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(54) **CHIMERIC ANTIGEN RECEPTOR
DENDRITIC CELL (CAR-DC) FOR
TREATMENT OF CANCER**

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(57) **ABSTRACT**

The current invention provides monocytic cells transfected with chimeric antigen receptor (CAR) to selectively home to tumors and upon homing differentiate into dendritic cells capable of activating immunity which is inhibitory to said tumor. In one embodiment of the invention, monocytic cells are transfected with a construct encoding an antigen binding domain, a transcellular or structural domain, and an intracellular signaling domain. In one specific aspect of the invention, the antigen binding domain interacts with sufficient affinity to a tumor antigen, capable of triggering said intracellular domain to induce an activation signal to induce monocyte differentiation into DC.

CHIMERIC ANTIGEN RECEPTOR DENDRITIC CELL (CAR-DC) FOR TREATMENT OF CANCER

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This application claims the benefit of U.S. Provisional Application No. 62/118,027 filed on Feb. 19, 2015, the contents of which are incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

[0002] The present disclosure generally relates to the fields of genetics, immunology and medicine. The invention pertains to the field of immunotherapy, more specifically the invention pertains to the utilization of monocytes that have been manipulated to home to tumor cells and upon binding to tumor antigens differentiating into monocytes with cytotoxic properties to tumors, or dendritic cells.

BACKGROUND OF THE INVENTION

[0003] The immune system possesses the power to cure cancers based on published reports of immunologically mediated spontaneous regressions, which have been documented in colon, lung, melanoma, liver, breast. Intriguingly, spontaneous regression clinically, as well as in an animal model of spontaneous regression, seems to be associated primarily with stimulation of the innate immune system, comprising of macrophages, NK cells, NKT cells and neutrophils. Despite the original promising of immunotherapy, which will be mentioned, the field has focused on the adaptive immune response, specifically stimulation of T and B cells, and only recently has interest re-ignited in the innate immune system.

[0004] The use of the immune system to treat cancer is theoretically appealing due to the possibility of low toxicity, immunological memory, and ability to attack metastatic disease. Early studies suggested that vaccination to tumor antigens and tumors themselves may be possible. Specifically, Prehn back in 1957, obtained murine tumors and exposed them to irradiation to increase immunogenicity. When these tumors were implanted into animals they were rejected. Subsequent administration of the original tumors resulted in rejection of the tumors, thus suggesting that tumor specific antigens exist, which can stimulate immunity, especially subsequent to addition of a cellular stress such as irradiation. Twenty years later, using the same system it was demonstrated that cytotoxic T cells infiltrated the tumors that were implanted after rejection of the radiation induced tumors, thus demonstrating conclusively that rejection was immunologically mediated, despite the fact that the tumors were syngeneic. In humans, one of the original observations of immunological response to neoplasia was in patients with paraneoplastic disease in which immune response to breast cancer antigens results in a multiple sclerosis-like disease caused by cross reactive immunity to neural antigens that are found on the breast cancer. Specific identification of tumor antigens on a molecular basis led to the discovery that some of the antigens are either self-proteins aberrantly expressed, or mutations of self proteins.

[0005] Originally observations were made in patients bearing metastatic melanomas, and then subsequently in other tumors, that the tumors are infiltrated with various

immunological components. These tumor infiltrating lymphocytes (TILs), contain populations of cells and individual clones that demonstrate tumor specificity; they lyse autologous tumor cells but not natural killer targets, allogeneic tumor cells, or autologous fibroblasts.

[0006] By isolating and expanding TILs in vitro, and then molecularly identifying what they are responding to, a variety of the well-known tumor agents have been discovered such as MAGE-1, and MAGE-3, GAGE-1, MART-1, Melan-A, gp100, gp75 (TRP-2), tyrosinase, NY-ESO-1, mutated p16, and beta catenin. It is interesting that in the case of some antigens, such as gp75, the peptide that elicits tumor rejection results from translation of an alternative open reading frame of the same gene. Thus, the gp75 gene encodes two completely different polypeptides, gp75 as an antigen recognized by immunoglobulin G antibodies in sera from a patient with cancer, and a 24-amino acid product as a tumor rejection antigen recognized by T cells. Peptides used for immunization generally are 8-9 amino acids which have been demonstrated to be displayed in association with class I MHC molecules for recognition by T cells, and tumor cells have been shown to express these naturally processed epitopes.

[0007] Despite the intellectual appeal of peptide based cancer vaccines, the response rate has been disappointingly low. According to a review by Steven Rosenberg's group at the NIH, the rate of objective response out of 440 patients treated at his institute was a dismal 2.6%.

[0008] The ability to make a universal yet versatile system to generate T cells that are capable of recognizing various types of cancers has important clinical implications for the use of T cell-based therapies, this concept was approached initially by Rosenberg's group in the ex vivo expansion of tumor infiltrating lymphocytes. One current strategy incorporates the use of genetic engineering to express a chimeric antigen receptor (CAR) on T cells. The extracellular domain of a typical CAR consists of the V_H and V_L domains—single-chain fragment variable (scFv)—from the antigen binding sites of a monoclonal antibody. The scFv is linked to a flexible transmembrane domain followed by a tyrosine-based activation motif such as that from CD3 ζ . The so-called second and third generation CARs include additional activation domains from co-stimulatory molecules such as CD28 and CD137 (41BB) which serve to enhance T cell survival and proliferation. CAR T cells offer the opportunity to seek out and destroy cancer cells by recognizing tumor-associated antigens (TAA) expressed on their surface. As such, the recognition of a tumor cells occurs via an MHC-independent mechanism.

[0009] Various preclinical and early-phase clinical trials highlight the efficacy of CAR T cells to treat cancer patients with solid tumors and hematopoietic malignancies. Despite of the promise that CAR T cells might have in treating cancer patients there are several limitations to the generalized clinical application of CAR T cells. First, since no single tumor antigen is universally expressed by all cancer types, scFv in CAR needs to be constructed for each tumor antigen to be targeted. Second, the financial cost and labor-intensive tasks associated with identifying and engineering scFvs against a variety of tumor antigens poses a major challenge. Third, tumor antigens targeted by CAR could be down-regulated or mutated in response to treatment resulting in tumor evasion. Since current CAR T cells recognize only one target antigen, such changes in tumors negate the

therapeutic effects. Therefore, the generation of CAR T cells capable of recognizing multiple tumor antigens is highly desired. Finally, CAR T cells react with target antigen weakly expressed on non-tumor cells, potentially causing severe adverse effects. To avoid such “on-target off-tumor” reaction, use of scFvs with higher specificity to tumor antigen is required. And although ongoing studies are focused on generating methods to shut off CAR T cells in vivo this system has yet to be developed and might pose additional inherent challenges.

[0010] The current patent seeks to apply chimeric antigen receptor technology to activation of monocytes, which naturally home into tumors, to differentiated intratumorally said monocytes into dendritic cells which are capable of antigen presentation, as well as direct killing of tumors.

DETAILED DESCRIPTION OF THE INVENTION

[0011] Chimeric antigen receptor (CAR) cellular therapeutics have revolutionized the treatment of B cell malignancies achieving stunning success rates. Unfortunately, solid tumors have yet to benefit from this treatment. Additionally, patients treated with CAR-T cells lack B cells for the rest of their lives, as well as having the possibility of tumor lysis syndrome. This is in part due to the permanence of the CAR-T cells in the patients after treatment. The current invention applies the use of CAR technology to monocytes with the purpose of inducing differentiation to dendritic cells (DC) subsequent to contact with tumor antigens. Given that monocytes have a fixed mitotic index, fears of permanent manipulation of the host are diminished.

[0012] “Treating a cancer”, “inhibiting cancer”, “reducing cancer growth” refers to inhibiting or preventing oncogenic activity of cancer cells. Oncogenic activity can comprise inhibiting migration, invasion, drug resistance, cell survival, anchorage-independent growth, non-responsiveness to cell death signals, angiogenesis, or combinations thereof of the cancer cells.

[0013] The terms “cancer”, “cancer cell”, “tumor”, and “tumor cell” are used interchangeably herein and refer generally to a group of diseases characterized by uncontrolled, abnormal growth of cells (e.g., a neoplasia). In some forms of cancer, the cancer cells can spread locally or through the bloodstream and lymphatic system to other parts of the body (“metastatic cancer”).

[0014] “Ex vivo activated lymphocytes”, “lymphocytes with enhanced antitumor activity” and “dendritic cell cytokine induced killers” are terms used interchangeably to refer to composition of cells that have been activated ex vivo and subsequently reintroduced within the context of the current invention. Although the word “lymphocyte” is used, this also includes heterogenous cells that have been expanded during the ex vivo culturing process including dendritic cells, NKT cells, gamma delta T cells, and various other innate and adaptive immune cells.

[0015] As used herein, “cancer” refers to all types of cancer or neoplasm or malignant tumors found in animals, including leukemias, carcinomas and sarcomas. Examples of cancers are cancer of the brain, melanoma, bladder, breast, cervix, colon, head and neck, kidney, lung, non-small cell lung, mesothelioma, ovary, prostate, sarcoma, stomach, uterus and Medulloblastoma.

[0016] The term “leukemia” is meant broadly progressive, malignant diseases of the hematopoietic organs/systems and

is generally characterized by a distorted proliferation and development of leukocytes and their precursors in the blood and bone marrow. Leukemia diseases include, for example, acute nonlymphocytic leukemia, chronic lymphocytic leukemia, acute granulocytic leukemia, chronic granulocytic leukemia, acute promyelocytic leukemia, adult T-cell leukemia, aleukemic leukemia, a leukocythemic leukemia, basophilic leukemia, blast cell leukemia, bovine leukemia, chronic myelocytic leukemia, leukemia cutis, embryonal leukemia, eosinophilic leukemia, Gross’ leukemia, Rieder cell leukemia, Schilling’s leukemia, stem cell leukemia, subleukemic leukemia, undifferentiated cell leukemia, hairy-cell leukemia, hemoblastic leukemia, hemocytoblastic leukemia, histiocytic leukemia, stem cell leukemia, acute monocytic leukemia, leukopenic leukemia, lymphatic leukemia, lymphoblastic leukemia, lymphocytic leukemia, lymphogenous leukemia, lymphoid leukemia, lymphosarcoma cell leukemia, mast cell leukemia, megakaryocytic leukemia, micromyeloblastic leukemia, monocytic leukemia, myeloblastic leukemia, myelocytic leukemia, myeloid granulocytic leukemia, myelomonocytic leukemia, Naegeli leukemia, plasma cell leukemia, plasmacytic leukemia, and promyelocytic leukemia.

[0017] The term “carcinoma” refers to a malignant new growth made up of epithelial cells tending to infiltrate the surrounding tissues, and/or resist physiological and non-physiological cell death signals and give rise to metastases. Exemplary carcinomas include, for example, acinar carcinoma, acinous carcinoma, adenocystic carcinoma, adenoid cystic carcinoma, carcinoma adenomatosum, carcinoma of adrenal cortex, alveolar carcinoma, alveolar cell carcinoma, basal cell carcinoma, carcinoma basocellulare, basaloid carcinoma, basosquamous cell carcinoma, bronchioalveolar carcinoma, bronchiolar carcinoma, bronchogenic carcinoma, cerebriiform carcinoma, cholangiocellular carcinoma, chorionic carcinoma, colloid carcinoma, comedo carcinoma, corpus carcinoma, cribriform carcinoma, carcinoma en cuirasse, carcinoma *cutaneum*, cylindrical carcinoma, cylindrical cell carcinoma, duct carcinoma, carcinoma durum, embryonal carcinoma, encephaloid carcinoma, epinoid carcinoma, carcinoma epitheliale adenoides, exophytic carcinoma, carcinoma ex ulcere, carcinoma fibrosum, gelatiniform carcinoma, gelatinous carcinoma, giant cell carcinoma, signet-ring cell carcinoma, carcinoma simplex, small-cell carcinoma, solanoid carcinoma, spheroidal cell carcinoma, spindle cell carcinoma, carcinoma spongiosum, squamous carcinoma, squamous cell carcinoma, string carcinoma, carcinoma telangiectaticum, carcinoma telangiectodes, transitional cell carcinoma, carcinoma *tuberosum*, tuberous carcinoma, verrucous carcinoma, carcinoma *villosum*, carcinoma gigantocellulare, glandular carcinoma, granulosa cell carcinoma, hair-matrix carcinoma, hematoid carcinoma, hepatocellular carcinoma, Hurthle cell carcinoma, hyaline carcinoma, hypemephroid carcinoma, infantile embryonal carcinoma, carcinoma in situ, intraepidermal carcinoma, intraepithelial carcinoma, Krompecher’s carcinoma, Kulchitzky-cell carcinoma, large-cell carcinoma, lenticular carcinoma, carcinoma lenticulare, lipomatous carcinoma, lymphoepithelial carcinoma, carcinoma medullare, medullary carcinoma, melanotic carcinoma, carcinoma molle, mucinous carcinoma, carcinoma muciparum, carcinoma mucocellulare, mucoepidermoid carcinoma, carcinoma *mucosum*, mucous carcinoma, carcinoma myxomatodes, nasopharyngeal carcinoma, oat cell carcinoma, carcinoma

ossificans, osteoid carcinoma, papillary carcinoma, periportal carcinoma, preinvasive carcinoma, prickle cell carcinoma, pultaceous carcinoma, renal cell carcinoma of kidney, reserve cell carcinoma, carcinoma sarcomatodes, schneiderian carcinoma, scirrhous carcinoma, and carcinoma scroti.

