tac cca gag agg acc cca ctc        499
Arg Lys Val Gln Pro Glu Val Thr Val Tyr Pro Glu Arg Thr Pro Leu
    120                 125                 130

ctg cac cag cat aat ctg ctg cac tgc tct gtg aca ggc ttc tat cca        547
Leu His Gln His Asn Leu Leu His Cys Ser Val Thr Gly Phe Tyr Pro
135                 140                 145                 150

ggg gat atc aag atc aag tgg ttc ctg aat ggg cag gag gag aga gct        595
Gly Asp Ile Lys Ile Lys Trp Phe Leu Asn Gly Gln Glu Glu Arg Ala
                155                 160                 165

ggg gtc atg tcc act ggc cct atc agg aat gga gac tgg acc ttt cag        643
Gly Val Met Ser Thr Gly Pro Ile Arg Asn Gly Asp Trp Thr Phe Gln
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act gtg gtg atg cta gaa atg act cct gaa ctt gga cat gtc tac acc        691
Thr Val Val Met Leu Glu Met Thr Pro Glu Leu Gly His Val Tyr Thr
        185                 190                 195

tgc ctt gtc gat cac tcc agc ctg ctg agc cct gtt tct gtg gag tgg        739
Cys Leu Val Asp His Ser Ser Leu Leu Ser Pro Val Ser Val Glu Trp
    200                 205                 210

aga gct cag tct gaa tat tct tgg aga aag atg ctg agt ggc att gca        787
Arg Ala Gln Ser Glu Tyr Ser Trp Arg Lys Met Leu Ser Gly Ile Ala
215                 220                 225                 230

gcc ttc cta ctt ggg cta atc ttc ctt ctg gtg gga atc gtc atc cag        835
Ala Phe Leu Leu Gly Leu Ile Phe Leu Leu Val Gly Ile Val Ile Gln
                235                 240                 245

cta agg gct cag aaa gga tat gtg agg acg cag atg tct ggt aat gag        883
Leu Arg Ala Gln Lys Gly Tyr Val Arg Thr Gln Met Ser Gly Asn Glu
            250                 255                 260

gtc tca aga gct gtt ctg ctc cct cag tca tgc taa ggtcctcact            929
Val Ser Arg Ala Val Leu Leu Pro Gln Ser Cys
        265                 270

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Phe Val Ile Gln Ala Lys Ala Asp Cys Tyr Phe Thr Asn Gly Thr Glu
        35                  40                  45


Lys Val Gln Phe Val Val Arg Phe Ile Phe Asn Leu Glu Glu Tyr Val
    50                  55                  60


Arg Phe Asp Ser Asp Val Gly Met Phe Val Ala Leu Thr Lys Leu Gly
65                  70                  75                  80
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Gln Pro Asp Ala Glu Gln Trp Asn Ser Arg Leu Asp Leu Leu Glu Arg
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Ser Arg Gln Ala Val Asp Gly Val Cys Arg His Asn Tyr Arg Leu Gly
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Ala Pro Phe Thr Val Gly Arg Lys Val Gln Pro Glu Val Thr Val Tyr
        115                 120                 125

Pro Glu Arg Thr Pro Leu Leu His Gln His Asn Leu Leu His Cys Ser
    130                 135                 140

Val Thr Gly Phe Tyr Pro Gly Asp Ile Lys Ile Lys Trp Phe Leu Asn
145                 150                 155                 160

Gly Gln Glu Glu Arg Ala Gly Val Met Ser Thr Gly Pro Ile Arg Asn
                165                 170                 175

Gly Asp Trp Thr Phe Gln Thr Val Val Met Leu Glu Met Thr Pro Glu
            180                 185                 190

Leu Gly His Val Tyr Thr Cys Leu Val Asp His Ser Ser Leu Leu Ser
        195                 200                 205

Pro Val Ser Val Glu Trp Arg Ala Gln Ser Glu Tyr Ser Trp Arg Lys
    210                 215                 220

Met Leu Ser Gly Ile Ala Ala Phe Leu Leu Gly Leu Ile Phe Leu Leu
225                 230                 235                 240

Val Gly Ile Val Ile Gln Leu Arg Ala Gln Lys Gly Tyr Val Arg Thr
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Gln Met Ser Gly Asn Glu Val Ser Arg Ala Val Leu Leu Pro Gln Ser
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