[0018] The term “sarcoma” generally refers to a tumor which is made up of a substance like the embryonic connective tissue and is generally composed of closely packed cells embedded in a fibrillar, heterogeneous, or homogeneous substance. Sarcomas include, chondrosarcoma, fibrosarcoma, lymphosarcoma, melanosarcoma, myxosarcoma, osteosarcoma, endometrial sarcoma, stromal sarcoma, Ewing’s sarcoma, fascial sarcoma, fibroblastic sarcoma, giant cell sarcoma, Abemethy’s sarcoma, adipose sarcoma, liposarcoma, alveolar soft part sarcoma, ameloblastic sarcoma, botryoid sarcoma, chloroma sarcoma, chorio carcinoma, embryonal sarcoma, Wilms’ tumor sarcoma, granulocytic sarcoma, Hodgkin’s sarcoma, idiopathic multiple pigmented hemorrhagic sarcoma, immunoblastic sarcoma of B cells, lymphoma, immunoblastic sarcoma of T-cells, Jensen’s sarcoma, Kaposi’s sarcoma, Kupffer cell sarcoma, angiosarcoma, leukosarcoma, malignant mesenchymoma sarcoma, parosteal sarcoma, reticulocytic sarcoma, Rous sarcoma, serocystic sarcoma, synovial sarcoma, and telangiectatic sarcoma. Additional exemplary neoplasias include, for example, Hodgkin’s Disease, Non-Hodgkin’s Lymphoma, multiple myeloma, neuroblastoma, breast cancer, ovarian cancer, lung cancer, rhabdomyosarcoma, primary thrombocytosis, primary macroglobulinemia, small-cell lung tumors, primary brain tumors, stomach cancer, colon cancer, malignant pancreatic insulanoma, malignant carcinoma, premalignant skin lesions, testicular cancer, lymphomas, thyroid cancer, neuroblastoma, esophageal cancer, genitourinary tract cancer, malignant hypercalcemia, cervical cancer, endometrial cancer, and adrenal cortical cancer.

[0019] In some particular embodiments of the invention, the cancer treated is a melanoma. The term “melanoma” is taken to mean a tumor arising from the melanocytic system of the skin and other organs. Melanomas include, for example, Harding-Passey melanoma, juvenile melanoma, lentigo maligna melanoma, malignant melanoma, acral-lentiginous melanoma, amelanotic melanoma, benign juvenile melanoma, Cloudman’s melanoma, S91 melanoma, nodular melanoma subungal melanoma, and superficial spreading melanoma.

[0020] The term “polypeptide” is used interchangeably with “peptide”, “altered peptide ligand”, and “fluorocarbonated peptides.”

[0021] The term “pharmaceutically acceptable carrier” includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active compound, use thereof in the therapeutic compositions is contemplated. Supplementary active compounds can also be incorporated into the compositions.

[0022] The term “T cell” is also referred to as T lymphocyte, and means a cell derived from thymus among lymphocytes involved in an immune response. The T cell includes any of a CD8-positive T cell (cytotoxic T cell: CTL), a CD4-positive T cell (helper T cell), a suppressor T cell, a regulatory T cell such as a controlling T cell, an

effector cell, a naive T cell, a memory T cell, an $\alpha\beta$ T cell expressing TCR α and β chains, and a $\gamma\delta$ T cell expressing TCR γ and δ chains. The T cell includes a precursor cell of a T cell in which differentiation into a T cell is directed.

[0023] Examples of “cell populations containing T cells” include, in addition to body fluids such as blood (peripheral blood, umbilical blood etc.) and bone marrow fluids, cell populations containing peripheral blood mononuclear cells (PBMC), hematopoietic cells, hematopoietic stem cells, umbilical blood mononuclear cells etc., which have been collected, isolated, purified or induced from the body fluids. Further, a variety of cell populations containing T cells and derived from hematopoietic cells can be used in the present invention. These cells may have been activated by cytokine such as IL-2 in vivo or ex vivo. As these cells, any of cells collected from a living body, or cells obtained via ex vivo culture, for example, a T cell population obtained by the method of the present invention as it is, or obtained by freeze preservation, can be used.

[0024] The term “antibody” is meant to include both intact molecules as well as fragments thereof that include the antigen-binding site. Whole antibody structure is often given as H_2L_2 and refers to the fact that antibodies commonly comprise 2 light (L) amino acid chains and 2 heavy (H) amino acid chains. Both chains have regions capable of interacting with a structurally complementary antigenic target. The regions interacting with the target are referred to as “variable” or “V” regions and are characterized by differences in amino acid sequence from antibodies of different antigenic specificity. The variable regions of either H or L chains contains the amino acid sequences capable of specifically binding to antigenic targets. Within these sequences are smaller sequences dubbed “hypervariable” because of their extreme variability between antibodies of differing specificity. Such hypervariable regions are also referred to as “complementarity determining regions” or “CDR” regions. These CDR regions account for the basic specificity of the antibody for a particular antigenic determinant structure. The CDRs represent non-contiguous stretches of amino acids within the variable regions but, regardless of species, the positional locations of these critical amino acid sequences within the variable heavy and light chain regions have been found to have similar locations within the amino acid sequences of the variable chains. The variable heavy and light chains of all antibodies each have 3 CDR regions, each non-contiguous with the others (termed L1, L2, L3, H1, H2, H3) for the respective light (L) and heavy (H) chains. The antibodies disclosed according to the invention may also be wholly synthetic, wherein the polypeptide chains of the antibodies are synthesized and, possibly, optimized for binding to the polypeptides disclosed herein as being receptors. Such antibodies may be chimeric or humanized antibodies and may be fully tetrameric in structure, or may be dimeric and comprise only a single heavy and a single light chain.

[0025] The term “effective amount” or “therapeutically effective amount” means a dosage sufficient to treat, inhibit, or alleviate one or more symptoms of a disease state being treated or to otherwise provide a desired pharmacologic and/or physiologic effect, especially enhancing T cell response to a selected antigen. The precise dosage will vary according to a variety of factors such as subject-dependent variables (e.g., age, immune system health, etc.), the disease, and the treatment being administered.

[0026] The terms “individual”, “host”, “subject”, and “patient” are used interchangeably herein, and refer to a mammal, including, but not limited to, primates, for example, human beings, as well as rodents, such as mice and rats, and other laboratory animals.

[0027] As used herein, the term “treatment regimen” refers to a treatment of a disease or a method for achieving a desired physiological change, such as increased or decreased response of the immune system to an antigen or immunogen, such as an increase or decrease in the number or activity of one or more cells, or cell types, that are involved in such response, wherein said treatment or method comprises administering to an animal, such as a mammal, especially a human being, a sufficient amount of two or more chemical agents or components of said regimen to effectively treat a disease or to produce said physiological change, wherein said chemical agents or components are administered together, such as part of the same composition, or administered separately and independently at the same time or at different times (i.e., administration of each agent or component is separated by a finite period of time from one or more of the agents or components) and where administration of said one or more agents or components achieves a result greater than that of any of said agents or components when administered alone or in isolation.

[0028] The term “anergy” and “unresponsiveness” includes unresponsiveness to an immune cell to stimulation, for example, stimulation by an activation receptor or cytokine. The anergy may occur due to, for example, exposure to an immune suppressor or exposure to an antigen in a high dose. Such anergy is generally antigen-specific, and continues even after completion of exposure to a tolerized antigen. For example, the anergy in a T cell and/or NK cell is characterized by failure of production of cytokine, for example, interleukin (IL)-2. The T cell anergy and/or NK cell anergy occurs in part when a first signal (signal via TCR or CD-3) is received in the absence of a second signal (costimulatory signal) upon exposure of a T cell and/or NK cell to an antigen.

[0029] The term “enhanced function of a T cell”, “enhanced cytotoxicity” and “augmented activity” means that the effector function of the T cell and/or NK cell is improved. The enhanced function of the T cell and/or NK cell, which does not limit the present invention, includes an improvement in the proliferation rate of the T cell and/or NK cell, an increase in the production amount of cytokine, or an improvement in cytotoxicity. Further, the enhanced function of the T cell and/or NK cell includes cancellation and suppression of tolerance of the T cell and/or NK cell in the suppressed state such as the anergy (unresponsive) state, or the rest state, that is, transfer of the T cell and/or NK cell from the suppressed state into the state where the T cell and/or NK cell responds to stimulation from the outside.

[0030] The term “expression” means generation of mRNA by transcription from nucleic acids such as genes, polynucleotides, and oligonucleotides, or generation of a protein or a polypeptide by transcription from mRNA. Expression may be detected by means including RT-PCR, Northern Blot, or in situ hybridization.

[0031] “Suppression of expression” refers to a decrease of a transcription product or a translation product in a significant amount as compared with the case of no suppression. The suppression of expression herein shows, for example, a decrease of a transcription product or a translation product

in an amount of 30% or more, preferably 50% or more, more preferably 70% or more, and further preferably 90% or more.

[0032] In one embodiment of the invention the CAR-DC are antigen-loaded and co-cultured with T-lymphocytes to produce antigen-specific T-cells. As used herein, the term “antigen-specific T-cells” refers to T-cells that proliferate upon exposure to the antigen-loaded APCs of the present invention, as well as to develop the ability to attack cells having the specific antigen on their surfaces. Such T-cells, e.g., cytotoxic T-cells, lyse target cells by a number of methods, e.g., releasing toxic enzymes such as granzymes and perforin onto the surface of the target cells or by effecting the entrance of these lytic enzymes into the target cell interior. Generally, cytotoxic T-cells express CD8 on their cell surface. T-cells that express the CD4 antigen CD4, commonly known as “helper” T-cells, can also help promote specific cytotoxic activity and may also be activated by the antigen-loaded APCs of the present invention. In certain embodiments, the cancer cells, the APCs and even the T-cells can be derived from the same donor whose MNC yielded the DC, which can be the patient or an HLA—or obtained from the individual patient that is going to be treated. Alternatively, the cancer cells, the APCs and/or the T-cells can be allogeneic.

[0033] The invention provides means of inducing an anti-cancer response in a mammal, comprising the steps of initially “priming” the mammal by administering an agent that causes local accumulation of CAR-DC. Subsequently, a tumor antigen is administered in the local area where said agents causing accumulation of antigen presenting cells is administered. A time period is allowed to pass to allow for said antigen presenting cells to traffic to the lymph nodes. Subsequently a maturation signal, or a plurality of maturation signals are administered to enhance the ability of said antigen presenting cell to activate adaptive immunity. In some embodiments of the invention activators of adaptive immunity are concurrently given, as well as inhibitors of the tumor derived inhibitors are administered to derepress the immune system.

[0034] In one embodiment priming of the patient is achieved by administration of GM-CSF subcutaneously in the area in which antigen is to be injected. Various scenarios are known in the art for administration of GM-CSF prior to administration, or concurrently with administration of antigen. The practitioner of the invention is referred to the following publications for dosage regimens of GM-CSF and also of peptide antigens.

[0035] Subsequent to priming, the invention calls for administration of tumor antigen. Various tumor antigens may be utilized, in one preferred embodiment, lysed tumor cells from the same patient area utilized. Means for generation of lysed tumor cells are well known in the art and described in the following references. One example method for generation of tumor lysate involves obtaining frozen autologous samples which are placed in hanks buffered saline solution (HBSS) and gentamycin 50 µg/ml followed by homogenization by a glass homogenizer. After repeated freezing and thawing, particle-containing samples are selected and frozen in aliquots after radiation with 25 kGy. Quality assessment for sterility and endotoxin content is performed before freezing. Cell lysates are subsequently administered into the patient in a preferred manner subcutaneously at the local areas where DC priming was initiated.

After 12-72 hours, the patient is subsequently administered with an agent capable of inducing maturation of DC. Agents useful for the practice of the invention, in a preferred embodiment include BCG and HMGB1 peptide. Other useful agents include: a) histone DNA; b) imiquimod; c) beta-glucan; d) hsp65; e) hsp90; f) HMGB-1; g) lipopolysaccharide; h) Pam3CSK4; i) Poly I: Poly C; j) Flagellin; k) MALP-2; l) Imidazoquinoline; m) Resiquimod; n) CpG oligonucleotides; o) zymosan; p) peptidoglycan; q) lipoteichoic acid; r) lipoprotein from gram-positive bacteria; s) lipoarabinomannan from mycobacteria; t) Polyadenylic-polyuridylic acid; u) monophosphoryl lipid A; v) single stranded RNA; w) double stranded RNA; x) 852A; y) rintatolimod; z) Gardiquimod; and aa) lipopolysaccharide peptides. The procedure is performed in a preferred embodiment with the administration of IDO silencing siRNA or shRNA containing the effector sequences a) UUAUAAUGACUGGAUGUUC; b) GUCUGGU-GUAUGAAGGGUU; c) CUCCUAUUUUGGUUUAUGC and d) GCAGCGUCUUUCAGUGCUU. siRNA or shRNA may be administered through various modalities including biodegradable matrices, pressure gradients or viral transfect. In another embodiment, autologous dendritic cells are generated and IDO is silenced, prior to, concurrent with or subsequent to silencing, said dendritic cells are pulsed with tumor antigen and administered systemically.

[0036] In one embodiment of the invention mature DC are modified with CAR transfection prior to administration. Culture of dendritic cells is well known in the art, for example, U.S. Pat. No. 6,936,468, issued to Robbins, et al., for the use of tolerogenic dendritic cells for enhancing tolerogenicity in a host and methods for making the same. Although the current invention aims to reduce tolerogenesis, the essential means of dendritic cell generation are disclosed in the patent. U.S. Pat. No. 6,734,014, issued to Hwu, et al., for methods and compositions for transforming dendritic cells and activating T cells. Briefly, recombinant dendritic cells are made by transforming a stem cell and differentiating the stem cell into a dendritic cell. The resulting dendritic cell is said to be an antigen presenting cell which activates T cells against MHC class I-antigen targets. Antigens for use in dendritic cell loading are taught in, e.g., U.S. Pat. No. 6,602,709, issued to Albert, et al. This patent teaches methods for use of apoptotic cells to deliver antigen to dendritic cells for induction or tolerization of T cells. The methods and compositions are said to be useful for delivering antigens to dendritic cells that are useful for inducing antigen-specific cytotoxic T lymphocytes and T helper cells. The disclosure includes assays for evaluating the activity of cytotoxic T lymphocytes. The antigens targeted to dendritic cells are apoptotic cells that may also be modified to express non-native antigens for presentation to the dendritic cells. The dendritic cells are said to be primed by the apoptotic cells (and fragments thereof) capable of processing and presenting the processed antigen and inducing cytotoxic T lymphocyte activity or may also be used in vaccine therapies. U.S. Pat. No. 6,455,299, issued to Steinman, et al., teaches methods of use for viral vectors to deliver antigen to dendritic cells. Methods and compositions are said to be useful for delivering antigens to dendritic cells, which are then useful for inducing T antigen specific cytotoxic T lymphocytes. The disclosure provides assays for evaluating the activity of cytotoxic T lymphocytes. Antigens are provided to dendritic cells using a viral vector such as influenza

virus that may be modified to express non-native antigens for presentation to the dendritic cells. The dendritic cells are infected with the vector and are said to be capable of presenting the antigen and inducing cytotoxic T lymphocyte activity or may also be used as vaccines.

[0037] Immune cells for use in the practice of the invention include DCs, the presence of which may be checked in the previously described method, are preferably selected from myeloid cells (such as monocytic cells and macrophages) expressing langerin, MHC (major histocompatibility complex) class II, CCR2 (chemokine (C—C motif) receptor 2), CX3CR1 and/or Gr1 molecules in mice; myeloid cells expressing CD14, CD16, HLA dR (human leukocyte antigen disease resistance) molecule, langerin, CCR2 and/or CX3CR1 in humans; dendritic cells expressing CD11c, MHC class II molecules, and/or CCR7 molecules; and IL-1 β producing dendritic cells. CD8 T cells, the presence of which may be checked in the previously described method, are preferably selected from CD3+, CD4+ and/or CD8+T lymphocytes, FOXP3 (forkhead box P3) T lymphocytes, Granzyme B/TIA (Tcell-restricted intracellular antigen) T lymphocytes, and Tc1 cells (IFN- γ producing CD8+T lymphocytes). Immune cells expressing a protein that binds calreticulin, such immune cells may be selected from cells expressing at least one of the following proteins: LRP1 (Low density lipoprotein receptor-related protein 1, CD91), Ca^{sup}.++-binding proteins such as SCARF1 and SCARF2, MSR1 (Macrophage scavenger receptor 1), SRA, CD59 (protectin), CD207 (langerin), and THSD1 (thrombospondin). There are numerous means known in the art to identify cells expressing various antigens, these include immunochemistry, immunophenotyping, flow cytometry, Elispots assays, classical tetramer staining, and intracellular cytokine stainings.

[0038] Macrophages selectively phagocytose tumor cells, but this process is countered by protective molecules on tumor cells such as CD47, which binds macrophage signal-regulatory protein a to inhibit phagocytosis. Blockade of CD47 on tumor cells leads to phagocytosis by macrophages. In one embodiment of the invention CAR-MSC are administered together with an agent that blocks CD47 activity. It has been demonstrated that activation of TLR signaling pathways in macrophages synergizes with blocking CD47 on tumor cells to enhance tumor phagocytosis. Bruton's tyrosine kinase (Btk) mediates TLR signaling in macrophages. Calreticulin, previously shown to be a protein found on cancer cells that activated macrophage phagocytosis of tumors, is activated in macrophages for secretion and cell-surface exposure by TLR and Btk to target cancer cells for phagocytosis, even if the cancer cells themselves do not express calreticulin. In one embodiment of the invention TLR agonists are administered that stimulate expression of calreticulin and/or enhance macrophage phagocytosis of tumors.

[0039] IL-27 induces macrophage ability to kill tumor cells in vitro and in vivo, as well as altering the tumor promoting M2/myeloid suppressor cells into tumoricidal cells. In one embodiment of the invention addition of IL-27 or compounds capable of activating the IL-27 receptor signaling are administered together with IL-27 to enhance tumor phagocytosis by macrophages.

[0040] Tumor-associated macrophages, deriving from monocytes or migrating into the tumor, are an important constituent of tumor microenvironments, which in many

cases modulates tumor growth, tumor angiogenesis, immune suppression, metastasis and chemoresistance. Mechanisms of macrophage promotion of tumor growth include production of EGF, M-CSF, VEGF.

[0041] Macrophage infiltration of tumors is associated with poor prognosis in renal, melanoma, breast, pancreatic, lung, endometrial, bladder, prostate.

[0042] Tumor growth are inhibited when monocytes/macrophages are ablated. There is ample evidence that many anticancer modalities currently used in the clinic have unique and distinct properties that modulate the recruitment, polarization and tumorigenic activities of macrophages in the tumor microenvironments. By manipulating tumor-associated macrophages significant impact on the clinical efficacies of and resistance to these anticancer modalities. Accordingly, in one aspect of the invention, CAR-DC, CAR-monocytes, or CAR-macrophages are utilized to force the tumor microenvironment to stimulate tumor killing and inhibit macrophage or macrophage related cells from promoting tumor growth. Within the context of the invention, the use of drugs targeting tumor-associated macrophages, especially c-Fms kinase inhibitors and humanized antibodies targeting colony-stimulating factor-1 receptor, are envisioned.

[0043] Tumors mediate various effects to reprogram macrophages, these are usually mediated via IL-10 and other cytokines such as VEGF, TGF-beta, and M-CSF, which cause macrophages to lose tumor cytotoxicity and shift into tumor promoting, immune suppressive, angiogenic supporting cells. Related to tumor manipulated monocytes are myeloid derived suppressor cells, which are similar to myeloid progenitor cells, or the previously described "natural suppressor" cell.

[0044] Irradiated tissues induce a TLR-1 reprogramming of macrophages to promote tumor growth and angiogenesis. Macrophage promotion of tumor growth is seen in numerous situations, in one example, treating of tumor bearing animals with BRAF inhibitors results in upregulation of macrophage production of VEGF which accelerates tumor growth. Mechanistically, it is known that tumors produce factors such as GM-CSF which in part stimulate macrophages to produce CCL18, which promotes tumor metastasis. Additionally, the lactic acid microenvironment of the tumor has been shown to promote skewing of macrophages towards at tumor-promoting M2 type. It has been shown that lactic acid produced by tumour cells, as a by-product of aerobic or anaerobic glycolysis, possesses an essential role in inducing the expression of VEGF and the M2-like polarization of tumour-associated macrophages, specifically inducing expression of arginase 1 through a HIF-1alpha dependent pathway. Mechanistically, it is known that lactic acid in tumors is generated in a large part by lactate dehydrogenase-A (LDH-A), which converts pyruvate to lactate. siRNA silencing of LDH-A in Pan02 pancreatic cancer cells that are injected in C57BL/6 mice results in development of smaller tumors than mice injected with wild type, non-silenced Pan02 cells. Associated with the reduced tumor growth were observations of a decrease in the frequency of myeloid-derived suppressor cells (MDSCs) in the spleens of mice carrying LDH-A-silenced tumors. NK cells from LDH-A-depleted tumors had improved cytolytic function. Exogenous lactate administration was shown to increase the frequency of MDSCs generated from mouse bone marrow cells with GM-CSF and IL-6 in vitro. Furthermore lactate

pretreatment of NK cells in vitro inhibited cytolytic function of both human and mouse NK cells. This reduction of NK cytotoxic activity was accompanied by lower expression of perforin and granzyme in NK cells. The expression of Nkp46 was lower in lactate-treated NK cells. Accordingly, in one embodiment of the invention, depletion of glucose levels using a ketogenic diet to lower lactate production by glycolytic tumors is utilized to augment therapeutic effects of CAR-DC. Utilization of ketogenic diet has been previously described for immune modulation, and cancer therapy. Specific quantification of intratumoral lactate and its manipulation has been described and incorporated by reference. Potentiation of chemotherapeutic and radiotherapeutic effects by ketogenic diets have been reported and techniques are incorporated by reference for use with the current CAR-DC invention. Suppression of tumor growth and activity induced by ketogenic diet may be augmented by addition of hyperbaric oxygen, thus in one embodiment of the invention, the utilization of oxidative therapies, as disclosed in references incorporated, together with ketogenic diet is utilized to augment therapeutic efficacy of CAR-DC.

[0045] Not only has it been well known that monocytes and macrophages infiltrate tumors and appear to support tumor growth through growth factor production and secretion of angiogenic agents, but suggestions have been made that tumors themselves, as part of the epithelial mesenchymal transition may actually differentiate into monocytes in part associated with TGF-beta production. Specifically, a study reported performing gene-profiling analysis of mouse mammary EpRas tumor cells that had been allowed to adopt an epithelial to mesenchymal transition program after long-term treatment with TGF- β 1 for 2 weeks. While the treated cells acquired traits of mesenchymal cell differentiation and migration, gene analysis revealed another cluster of induced genes, which was specifically enriched in monocyte-derived macrophages, mast cells, and myeloid dendritic cells, but less in other types of immune cells. Further studies revealed that this monocyte/macrophage gene cluster was enriched in human breast cancer cell lines displaying an EMT or a Basal B profile, and in human breast tumors with EMT and undifferentiated (ER-/PR-) characteristics. The plasticity of tumor cells to potentially monocytic lineages should come as no surprise given that tumor cells have been shown to differentiate directly into pericytes, and endothelial cells/vascular channels.

[0046] Dopamine possesses antiangiogenic effects as well as myeloprotective effects, in one embodiment of the invention addition of dopamine to the CAR-DC treatment is disclosed.

[0047] Vinblastine is a widely used chemotherapeutic agent that has been demonstrated to induce dendritic cell maturation. In one embodiment of the invention CAR-DC are utilized together with vinblastine therapy to induce augmented anticancer activity. Oxiplatin and anthracyclines have been demonstrated to not only directly kill tumor cells but also stimulate T cell immunity against tumor cells. It was demonstrated that these agents induce a rapid and prominent invasion of interleukin (IL)-17-producing $\gamma\delta$ (V γ 4(+)) and V γ 6(+)) T lymphocytes ($\gamma\delta$ T17 cells) that precedes the accumulation of CD8 CTLs within the tumor bed. In T cell receptor δ (-/-) or V γ 4/6(-/-) mice, the therapeutic efficacy of chemotherapy was reduced and furthermore no IL-17 was produced by tumor-infiltrating T cells, and CD8 CTLs did not invade the tumor after treatment. Although $\gamma\delta$ Th17 cells

could produce both IL-17A and IL-22, the absence of a functional IL-17A-IL-17R pathway significantly reduced tumor-specific T cell responses elicited by tumor cell death, and the efficacy of chemotherapy in four independent transplantable tumor models. The adoptive transfer of $\gamma\delta$ T cells to naïve mice restored the efficacy of chemotherapy in IL-17A(−/−) hosts. The anticancer effect of infused $\gamma\delta$ T cells was lost when they lacked either IL-1R1 or IL-17A.

[0048] Intratumoral injection of dendritic cells stimulates antitumor immunity in vivo in clinical situations, suggesting that modulating the antigen presenting cell in the tumor microenvironment will induce an antitumor response. Administration of radiotherapy to tumors to induce immunogenic cell death, followed by intratumoral administration of DC has been demonstrated to result in enhanced antigen presentation, accordingly, this technique may be modified to enhance effects of CAR-DC. The induction of immunity to tumors in the present invention is associated with the unique nature of: a) ongoing basal cell death within the tumor; and b) cell death induced by chemotherapy, radiotherapy, hyperthermia, or otherwise induced cell death. Cell death can be classified according to the morphological appearance of the lethal process (that may be apoptotic, necrotic, autophagic or associated with mitosis), enzymological criteria (with and without the involvement of nucleases or distinct classes of proteases, like caspases), functional aspects (programmed or accidental, physiological or pathological) or immunological characteristics (immunogenic or non-immunogenic). Cell death is defined as “immunogenic” or “immune stimulatory” if dying cells that express a specific antigen (for example a tumor associated antigen, phosphatidyl serine, or calreticulin), yet are uninfected (and hence lack pathogen-associated molecular patterns), and are injected subcutaneously into mice, in the absence of any adjuvant, cause a protective immune response against said specific antigen. Such a protective immune response precludes the growth of living transformed cells expressing the specific antigen injected into mice. When cancer cells succumb to an immunogenic cell death (or immunogenic apoptosis) modality, they stimulate the immune system, which then mounts a therapeutic anti-cancer immune response and contributes to the eradication of residual tumor cells. Conversely, when cancer cells succumb to a non-immunogenic death modality, they fail to elicit such a protective immune response. Regardless of the types of cell death that are ongoing, the tumor derived immune suppressive molecules contribute to general inhibition or inability of the tumor to be eliminated.

[0049] Within the practice of the invention, CAR-DC are administered concurrently, prior to, or subsequent to administration of an agent that induces immunogenic cell death in a patient. Methods of determining whether compounds induce immunogenic cell death are known in the art and include the following, which was described by Zitvogel et al. (a) treating the cells, the mammalian cells and inducing the cell death or apoptosis, typically of mammalian cancer cells capable of expressing calreticulin (CRT), by exposing said mammalian cells to a particular drug (the test drug), for example 18 hours; (b) inoculating (for example intradermally) the dying mammalian cells from step (a) in a particular area (for example a flank) of the mammal, typically a mouse, to induce an immune response in this area of the mammal; (c) inoculating (for example intradermally) the minimal tumorigenic dose of syngeneic live tumor cells in a distinct area (for example the opposite flank) from the same

mammal, for example 7 days after step (b); and (d) comparing the size of the tumor in the inoculated mammal with a control mammal also exposed to the minimal tumorigenic dose of syngeneic live tumor cells of step (c) [for example a mouse devoid of T lymphocyte], the stabilization or regression of the tumor in the inoculated mammal being indicative of the drug immunogenicity. Other in vitro means are available for assessing the ability of various drugs or therapeutic approaches to induce immunogenic cell death. Specific characteristics to assess when screening for immunogenic cell death include: a) ability to induce dendritic cell maturation in vitro; b) ability to activate NK cells; and c) ability to induce activation of gamma delta T cells or NKT cells. Specific drugs known to induce immunogenic cell death include oxiplatine and anthracyclines, as well as radiotherapy, and hyperthermia. In the case of chemotherapies, certain chemotherapies that activate TLR4 through induction of HMGB1 have been observed to function sub-optimally in patients that have a TLR4 polymorphism, thus suggesting actual contribution of TLR activation as a means of chemotherapy inhibition of cancer. Additionally, oncoviruses or oncolytic viruses are known to induce immunogenic cell death and may be useful for the practice of the invention.

[0050] The CAR-DC disclosed in the invention may be utilized in combination with conventional immune modulators including BCG, CpG DNA, interferon alpha, tumor bacterial therapy, checkpoint inhibitors, Treg depleting agents, and low dose cyclophosphamide.

[0051] In one embodiment of the invention CAR-DC cells are generated with specificity towards ROBO-4. Numerous means of generating CAR-T cells are known in the art, which are applied to CAR-DC. In one embodiment of the invention FMC63-28z CAR (Genbank identifier HM852952.1), is used as the template for the CAR except the anti-CD19, single-chain variable fragment sequence is replaced with an ROBO-4 fragment. The construct is synthesized and inserted into a pLNCX retroviral vector. Retroviruses encoding the ROBO-4-specific CAR are generated using the retrovirus packaging kit, Amphi (Takara), following the manufacturer's protocol. For generation of CAR-DC cells donor blood is obtained and after centrifugation on Ficoll-Hypaque density gradients (Sigma-Aldrich), PBMCs are plated at 2×10^6 cells/mL in cell culture for 2 hours and the adherent cells are collected. The cells were then stimulated for 2 days on a tissue-culture-treated 24-well plate containing M-CSF at a concentration of 100 ng/ml. For retrovirus transduction, a 24-well plate are coated with RetroNectin (Takara) at 4° C. overnight, according to the manufacturer's protocol, and then blocked with 2% BSA at room temperature for 30 min. The plate was then loaded with retrovirus supernatants at 300 μ L/well and incubated at 37° C. for 6 h. Next, 1×10^6 stimulated adherent cells in 1 mL of medium are added to 1 mL of retrovirus supernatants before being transferred to the pre-coated wells and cultured at 37° C. for 2 d. The cells are then transferred to a tissue-culture-treated plate at 1×10^6 cells/mL and cultured in the presence of 100 U/mL of recombinant human M-CSF, applying the T cell protocol but not utilizing IL-2 or antiCD3/antiCD28.

[0052] Other means of generating CARs are known in the art and incorporated by reference. For example, Groner's group genetically modified T lymphocytes and endowed them with the ability to specifically recognize cancer cells. Tumor cells overexpressing the ErbB-2 receptor served as a

model. The target cell recognition specificity was conferred to T lymphocytes by transduction of a chimeric gene encoding the zeta-chain of the TCR and a single chain antibody (scFv(FRPS)) directed against the human ErbB-2 receptor. The chimeric scFv(FRPS)-zeta gene was introduced into primary mouse T lymphocytes via retroviral gene transfer. Naïve T lymphocytes were activated and infected by cocultivation with a retrovirus-producing packaging cell line. The scFv(FRPS)-zeta fusion gene was expressed in >75% of the T cells. These T cells lysed ErbB-2-expressing target cells in vitro with high specificity. In a syngeneic mouse model, mice were treated with autologous, transduced T cells. The adoptively transferred scFv(FRP5)-zeta-expressing T cells caused total regression of ErbB-2-expressing tumors. The presence of the transduced T lymphocytes in the tumor tissue was monitored. No humoral response directed against the transduced T cells was observed. Abs directed against the ErbB-2 receptor were detected upon tumor lysis. Hombach et al. constructed an anti-CEA chimeric receptor whose extracellular moiety is composed of a humanized scFv derived from the anti-CEA mAb BW431/26 and the CH2/CH3 constant domains of human IgG. The intracellular moiety consists of the gamma-signaling chain of the human Fc epsilon RI receptor constituting a completely humanized chimeric receptor. After transfection, the humBW431/26 scFv-CH2CH3-gamma receptor is expressed as a homodimer on the surface of MD45 T cells. Co-incubation with CEA+ tumor cells specifically activates grafted MD45 T cells indicated by IL-2 secretion and cytolytic activity against CEA+ tumor cells. Notably, the efficacy of receptor-mediated activation is not affected by soluble CEA up to 25 micrograms/ml demonstrating the usefulness of this chimeric receptor for specific cellular activation by membrane-bound CEA even in the presence of high concentrations of CEA, as found in patients during progression of the disease (200). These methods are described to guide one of skill in the art to practicing the invention, which in one embodiment is the utilization of CAR T cell approaches towards targeting tumor endothelium as compared to simply targeting the tumor itself.

[0053] Targeting of mucins associated with cancers has been performed with CAR T cells by grafting the antibody that binds to the mucin with CD3 zeta chain. For the purpose of the invention, this procedure is modified for CAR-DC. In an older publication chimeric immune receptor consisting of an extracellular antigen-binding domain derived from the CC49 humanized single-chain antibody, linked to the CD3zeta signaling domain of the T cell receptor, was generated (CC49-zeta). This receptor binds to TAG-72, a mucin antigen expressed by most human adenocarcinomas. CC49-zeta was expressed in CD4+ and CD8+ T cells and induced cytokine production on stimulation. Human T cells expressing CC49-zeta recognized and killed tumor cell lines and primary tumor cells expressing TAG-72. CC49-zeta T cells did not mediate bystander killing of TAG-72-negative cells. In addition, CC49-zeta T cells not only killed FasL-positive tumor cells in vitro and in vivo, but also survived in their presence, and were immunoprotective in intraperitoneal and subcutaneous murine tumor xenograft models with TAG-72-positive human tumor cells. Finally, receptor-positive T cells were still effective in killing TAG-72-positive targets in the presence of physiological levels of soluble TAG-72, and did not induce killing of TAG-72-negative cells under the same conditions.

[0054] For clinical practice of the invention several reports exist in the art that would guide the skilled artisan as to concentrations, cell numbers, and dosing protocols useful. While in the art CAR T cells have been utilized targeting surface tumor antigens, the main issue with this approach is the difficulty of T cells to enter tumors due to features specific to the tumor microenvironment. These include higher interstitial pressure inside the tumor compared to the surroundings, acidosis inside the tumor, and expression in the tumor of FasL which kills activated T cells. Accordingly the invention seeks to more effectively utilize CAR-DC cells by directly targeting them to tumor endothelium, which is in direct contact with blood and therefore not susceptible to intratumoral factors the limit efficacy of conventional T cell therapies. In other embodiments CAR-DC are targeting to tumor antigens.

[0055] In one embodiment of the invention, protocols similar to Kershaw et al. are utilized with the exception that tumor endothelial antigens are targeted as opposed to conventional tumor antigens. Such tumor endothelial antigens include CD93, TEM-1, VEGFR1, and survivin. Antibodies can be made for these proteins, methodologies for which are described in U.S. Pat. Nos. 5,225,539, 5,585,089, 5,693,761, and 5,639,641. In one example that may be utilized as a template for clinical development, T cells with reactivity against the ovarian cancer-associated antigen alpha-folate receptor (FR) were generated by genetic modification of autologous T cells with a chimeric gene incorporating an anti-FR single-chain antibody linked to the signaling domain of the Fc receptor gamma chain. Patients were assigned to one of two cohorts in the study. Eight patients in cohort 1 received a dose escalation of T cells in combination with high-dose interleukin-2, and six patients in cohort 2 received dual-specific T cells (reactive with both FR and allogeneic cells) followed by immunization with allogeneic peripheral blood mononuclear cells. Five patients in cohort 1 experienced some grade 3 to 4 treatment-related toxicity that was probably due to interleukin-2 administration, which could be managed using standard measures. Patients in cohort 2 experienced relatively mild side effects with grade 1 to 2 symptoms. No reduction in tumor burden was seen in any patient. Tracking ¹¹¹In-labeled adoptively transferred T cells in cohort 1 revealed a lack of specific localization of T cells to tumor except in one patient where some signal was detected in a peritoneal deposit. PCR analysis showed that gene-modified T cells were present in the circulation in large numbers for the first 2 days after transfer, but these quickly declined to be barely detectable 1 month later in most patients. Similar CAR-T clinical studies have been reported for neuroblastoma, B cell malignancies, melanoma, ovarian cancer, renal cancer, mesothelioma, and head and neck cancer.

[0056] In one embodiment of the invention, PBMCs are derived from leukapheresis and CD14 monocytes are collected by MACS. After 3 days of culture, M-CSF at 100 ng/ml plasmid encoding the chimeric CAR-DC recognizing tumor-endothelium specific antigen and subsequently selected for gene integration by culture in G418. In another embodiment the generation of dual-specific T cells is performed, stimulation of allogeneic monocytic cells is achieved by coculture of patient PBMCs with irradiated (5,000 cGy) allogeneic donor PBMCs from cryopreserved apheresis product (mixed lymphocyte reaction). The MHC haplotype of allogeneic donors is determined before use, and

donors that differed in at least four MHC class I alleles from the patient are used. Culture medium consisted of AimV medium (Invitrogen, Carlsbad, Calif.) supplemented with 5% human AB⁺ serum (Valley Biomedical, Winchester, Va.), penicillin (50 units/mL), streptomycin (50 mg/mL; Bio Whittaker, Walkersville, Md.), amphotericin B (Fungizone, 1.25 mg/mL; Biofluids, Rockville, Md.), L-glutamine (2 mmol/L; Mediatech, Herndon, Va.), and human recombinant IL-2 (Proleukin, 300 IU/mL; Chiron). Mixed lymphocyte reaction consisted of 2×10^6 patient monocytes and 1×10^7 allogeneic stimulator PBMCs in 2 mL AimV per well in 24-well plates. Between 24 and 48 wells are cultured per patient for 3 days, at which time transduction is done by aspirating 1.5 mL of medium and replacing with 2.0 mL retroviral supernatant containing 300 IU/mL IL-2, 10 mmol/L HEPES, and 8 μ g/mL polybrene (Sigma, St. Louis, Mo.) followed by covering with plastic wrap and centrifugation at $1,000 \times g$ for 1 hour at room temperature. After overnight culture at $37^\circ \text{C}/5\% \text{CO}_2$, transduction is repeated on the following day, and then medium was replaced after another 24 hours. Cells are then resuspended at $1 \times 10^6/\text{mL}$ in fresh medium containing 0.5 mg/mL G418 (Invitrogen) in 175-cm² flasks for 5 days before resuspension in media lacking G418. Cells are expanded to 2×10^9 and then restimulated with allogeneic PBMCs from the same donor to enrich for T cells specific for the donor allogeneic haplotype. Restimulation is done by incubating patient T cells ($1 \times 10^6/\text{mL}$) and stimulator PBMCs ($2 \times 10^6/\text{mL}$) in 3-liter Fenwall culture bags in AimV+additives and IL-2 (no G418). Cell numbers were adjusted to $1 \times 10^6/\text{mL}$, and IL-2 was added every 2 days, until sufficient numbers for treatment were achieved.

[0057] The present invention relates to a strategy of adoptive cell transfer of monocytes or DC transduced to express a chimeric antigen receptor (CAR). CARs are molecules that combine antibody-based specificity for a desired antigen (e.g., tumor endothelial antigen) with a T cell receptor-activating intracellular domain to generate a chimeric protein that exhibits a specific anti-tumor endothelium cellular immune activity. In one embodiment the present invention relates generally to the use of monocytes or DC cells genetically modified to stably express a desired CAR that possesses high affinity towards tumor associated endothelium. Monocytes or DC cells expressing a CAR are referred to herein as CAR-DC cells or CAR modified DC cells. Preferably, the cell can be genetically modified to stably express an antibody binding domain on its surface, conferring novel antigen specificity that is MHC independent. In some instances, the monocyte or DC cell is genetically modified to stably express a CAR that combines an antigen recognition domain of a specific antibody with an intracellular domain of the CD3-zeta chain or Fc.gamma.RI protein into a single chimeric protein. In another embodiment, TLR signaling molecules are engineered in the intracellular portion of the CAR, said molecules include TRIF, TRADD, and MyD99. In one embodiment, the CAR of the invention comprises an extracellular domain having an antigen recognition domain, a transmembrane domain, and a cytoplasmic domain. In one embodiment, the transmembrane domain that naturally is associated with one of the domains in the CAR is used. In another embodiment, the transmembrane domain can be selected or modified by amino acid substitution to avoid binding of such domains to the transmembrane domains of the same or different surface membrane

proteins to minimize interactions with other members of the receptor complex. Preferably, the transmembrane domain is the CD8a hinge domain.

[0058] With respect to the cytoplasmic domain, the CAR of the invention can be designed to comprise the CD80 and/or CD86 and/or CD40L and/or OX40L signaling domain by itself or be combined with any other desired cytoplasmic domain(s) useful in the context of the CAR of the invention. In one embodiment, the cytoplasmic domain of the CAR can be designed to further comprise the signaling domain of MyD88. For example, the cytoplasmic domain of the CAR can include but is not limited to CD80 and/or CD86 and/or CD40L and/or OX40L signaling modules and combinations thereof. In another embodiment of the invention inhibition of TGF-beta is performed either by transfection with an shRNA possessing selectivity towards TGF-beta or by constructing the CAR to possess a dominant negative mutant of TGF-beta receptor. This would render the CAR-DC cell resistant to inhibitory activities of the tumors. Accordingly, the invention provides CAR-DC cells and methods of their use for adoptive therapy. In one embodiment, the CAR-DC cells of the invention can be generated by introducing a lentiviral vector comprising a desired CAR, for example a CAR comprising anti-CD19, CD8a hinge and transmembrane domain, and MyD88, into the cells. The CAR-DC cells of the invention are able to replicate in vivo resulting in long-term persistence that can lead to sustained tumor control.

[0059] One skilled in the art will appreciate that these methods, compositions, and cells are and may be adapted to carry out the objects and obtain the ends and advantages mentioned, as well as those inherent therein. The methods, procedures, and devices described herein are presently representative of preferred embodiments and are exemplary and are not intended as limitations on the scope of the invention. Changes therein and other uses will occur to those skilled in the art which are encompassed within the spirit of the invention and are defined by the scope of the disclosure. It will be apparent to one skilled in the art that varying substitutions and modifications may be made to the invention disclosed herein without departing from the scope and spirit of the invention. Those skilled in the art recognize that the aspects and embodiments of the invention set forth herein may be practiced separate from each other or in conjunction with each other. Therefore, combinations of separate embodiments are within the scope of the invention as disclosed herein. All patents and publications mentioned in the specification are indicative of the levels of those skilled in the art to which the invention pertains. All patents and publications are herein incorporated by reference to the same extent as if each individual publication was specifically and individually indicated to be incorporated by reference.

[0060] The invention illustratively described herein suitably may be practiced in the absence of any element or elements, limitation or limitations which is not specifically disclosed herein. Thus, for example, in each instance herein any of the terms "comprising," "consisting essentially of" and "consisting of" may be replaced with either of the other two terms. The terms and expressions which have been employed are used as terms of description and not of limitation, and there is no intention that in the use of such terms and expressions indicates the exclusion of equivalents

of the features shown and described or portions thereof. It is recognized that various modifications are possible within the scope of the invention disclosed. Thus, it should be understood that although the present invention has been specifically disclosed by preferred embodiments and optional

features, modification and variation of the concepts herein disclosed may be resorted to by those skilled in the art, and that such modifications and variations are considered to be within the scope of this invention as defined by the disclosure.

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

Val	Val	Arg	Pro	Arg	Asp	Gln	Ile	Val	Ala	Gln	Gly	Arg	Thr	Val	Thr	
				325					330					335		
Phe	Pro	Cys	Glu	Thr	Lys	Gly	Asn	Pro	Gln	Pro	Ala	Val	Phe	Trp	Gln	
				340					345					350		
Lys	Glu	Gly	Ser	Gln	Asn	Leu	Leu	Phe	Pro	Asn	Gln	Pro	Gln	Gln	Pro	
				355					360					365		
Asn	Ser	Arg	Cys	Ser	Val	Ser	Pro	Thr	Gly	Asp	Leu	Thr	Ile	Thr	Asn	
				370					375					380		
Ile	Gln	Arg	Ser	Asp	Ala	Gly	Tyr	Tyr	Ile	Cys	Gln	Ala	Leu	Thr	Val	
				385					390					395		
Ala	Gly	Ser	Ile	Leu	Ala	Lys	Ala	Gln	Leu	Glu	Val	Thr	Asp	Val	Leu	
				405					410					415		
Thr	Asp	Arg	Pro	Pro	Pro	Ile	Ile	Leu	Gln	Gly	Pro	Ala	Asn	Gln	Thr	
				420					425					430		
Leu	Ala	Val	Asp	Gly	Thr	Ala	Leu	Leu	Lys	Cys	Lys	Ala	Thr	Gly	Asp	
				435					440					445		
Pro	Leu	Pro	Val	Ile	Ser	Trp	Leu	Lys	Glu	Gly	Phe	Thr	Phe	Pro	Gly	
				450					455					460		
Arg	Asp	Pro	Arg	Ala	Thr	Ile	Gln	Glu	Gln	Gly	Thr	Leu	Gln	Ile	Lys	
				465					470					475		
Asn	Leu	Arg	Ile	Ser	Asp	Thr	Gly	Thr	Tyr	Thr	Cys	Val	Ala	Thr	Ser	
				485					490					495		
Ser	Ser	Gly	Glu	Thr	Ser	Trp	Ser	Ala	Val	Leu	Asp	Val	Thr	Glu	Ser	
				500					505					510		
Gly	Ala	Thr	Ile	Ser	Lys	Asn	Tyr	Asp	Leu	Ser	Asp	Leu	Pro	Gly	Pro	
				515					520					525		
Pro	Ser	Lys	Pro	Gln	Val	Thr	Asp	Val	Thr	Lys	Asn	Ser	Val	Thr	Leu	
				530					535					540		
Ser	Trp	Gln	Pro	Gly	Thr	Pro	Gly	Thr	Leu	Pro	Ala	Ser	Ala	Tyr	Ile	
				545					550					555		
Ile	Glu	Ala	Phe	Ser	Gln	Ser	Val	Ser	Asn	Ser	Trp	Gln	Thr	Val	Ala	
				565					570					575		
Asn	His	Val	Lys	Thr	Thr	Leu	Tyr	Thr	Val	Arg	Gly	Leu	Arg	Pro	Asn	
				580					585					590		
Thr	Ile	Tyr	Leu	Phe	Met	Val	Arg	Ala	Ile	Asn	Pro	Gln	Gly	Leu	Ser	
				595					600					605		
Asp	Pro	Ser	Pro	Met	Ser	Asp	Pro	Val	Arg	Thr	Gln	Asp	Ile	Ser	Pro	
				610					615					620		
Pro	Ala	Gln	Gly	Val	Asp	His	Arg	Gln	Val	Gln	Lys	Glu	Leu	Gly	Asp	
				625					630					635		
Val	Leu	Val	Arg	Leu	His	Asn	Pro	Val	Val	Leu	Thr	Pro	Thr	Thr	Val	
				645					650					655		
Gln	Val	Thr	Trp	Thr	Val	Asp	Arg	Gln	Pro	Gln	Phe	Ile	Gln	Gly	Tyr	
				660					665					670		
Arg	Val	Met	Tyr	Arg	Gln	Thr	Ser	Gly	Leu	Gln	Ala	Thr	Ser	Ser	Trp	
				675					680					685		
Gln	Asn	Leu	Asp	Ala	Lys	Val	Pro	Thr	Glu	Arg	Ser	Ala	Val	Leu	Val	
				690					695					700		
Asn	Leu	Lys	Lys	Gly	Val	Thr	Tyr	Glu	Ile	Lys	Val	Arg	Pro	Tyr	Phe	
				705					710					715		
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Asn	Glu	Phe	Gln	Gly	Met	Asp	Ser	Glu	Ser	Lys	Thr	Val	Arg	Thr	Thr	
				725						730					735	
Glu	Glu	Ala	Pro	Ser	Ala	Pro	Pro	Gln	Ser	Val	Thr	Val	Leu	Thr	Val	
			740					745					750			
Gly	Ser	Tyr	Asn	Ser	Thr	Ser	Ile	Ser	Val	Ser	Trp	Asp	Pro	Pro	Pro	
		755					760					765				
Pro	Asp	His	Gln	Asn	Gly	Ile	Ile	Gln	Glu	Tyr	Lys	Ile	Trp	Cys	Leu	
	770					775					780					
Gly	Asn	Glu	Thr	Arg	Phe	His	Ile	Asn	Lys	Thr	Val	Asp	Ala	Ala	Ile	
	785				790					795					800	
Arg	Ser	Val	Ile	Ile	Gly	Gly	Leu	Phe	Pro	Gly	Ile	Gln	Tyr	Arg	Val	
			805						810					815		
Glu	Val	Ala	Ala	Ser	Thr	Ser	Ala	Gly	Val	Gly	Val	Lys	Ser	Glu	Pro	
			820					825					830			
Gln	Pro	Ile	Ile	Ile	Gly	Arg	Arg	Asn	Glu	Val	Val	Ile	Thr	Glu	Asn	
		835				840						845				
Asn	Asn	Ser	Ile	Thr	Glu	Gln	Ile	Thr	Asp	Val	Val	Lys	Gln	Pro	Ala	
	850					855					860					
Phe	Ile	Ala	Gly	Ile	Gly	Gly	Ala	Cys	Trp	Val	Ile	Leu	Met	Gly	Phe	
	865				870					875					880	
Ser	Ile	Trp	Leu	Tyr	Trp	Arg	Arg	Lys	Lys	Arg	Lys	Gly	Leu	Ser	Asn	
			885					890						895		
Tyr	Ala	Val	Thr	Phe	Gln	Arg	Gly	Asp	Gly	Gly	Leu	Met	Ser	Asn	Gly	
			900					905					910			
Ser	Arg	Pro	Gly	Leu	Leu	Asn	Ala	Gly	Asp	Pro	Ser	Tyr	Pro	Trp	Leu	
		915					920					925				
Ala	Asp	Ser	Trp	Pro	Ala	Thr	Ser	Leu	Pro	Val	Asn	Asn	Ser	Asn	Ser	
	930					935						940				
Gly	Pro	Asn	Glu	Ile	Gly	Asn	Phe	Gly	Arg	Gly	Asp	Val	Leu	Pro	Pro	
	945				950					955					960	
Val	Pro	Gly	Gln	Gly	Asp	Lys	Thr	Ala	Thr	Met	Leu	Ser	Asp	Gly	Ala	
			965					970						975		
Ile	Tyr	Ser	Ser	Ile	Asp	Phe	Thr	Thr	Lys	Thr	Ser	Tyr	Asn	Ser	Ser	
			980					985					990			
Ser	Gln	Ile	Thr	Gln	Ala	Thr	Pro	Tyr	Ala	Thr	Thr	Gln	Ile	Leu	His	
		995					1000					1005				
Ser	Asn	Ser	Ile	His	Glu	Leu	Ala	Val	Asp	Leu	Pro	Asp	Pro	Gln		
	1010					1015						1020				
Trp	Lys	Ser	Ser	Ile	Gln	Gln	Lys	Thr	Asp	Leu	Met	Gly	Phe	Gly		
	1025					1030						1035				
Tyr	Ser	Leu	Pro	Asp	Gln	Asn	Lys	Gly	Asn	Asn	Gly	Gly	Lys	Gly		
	1040					1045						1050				
Gly	Lys	Lys	Lys	Lys	Asn	Lys	Asn	Ser	Ser	Lys	Pro	Gln	Lys	Asn		
	1055					1060						1065				
Asn	Gly	Ser	Thr	Trp	Ala	Asn	Val	Pro	Leu	Pro	Pro	Pro	Pro	Val		
	1070					1075						1080				
Gln	Pro	Leu	Pro	Gly	Thr	Glu	Leu	Glu	His	Tyr	Ala	Val	Glu	Gln		
	1085					1090					1095					
Gln	Glu	Asn	Gly	Tyr	Asp	Ser	Asp	Ser	Trp	Cys	Pro	Pro	Leu	Pro		
	1100					1105					1110					
Val	Gln	Thr	Tyr	Leu	His	Gln	Gly	Leu	Glu	Asp	Glu	Leu	Glu	Glu		

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1115	1120	1125
Asp Asp Asp Arg Val Pro Thr	Pro Pro Val Arg Gly	Val Ala Ser
1130	1135	1140
Ser Pro Ala Ile Ser Phe Gly	Gln Gln Ser Thr Ala	Thr Leu Thr
1145	1150	1155
Pro Ser Pro Arg Glu Glu Met	Gln Pro Met Leu Gln	Ala His Leu
1160	1165	1170
Asp Glu Leu Thr Arg Ala Tyr	Gln Phe Asp Ile Ala	Lys Gln Thr
1175	1180	1185
Trp His Ile Gln Ser Asn Asn	Gln Pro Pro Gln Pro	Pro Val Pro
1190	1195	1200
Pro Leu Gly Tyr Val Ser Gly	Ala Leu Ile Ser Asp	Leu Glu Thr
1205	1210	1215
Asp Val Ala Asp Asp Asp Ala	Asp Asp Glu Glu Glu	Ala Leu Glu
1220	1225	1230
Ile Pro Arg Pro Leu Arg Ala	Leu Asp Gln Thr Pro	Gly Ser Ser
1235	1240	1245
Met Asp Asn Leu Asp Ser Ser	Val Thr Gly Ser Met	Val Asn Gly
1250	1255	1260
Trp Gly Ser Ala Ser Asp Glu	Asp Arg Asn Phe Ser	Ser His Arg
1265	1270	1275
Ser Ser Val Gly Ser Ser Ser	Asp Gly Ser Ile Phe	Ala Ser Gly
1280	1285	1290
Ser Phe Ala Gln Ala Leu Val	Ala Ala Ala Asp Lys	Ala Gly Phe
1295	1300	1305
Arg Leu Asp Gly Thr Ser Leu	Thr Arg Thr Gly Lys	Ala Phe Thr
1310	1315	1320
Ser Ser Gln Arg Pro Arg Pro	Thr Ser Pro Phe Ser	Thr Asp Ser
1325	1330	1335
Asn Thr Ser Ala Ala Leu Ser	Gln Ser Gln Arg Pro	Arg Pro Thr
1340	1345	1350
Lys Lys His Lys Gly Gly Arg	Met Asp Gln Gln Pro	Ala Leu Pro
1355	1360	1365
His Arg Arg Glu Gly Met Thr	Asp Glu Glu Ala Leu	Val Pro Tyr
1370	1375	1380
Ser Lys Pro Ser Phe Pro Ser	Pro Gly Gly His Ser	Ser Ser Gly
1385	1390	1395
Thr Ala Ser Ser Lys Gly Ser	Thr Gly Pro Arg Lys	Thr Glu Val
1400	1405	1410
Leu Arg Ala Gly His Gln Arg	Asn Ala Ser Asp Leu	Leu Asp Ile
1415	1420	1425
Gly Tyr Met Gly Ser Asn Ser	Gln Gly Gln Phe Thr	Gly Glu Leu
1430	1435	1440

<210> SEQ ID NO 3

<211> LENGTH: 712

<212> TYPE: PRT

<213> ORGANISM: Human

<400> SEQUENCE: 3

Met Gln Ser Lys Val Leu Leu Ala Val Ala Leu Trp Leu Cys Val Glu

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5

10

15

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Thr	Arg	Ala	Ala	Ser	Val	Gly	Leu	Pro	Ser	Val	Ser	Leu	Asp	Leu	Pro
		20						25					30		
Arg	Leu	Ser	Ile	Gln	Lys	Asp	Ile	Leu	Thr	Ile	Lys	Ala	Asn	Thr	Thr
	35						40					45			
Leu	Gln	Ile	Thr	Cys	Arg	Gly	Gln	Arg	Asp	Leu	Asp	Trp	Leu	Trp	Pro
	50					55					60				
Asn	Asn	Gln	Ser	Gly	Ser	Glu	Gln	Arg	Val	Glu	Val	Thr	Glu	Cys	Ser
65					70					75					80
Asp	Gly	Leu	Phe	Cys	Lys	Thr	Leu	Thr	Ile	Pro	Lys	Val	Ile	Gly	Asn
			85						90					95	
Asp	Thr	Gly	Ala	Tyr	Lys	Cys	Phe	Tyr	Arg	Glu	Thr	Asp	Leu	Ala	Ser
			100					105					110		
Val	Ile	Tyr	Val	Tyr	Val	Gln	Asp	Tyr	Arg	Ser	Pro	Phe	Ile	Ala	Ser
		115					120					125			
Val	Ser	Asp	Gln	His	Gly	Val	Val	Tyr	Ile	Thr	Glu	Asn	Lys	Asn	Lys
	130					135					140				
Thr	Val	Val	Ile	Pro	Cys	Leu	Gly	Ser	Ile	Ser	Asn	Leu	Asn	Val	Ser
145					150					155					160
Leu	Cys	Ala	Arg	Tyr	Pro	Glu	Lys	Arg	Phe	Val	Pro	Asp	Gly	Asn	Arg
			165						170					175	
Ile	Ser	Trp	Asp	Ser	Lys	Lys	Gly	Phe	Thr	Ile	Pro	Ser	Tyr	Met	Ile
		180						185						190	
Ser	Tyr	Ala	Gly	Met	Val	Phe	Cys	Glu	Ala	Lys	Ile	Asn	Asp	Glu	Ser
	195						200					205			
Tyr	Gln	Ser	Ile	Met	Tyr	Ile	Val	Val	Val	Val	Gly	Tyr	Arg	Ile	Tyr
	210					215					220				
Asp	Val	Val	Leu	Ser	Pro	Ser	His	Gly	Ile	Glu	Leu	Ser	Val	Gly	Glu
225					230					235					240
Lys	Leu	Val	Leu	Asn	Cys	Thr	Ala	Arg	Thr	Glu	Leu	Asn	Val	Gly	Ile
			245						250					255	
Asp	Phe	Asn	Trp	Glu	Tyr	Pro	Ser	Ser	Lys	His	Gln	His	Lys	Lys	Leu
		260						265					270		
Val	Asn	Arg	Asp	Leu	Lys	Thr	Gln	Ser	Gly	Ser	Glu	Met	Lys	Lys	Phe
		275					280					285			
Leu	Ser	Thr	Leu	Thr	Ile	Asp	Gly	Val	Thr	Arg	Ser	Asp	Gln	Gly	Leu
	290					295					300				
Tyr	Thr	Cys	Ala	Ala	Ser	Ser	Gly	Leu	Met	Thr	Lys	Lys	Asn	Ser	Thr
305					310					315					320
Phe	Val	Arg	Val	His	Glu	Lys	Pro	Phe	Val	Ala	Phe	Gly	Ser	Gly	Met
			325						330					335	
Glu	Ser	Leu	Val	Glu	Ala	Thr	Val	Gly	Glu	Arg	Val	Arg	Ile	Pro	Ala
		340						345					350		
Lys	Tyr	Leu	Gly	Tyr	Pro	Pro	Pro	Glu	Ile	Lys	Trp	Tyr	Lys	Asn	Gly
	355						360					365			
Ile	Pro	Leu	Glu	Ser	Asn	His	Thr	Ile	Lys	Ala	Gly	His	Val	Leu	Thr
	370					375					380				
Ile	Met	Glu	Val	Ser	Glu	Arg	Asp	Thr	Gly	Asn	Tyr	Thr	Val	Ile	Leu
385					390				395						400
Thr	Asn	Pro	Ile	Ser	Lys	Glu	Lys	Gln	Ser	His	Val	Val	Ser	Leu	Val
			405					410					415		
Val	Tyr	Val	Pro	Pro	Gln	Ile	Gly	Glu	Lys	Ser	Leu	Ile	Ser	Pro	Val

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420							425					430				
Asp	Ser	Tyr	Gln	Tyr	Gly	Thr	Thr	Gln	Thr	Leu	Thr	Cys	Thr	Val	Tyr	
435							440					445				
Ala	Ile	Pro	Pro	Pro	His	His	Ile	His	Trp	Tyr	Trp	Gln	Leu	Glu	Glu	
450							455					460				
Glu	Cys	Ala	Asn	Glu	Pro	Ser	Gln	Ala	Val	Ser	Val	Thr	Asn	Pro	Tyr	
465							470					475				
Pro	Cys	Glu	Glu	Trp	Arg	Ser	Val	Glu	Asp	Phe	Gln	Gly	Gly	Asn	Lys	
485							490					495				
Ile	Glu	Val	Asn	Lys	Asn	Gln	Phe	Ala	Leu	Ile	Glu	Gly	Lys	Asn	Lys	
500							505					510				
Thr	Val	Ser	Thr	Leu	Val	Ile	Gln	Ala	Ala	Asn	Val	Ser	Ala	Leu	Tyr	
515							520					525				
Lys	Cys	Glu	Ala	Val	Asn	Lys	Val	Gly	Arg	Gly	Glu	Arg	Val	Ile	Ser	
530							535					540				
Phe	His	Val	Thr	Arg	Gly	Pro	Glu	Ile	Thr	Leu	Gln	Pro	Asp	Met	Gln	
545							550					555				
Pro	Thr	Glu	Gln	Glu	Ser	Val	Ser	Leu	Trp	Cys	Thr	Ala	Asp	Arg	Ser	
565							570					575				
Thr	Phe	Glu	Asn	Leu	Thr	Trp	Tyr	Lys	Leu	Gly	Pro	Gln	Pro	Leu	Pro	
580							585					590				
Ile	His	Val	Gly	Glu	Leu	Pro	Thr	Pro	Val	Cys	Lys	Asn	Leu	Asp	Thr	
595							600					605				
Leu	Trp	Lys	Leu	Asn	Ala	Thr	Met	Phe	Ser	Asn	Ser	Thr	Asn	Asp	Ile	
610							615					620				
Leu	Ile	Met	Glu	Leu	Lys	Asn	Ala	Ser	Leu	Gln	Asp	Gln	Gly	Asp	Tyr	
625							630					635				
Val	Cys	Leu	Ala	Gln	Asp	Arg	Lys	Thr	Lys	Lys	Arg	His	Cys	Val	Val	
645							650					655				
Arg	Gln	Leu	Thr	Val	Leu	Glu	Arg	Val	Ala	Pro	Thr	Ile	Thr	Gly	Asn	
660							665					670				
Leu	Glu	Asn	Gln	Thr	Thr	Ser	Ile	Gly	Glu	Ser	Ile	Glu	Val	Ser	Cys	
675							680					685				
Thr	Ala	Ser	Gly	Asn	Pro	Pro	Pro	Gln	Ile	Met	Trp	Phe	Lys	Asp	Asn	
690							695					700				
Glu	Thr	Leu	Val	Glu	Asp	Ser	Glu									
705							710									
<210> SEQ ID NO 4																
<211> LENGTH: 658																
<212> TYPE: PRT																
<213> ORGANISM: Human																
<400> SEQUENCE: 4																
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Cys	Ser	Leu	Ser	Pro	Thr	Ser	Leu	Ala	Glu	Thr	Val	His	Cys	Asp	Leu	
							20			25			30			
Gln	Pro	Val	Gly	Pro	Glu	Arg	Gly	Glu	Val	Thr	Tyr	Thr	Thr	Ser	Gln	
35							40			45						
Val	Ser	Lys	Gly	Cys	Val	Ala	Gln	Ala	Pro	Asn	Ala	Ile	Leu	Glu	Val	
50							55			60						

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His	Val	Leu	Phe	Leu	Glu	Phe	Pro	Thr	Gly	Pro	Ser	Gln	Leu	Glu	Leu	65	70	75	80
Thr	Leu	Gln	Ala	Ser	Lys	Gln	Asn	Gly	Thr	Trp	Pro	Arg	Glu	Val	Leu	85	90	95	
Leu	Val	Leu	Ser	Val	Asn	Ser	Ser	Val	Phe	Leu	His	Leu	Gln	Ala	Leu	100	105	110	
Gly	Ile	Pro	Leu	His	Leu	Ala	Tyr	Asn	Ser	Ser	Leu	Val	Thr	Phe	Gln	115	120	125	
Glu	Pro	Pro	Gly	Val	Asn	Thr	Thr	Glu	Leu	Pro	Ser	Phe	Pro	Lys	Thr	130	135	140	
Gln	Ile	Leu	Glu	Trp	Ala	Ala	Glu	Arg	Gly	Pro	Ile	Thr	Ser	Ala	Ala	145	150	155	160
Glu	Leu	Asn	Asp	Pro	Gln	Ser	Ile	Leu	Leu	Arg	Leu	Gly	Gln	Ala	Gln	165	170	175	
Gly	Ser	Leu	Ser	Phe	Cys	Met	Leu	Glu	Ala	Ser	Gln	Asp	Met	Gly	Arg	180	185	190	
Thr	Leu	Glu	Trp	Arg	Pro	Arg	Thr	Pro	Ala	Leu	Val	Arg	Gly	Cys	His	195	200	205	
Leu	Glu	Gly	Val	Ala	Gly	His	Lys	Glu	Ala	His	Ile	Leu	Arg	Val	Leu	210	215	220	
Pro	Gly	His	Ser	Ala	Gly	Pro	Arg	Thr	Val	Thr	Val	Lys	Val	Glu	Leu	225	230	235	240
Ser	Cys	Ala	Pro	Gly	Asp	Leu	Asp	Ala	Val	Leu	Ile	Leu	Gln	Gly	Pro	245	250	255	
Pro	Tyr	Val	Ser	Trp	Leu	Ile	Asp	Ala	Asn	His	Asn	Met	Gln	Ile	Trp	260	265	270	
Thr	Thr	Gly	Glu	Tyr	Ser	Phe	Lys	Ile	Phe	Pro	Glu	Lys	Asn	Ile	Arg	275	280	285	
Gly	Phe	Lys	Leu	Pro	Asp	Thr	Pro	Gln	Gly	Leu	Leu	Gly	Glu	Ala	Arg	290	295	300	
Met	Leu	Asn	Ala	Ser	Ile	Val	Ala	Ser	Phe	Val	Glu	Leu	Pro	Leu	Ala	305	310	315	320
Ser	Ile	Val	Ser	Leu	His	Ala	Ser	Ser	Cys	Gly	Gly	Arg	Leu	Gln	Thr	325	330	335	
Ser	Pro	Ala	Pro	Ile	Gln	Thr	Thr	Pro	Pro	Lys	Asp	Thr	Cys	Ser	Pro	340	345	350	
Glu	Leu	Leu	Met	Ser	Leu	Ile	Gln	Thr	Lys	Cys	Ala	Asp	Asp	Ala	Met	355	360	365	
Thr	Leu	Val	Leu	Lys	Lys	Glu	Leu	Val	Ala	His	Leu	Lys	Cys	Thr	Ile	370	375	380	
Thr	Gly	Leu	Thr	Phe	Trp	Asp	Pro	Ser	Cys	Glu	Ala	Glu	Asp	Arg	Gly	385	390	395	400
Asp	Lys	Phe	Val	Leu	Arg	Ser	Ala	Tyr	Ser	Ser	Cys	Gly	Met	Gln	Val	405	410	415	
Ser	Ala	Ser	Met	Ile	Ser	Asn	Glu	Ala	Val	Val	Asn	Ile	Leu	Ser	Ser	420	425	430	
Ser	Ser	Pro	Gln	Arg	Lys	Lys	Val	His	Cys	Leu	Asn	Met	Asp	Ser	Leu	435	440	445	
Ser	Phe	Gln	Leu	Gly	Leu	Tyr	Leu	Ser	Pro	His	Phe	Leu	Gln	Ala	Ser	450	455	460	
Asn	Thr	Ile	Glu	Pro	Gly	Gln	Gln	Ser	Phe	Val	Gln	Val	Arg	Val	Ser				

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465	470	475	480
Pro Ser Val Ser Glu Phe Leu Leu Gln Leu Asp Ser Cys His Leu Asp	485	490	495
Leu Gly Pro Glu Gly Gly Thr Val Glu Leu Ile Gln Gly Arg Ala Ala	500	505	510
Lys Gly Asn Cys Val Ser Leu Leu Ser Pro Ser Pro Glu Gly Asp Pro	515	520	525
Arg Phe Ser Phe Leu Leu His Phe Tyr Thr Val Pro Ile Pro Lys Thr	530	535	540
Gly Thr Leu Ser Cys Thr Val Ala Leu Arg Pro Lys Thr Gly Ser Gln	545	550	555
Asp Gln Glu Val His Arg Thr Val Phe Met Arg Leu Asn Ile Ile Ser	565	570	575
Pro Asp Leu Ser Gly Cys Thr Ser Lys Gly Leu Val Leu Pro Ala Val	580	585	590
Leu Gly Ile Thr Phe Gly Ala Phe Leu Ile Gly Ala Leu Leu Thr Ala	595	600	605
Ala Leu Trp Tyr Ile Tyr Ser His Thr Arg Ser Pro Ser Lys Arg Glu	610	615	620
Pro Val Val Ala Val Ala Ala Pro Ala Ser Ser Glu Ser Ser Ser Thr	625	630	635
Asn His Ser Ile Gly Ser Thr Gln Ser Thr Pro Cys Ser Thr Ser Ser	645	650	655
Met Ala			

<210> SEQ ID NO 5
 <211> LENGTH: 117
 <212> TYPE: PRT
 <213> ORGANISM: Human

<400> SEQUENCE: 5

Met Gly Ala Pro Thr Leu Pro Pro Ala Trp Gln Pro Phe Leu Lys Asp	1	5	10	15
His Arg Ile Ser Thr Phe Lys Asn Trp Pro Phe Leu Glu Gly Cys Ala	20	25	30	
Cys Thr Pro Glu Arg Met Ala Glu Ala Gly Phe Ile His Cys Pro Thr	35	40	45	
Glu Asn Glu Pro Asp Leu Ala Gln Trp Val Phe Cys Phe Lys Glu Leu	50	55	60	
Glu Gly Trp Glu Pro Asp Asp Asp Pro Ile Glu Glu His Lys Lys His	65	70	75	80
Ser Ser Gly Cys Ala Phe Leu Ser Val Lys Lys Gln Phe Glu Glu Leu	85	90	95	
Thr Leu Gly Glu Phe Leu Lys Leu Val Arg Glu Thr Leu Pro Pro Pro	100	105	110	
Arg Ser Phe Ile Arg	115			

<210> SEQ ID NO 6
 <211> LENGTH: 652
 <212> TYPE: PRT
 <213> ORGANISM: Human

<400> SEQUENCE: 6

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Met	Ala	Thr	Ser	Met	Gly	Leu	Leu	Leu	Leu	Leu	Leu	Leu	Leu	Thr	1	5	10	15	
Gln	Pro	Gly	Ala	Gly	Thr	Gly	Ala	Asp	Thr	Glu	Ala	Val	Val	Cys	Val	20	25	30	
Gly	Thr	Ala	Cys	Tyr	Thr	Ala	His	Ser	Gly	Lys	Leu	Ser	Ala	Ala	Glu	35	40	45	
Ala	Gln	Asn	His	Cys	Asn	Gln	Asn	Gly	Gly	Asn	Leu	Ala	Thr	Val	Lys	50	55	60	
Ser	Lys	Glu	Glu	Ala	Gln	His	Val	Gln	Arg	Val	Leu	Ala	Gln	Leu	Leu	65	70	75	80
Arg	Arg	Glu	Ala	Ala	Leu	Thr	Ala	Arg	Met	Ser	Lys	Phe	Trp	Ile	Gly	85	90	95	
Leu	Gln	Arg	Glu	Lys	Gly	Lys	Cys	Leu	Asp	Pro	Ser	Leu	Pro	Leu	Lys	100	105	110	
Gly	Phe	Ser	Trp	Val	Gly	Gly	Gly	Glu	Asp	Thr	Pro	Tyr	Ser	Asn	Trp	115	120	125	
His	Lys	Glu	Leu	Arg	Asn	Ser	Cys	Ile	Ser	Lys	Arg	Cys	Val	Ser	Leu	130	135	140	
Leu	Leu	Asp	Leu	Ser	Gln	Pro	Leu	Leu	Pro	Ser	Arg	Leu	Pro	Lys	Trp	145	150	155	160
Ser	Glu	Gly	Pro	Cys	Gly	Ser	Pro	Gly	Ser	Pro	Gly	Ser	Asn	Ile	Glu	165	170	175	
Gly	Phe	Val	Cys	Lys	Phe	Ser	Phe	Lys	Gly	Met	Cys	Arg	Pro	Leu	Ala	180	185	190	
Leu	Gly	Gly	Pro	Gly	Gln	Val	Thr	Tyr	Thr	Thr	Pro	Phe	Gln	Thr	Thr	195	200	205	
Ser	Ser	Ser	Leu	Glu	Ala	Val	Pro	Phe	Ala	Ser	Ala	Ala	Asn	Val	Ala	210	215	220	
Cys	Gly	Glu	Gly	Asp	Lys	Asp	Glu	Thr	Gln	Ser	His	Tyr	Phe	Leu	Cys	225	230	235	240
Lys	Glu	Lys	Ala	Pro	Asp	Val	Phe	Asp	Trp	Gly	Ser	Ser	Gly	Pro	Leu	245	250	255	
Cys	Val	Ser	Pro	Lys	Tyr	Gly	Cys	Asn	Phe	Asn	Asn	Gly	Gly	Cys	His	260	265	270	
Gln	Asp	Cys	Phe	Glu	Gly	Gly	Asp	Gly	Ser	Phe	Leu	Cys	Gly	Cys	Arg	275	280	285	
Pro	Gly	Phe	Arg	Leu	Leu	Asp	Asp	Leu	Val	Thr	Cys	Ala	Ser	Arg	Asn	290	295	300	
Pro	Cys	Ser	Ser	Ser	Pro	Cys	Arg	Gly	Gly	Ala	Thr	Cys	Val	Leu	Gly	305	310	315	320
Pro	His	Gly	Lys	Asn	Tyr	Thr	Cys	Arg	Cys	Pro	Gln	Gly	Tyr	Gln	Leu	325	330	335	
Asp	Ser	Ser	Gln	Leu	Asp	Cys	Val	Asp	Val	Asp	Glu	Cys	Gln	Asp	Ser	340	345	350	
Pro	Cys	Ala	Gln	Glu	Cys	Val	Asn	Thr	Pro	Gly	Gly	Phe	Arg	Cys	Glu	355	360	365	
Cys	Trp	Val	Gly	Tyr	Glu	Pro	Gly	Gly	Pro	Gly	Glu	Gly	Ala	Cys	Gln	370	375	380	
Asp	Val	Asp	Glu	Cys	Ala	Leu	Gly	Arg	Ser	Pro	Cys	Ala	Gln	Gly	Cys	385	390	395	400

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

<210> SEQ ID NO 7

<211> LENGTH: 277

<212> TYPE: PRT

<213> ORGANISM: Human

<400> SEQUENCE: 7

Met	Trp	Pro	Gly	Ile	Leu	Val	Gly	Gly	Ala	Arg	Val	Ala	Ser	Cys	Arg
1			5					10					15		
Tyr	Pro	Ala	Leu	Gly	Pro	Arg	Leu	Ala	His	Phe	Pro	Ala	Gln	Arg	
		20					25					30			
Pro	Pro	Gln	Arg	Thr	Leu	Gln	Asn	Gly	Leu	Ala	Leu	Gln	Arg	Cys	Leu
		35				40					45				
His	Ala	Thr	Ala	Thr	Arg	Ala	Leu	Pro	Leu	Ile	Pro	Ile	Val	Val	Glu
	50				55					60					
Gln	Thr	Gly	Arg	Gly	Glu	Arg	Ala	Tyr	Asp	Ile	Tyr	Ser	Arg	Leu	Leu
65				70					75					80	
Arg	Glu	Arg	Ile	Val	Cys	Val	Met	Gly	Pro	Ile	Asp	Asp	Ser	Val	Ala
			85					90					95		
Ser	Leu	Val	Ile	Ala	Gln	Leu	Leu	Phe	Leu	Gln	Ser	Glu	Ser	Asn	Lys
			100					105						110	

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Lys Pro Ile His Met Tyr Ile Asn Ser Pro Gly Gly Val Val Thr Ala
 115 120 125
 Gly Leu Ala Ile Tyr Asp Thr Met Gln Tyr Ile Leu Asn Pro Ile Cys
 130 135 140
 Thr Trp Cys Val Gly Gln Ala Ala Ser Met Gly Ser Leu Leu Leu Ala
 145 150 155 160
 Ala Gly Thr Pro Gly Met Arg His Ser Leu Pro Asn Ser Arg Ile Met
 165 170 175
 Ile His Gln Pro Ser Gly Gly Ala Arg Gly Gln Ala Thr Asp Ile Ala
 180 185 190
 Ile Gln Ala Glu Glu Ile Met Lys Leu Lys Lys Gln Leu Tyr Asn Ile
 195 200 205
 Tyr Ala Lys His Thr Lys Gln Ser Leu Gln Val Ile Glu Ser Ala Met
 210 215 220
 Glu Arg Asp Arg Tyr Met Ser Pro Met Glu Ala Gln Glu Phe Gly Ile
 225 230 235 240
 Leu Asp Lys Val Leu Val His Pro Pro Gln Asp Gly Glu Asp Glu Pro
 245 250 255
 Thr Leu Val Gln Lys Glu Pro Val Glu Ala Ala Pro Ala Ala Glu Pro
 260 265 270
 Val Pro Ala Ser Thr
 275

<210> SEQ ID NO 8
 <211> LENGTH: 285
 <212> TYPE: PRT
 <213> ORGANISM: Human

<400> SEQUENCE: 8

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

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180					185					190					
Asp	Tyr	Val	His	Ala	Leu	Val	Ala	Tyr	Phe	Asn	Ile	Glu	Phe	Thr	Arg
		195					200					205			
Cys	His	Lys	Arg	Thr	Gly	Phe	Ser	Thr	Ser	Pro	Glu	Ser	Pro	Tyr	Thr
		210					215					220			
His	Trp	Lys	Gln	Thr	Val	Phe	Tyr	Met	Glu	Asp	Tyr	Leu	Thr	Val	Lys
		225					230					235			240
Thr	Gly	Glu	Glu	Ile	Phe	Gly	Thr	Ile	Gly	Met	Arg	Pro	Asn	Ala	Lys
				245					250					255	
Asn	Asn	Arg	Asp	Leu	Asp	Phe	Thr	Ile	Asp	Leu	Asp	Phe	Lys	Gly	Gln
			260					265					270		
Leu	Cys	Glu	Leu	Ser	Cys	Ser	Thr	Asp	Tyr	Arg	Met	Arg			
		275					280					285			
<210> SEQ ID NO 9															
<211> LENGTH: 609															
<212> TYPE: PRT															
<213> ORGANISM: Human															
<400> SEQUENCE: 9															
Met	Lys	Trp	Val	Glu	Ser	Ile	Phe	Leu	Ile	Phe	Leu	Leu	Asn	Phe	Thr
1				5					10					15	
Glu	Ser	Arg	Thr	Leu	His	Arg	Asn	Glu	Tyr	Gly	Ile	Ala	Ser	Ile	Leu
			20					25					30		
Asp	Ser	Tyr	Gln	Cys	Thr	Ala	Glu	Ile	Ser	Leu	Ala	Asp	Leu	Ala	Thr
		35					40					45			
Ile	Phe	Phe	Ala	Gln	Phe	Val	Gln	Glu	Ala	Thr	Tyr	Lys	Glu	Val	Ser
	50					55					60				
Lys	Met	Val	Lys	Asp	Ala	Leu	Thr	Ala	Ile	Glu	Lys	Pro	Thr	Gly	Asp
	65					70					75				80
Glu	Gln	Ser	Ser	Gly	Cys	Leu	Glu	Asn	Gln	Leu	Pro	Ala	Phe	Leu	Glu
				85				90						95	
Glu	Leu	Cys	His	Glu	Lys	Glu	Ile	Leu	Glu	Lys	Tyr	Gly	His	Ser	Asp
			100					105					110		
Cys	Cys	Ser	Gln	Ser	Glu	Glu	Gly	Arg	His	Asn	Cys	Phe	Leu	Ala	His
			115					120					125		
Lys	Lys	Pro	Thr	Pro	Ala	Ser	Ile	Pro	Leu	Phe	Gln	Val	Pro	Glu	Pro
		130					135					140			
Val	Thr	Ser	Cys	Glu	Ala	Tyr	Glu	Glu	Asp	Arg	Glu	Thr	Phe	Met	Asn
			145			150					155				160
Lys	Phe	Ile	Tyr	Glu	Ile	Ala	Arg	Arg	His	Pro	Phe	Leu	Tyr	Ala	Pro
			165					170						175	
Thr	Ile	Leu	Leu	Trp	Ala	Ala	Arg	Tyr	Asp	Lys	Ile	Ile	Pro	Ser	Cys
			180					185					190		
Cys	Lys	Ala	Glu	Asn	Ala	Val	Glu	Cys	Phe	Gln	Thr	Lys	Ala	Ala	Thr
			195					200					205		
Val	Thr	Lys	Glu	Leu	Arg	Glu	Ser	Ser	Leu	Leu	Asn	Gln	His	Ala	Cys
		210						215					220		
Ala	Val	Met	Lys	Asn	Phe	Gly	Thr	Arg	Thr	Phe	Gln	Ala	Ile	Thr	Val
		225				230					235				240
Thr	Lys	Leu	Ser	Gln	Lys	Phe	Thr	Lys	Val	Asn	Phe	Thr	Glu	Ile	Gln
			245					250					255		

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Lys	Leu	Val	Leu	Asp	Val	Ala	His	Val	His	Glu	His	Cys	Cys	Arg	Gly	260	265	270
Asp	Val	Leu	Asp	Cys	Leu	Gln	Asp	Gly	Glu	Lys	Ile	Met	Ser	Tyr	Ile	275	280	285
Cys	Ser	Gln	Gln	Asp	Thr	Leu	Ser	Asn	Lys	Ile	Thr	Glu	Cys	Cys	Lys	290	295	300
Leu	Thr	Thr	Leu	Glu	Arg	Gly	Gln	Cys	Ile	Ile	His	Ala	Glu	Asn	Asp	305	310	315
Glu	Lys	Pro	Glu	Gly	Leu	Ser	Pro	Asn	Leu	Asn	Arg	Phe	Leu	Gly	Asp	325	330	335
Arg	Asp	Phe	Asn	Gln	Phe	Ser	Ser	Gly	Glu	Lys	Asn	Ile	Phe	Leu	Ala	340	345	350
Ser	Phe	Val	His	Glu	Tyr	Ser	Arg	Arg	His	Pro	Gln	Leu	Ala	Val	Ser	355	360	365
Val	Ile	Leu	Arg	Val	Ala	Lys	Gly	Tyr	Gln	Glu	Leu	Leu	Glu	Lys	Cys	370	375	380
Phe	Gln	Thr	Glu	Asn	Pro	Leu	Glu	Cys	Gln	Asp	Lys	Gly	Glu	Glu	Glu	385	390	395
Leu	Gln	Lys	Tyr	Ile	Gln	Glu	Ser	Gln	Ala	Leu	Ala	Lys	Arg	Ser	Cys	405	410	415
Gly	Leu	Phe	Gln	Lys	Leu	Gly	Glu	Tyr	Tyr	Leu	Gln	Asn	Ala	Phe	Leu	420	425	430
Val	Ala	Tyr	Thr	Lys	Lys	Ala	Pro	Gln	Leu	Thr	Ser	Ser	Glu	Leu	Met	435	440	445
Ala	Ile	Thr	Arg	Lys	Met	Ala	Ala	Thr	Ala	Ala	Thr	Cys	Cys	Gln	Leu	450	455	460
Ser	Glu	Asp	Lys	Leu	Leu	Ala	Cys	Gly	Glu	Gly	Ala	Ala	Asp	Ile	Ile	465	470	475
Ile	Gly	His	Leu	Cys	Ile	Arg	His	Glu	Met	Thr	Pro	Val	Asn	Pro	Gly	485	490	495
Val	Gly	Gln	Cys	Cys	Thr	Ser	Ser	Tyr	Ala	Asn	Arg	Arg	Pro	Cys	Phe	500	505	510
Ser	Ser	Leu	Val	Val	Asp	Glu	Thr	Tyr	Val	Pro	Pro	Ala	Phe	Ser	Asp	515	520	525
Asp	Lys	Phe	Ile	Phe	His	Lys	Asp	Leu	Cys	Gln	Ala	Gln	Gly	Val	Ala	530	535	540
Leu	Gln	Thr	Met	Lys	Gln	Glu	Phe	Leu	Ile	Asn	Leu	Val	Lys	Gln	Lys	545	550	555
Pro	Gln	Ile	Thr	Glu	Glu	Gln	Leu	Glu	Ala	Val	Ile	Ala	Asp	Phe	Ser	565	570	575
Gly	Leu	Leu	Glu	Lys	Cys	Cys	Gln	Gly	Gln	Glu	Gln	Glu	Val	Cys	Phe	580	585	590
Ala	Glu	Glu	Gly	Gln	Lys	Leu	Ile	Ser	Lys	Thr	Arg	Ala	Ala	Leu	Gly	595	600	605

Val

<210> SEQ ID NO 10
 <211> LENGTH: 43
 <212> TYPE: PRT
 <213> ORGANISM: Human

<400> SEQUENCE: 10

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Met Ala Ala Arg Ala Val Phe Leu Ala Leu Ser Ala Gln Leu Leu Gln
1           5           10           15

Ala Arg Leu Met Lys Glu Glu Ser Pro Val Val Ser Trp Arg Leu Glu
          20           25           30

Pro Glu Asp Gly Thr Ala Leu Cys Phe Ile Phe
          35           40

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<210> SEQ ID NO 11
<211> LENGTH: 198
<212> TYPE: PRT
<213> ORGANISM: Human

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<400> SEQUENCE: 11

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Leu Val Ser Glu Val Ile Arg Phe Ile Leu Phe Lys Phe His Gln Ser
1           5           10           15

Ser Gly Thr Pro Ile Lys Arg Glu Asp Leu Thr Gln Ile Val Thr Lys
          20           25           30

Asn Tyr Arg Gln Arg Asn Leu Ala Thr His Val Ile Asn Glu Ala Lys
          35           40           45

Lys Lys Leu Ser Asn Val Phe Gly Tyr Asp Leu Lys Glu Leu Gln Arg
          50           55           60

Ala Arg Ala Ser Ser Thr Gly Gln Ser Arg Leu Pro Gln Ser Gln Ser
          65           70           75           80

Ser Val Asp Ser Lys Ser Tyr Val Leu Val Ser Glu Leu Pro Leu Glu
          85           90           95

Val Phe Lys Lys His Val Val Asp Glu Thr Thr Ser Pro Val Thr Gly
          100          105          110

Phe Thr Phe Val Val Leu Ala Ile Val Gln Leu Ala Gly Gly Lys Ile
          115          120          125

Pro Glu Glu Thr Leu Trp His His Leu Lys Arg Met Gly Leu His Glu
          130          135          140

Asn Asp Glu His Asn Pro Val Phe Gly Asn Asn Lys Gln Thr Leu Glu
          145          150          155          160

Thr Leu Val Gln Gln Arg Phe Leu Gln Lys Glu Lys Val Ser Gly Pro
          165          170          175

Glu Gly Ser Thr Leu Val Tyr Asp Leu Ala Glu Arg Ala Leu Asp Pro
          180          185          190

Gln Val Ser Glu Lys Val
          195

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<210> SEQ ID NO 12
<211> LENGTH: 562
<212> TYPE: PRT
<213> ORGANISM: Human

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<400> SEQUENCE: 12

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Met Ser Asn Gln Tyr Gln Glu Glu Gly Cys Ser Glu Arg Pro Glu Cys
1           5           10           15

Lys Ser Lys Ser Pro Thr Leu Leu Ser Ser Tyr Cys Ile Asp Ser Ile
          20           25           30

Leu Gly Arg Arg Ser Pro Cys Lys Met Arg Leu Leu Gly Ala Ala Gln
          35           40           45

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

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Gln	Gly	Ser	Pro	Lys	Ser	Ser	Ser	Ala	Pro	Phe	Glu	Ala	Glu	Leu	His	
65					70					75					80	
Leu	Pro	Pro	Lys	Leu	Arg	Arg	Leu	Tyr	Gly	Pro	Gly	Gly	Gly	Arg	Leu	
			85					90						95		
Leu	Gln	Gly	Ala	Ala	Ala	Ala	Ala	Ala	Ala	Ala	Ala	Ala	Ala	Ala	Ala	
			100					105						110		
Ala	Ala	Ala	Thr	Ala	Thr	Ala	Gly	Pro	Arg	Gly	Glu	Ala	Pro	Pro	Pro	
			115				120					125				
Pro	Pro	Pro	Thr	Ala	Arg	Pro	Gly	Glu	Arg	Pro	Asp	Gly	Ala	Gly	Ala	
			130			135					140					
Ala	Ala	Ala	Ala	Ala	Ala	Ala	Ala	Ala	Ala	Ala	Trp	Asp	Thr	Leu	Lys	
145					150					155					160	
Ile	Ser	Gln	Ala	Pro	Gln	Val	Ser	Ile	Ser	Arg	Ser	Lys	Ser	Tyr	Arg	
				165				170						175		
Glu	Asn	Gly	Ala	Pro	Phe	Val	Pro	Pro	Pro	Pro	Ala	Leu	Asp	Glu	Leu	
			180					185					190			
Gly	Gly	Pro	Gly	Gly	Val	Thr	His	Pro	Glu	Glu	Arg	Leu	Gly	Val	Ala	
		195					200					205				
Gly	Gly	Pro	Gly	Ser	Ala	Pro	Ala	Ala	Gly	Gly	Gly	Thr	Gly	Thr	Glu	
		210				215					220					
Asp	Asp	Glu	Glu	Glu	Leu	Leu	Glu	Asp	Glu	Glu	Asp	Glu	Asp	Glu	Glu	
225					230					235					240	
Glu	Glu	Leu	Leu	Glu	Asp	Asp	Glu	Glu	Glu	Leu	Leu	Glu	Asp	Asp	Ala	
				245					250					255		
Arg	Ala	Leu	Leu	Lys	Glu	Pro	Arg	Arg	Cys	Pro	Val	Ala	Ala	Thr	Gly	
			260					265						270		
Ala	Val	Ala	Ala	Ala	Ala	Ala	Ala	Ala	Val	Ala	Thr	Glu	Gly	Gly	Glu	
			275					280					285			
Leu	Ser	Pro	Lys	Glu	Glu	Leu	Leu	Leu	His	Pro	Glu	Asp	Ala	Glu	Gly	
		290				295					300					
Lys	Asp	Gly	Glu	Asp	Ser	Val	Cys	Leu	Ser	Ala	Gly	Ser	Asp	Ser	Glu	
305					310					315					320	
Glu	Gly	Leu	Leu	Lys	Arg	Lys	Gln	Arg	Arg	Tyr	Arg	Thr	Thr	Phe	Thr	
				325					330					335		
Ser	Tyr	Gln	Leu	Glu	Glu	Leu	Glu	Arg	Ala	Phe	Gln	Lys	Thr	His	Tyr	
			340					345					350			
Pro	Asp	Val	Phe	Thr	Arg	Glu	Glu	Leu	Ala	Met	Arg	Leu	Asp	Leu	Thr	
		355					360					365				
Glu	Ala	Arg	Val	Gln	Val	Trp	Phe	Gln	Asn	Arg	Arg	Ala	Lys	Trp	Arg	
		370				375					380					
Lys	Arg	Glu	Lys	Ala	Gly	Ala	Gln	Thr	His	Pro	Pro	Gly	Leu	Pro	Phe	
385					390					395					400	
Pro	Gly	Pro	Leu	Ser	Ala	Thr	His	Pro	Leu	Ser	Pro	Tyr	Leu	Asp	Ala	
				405					410					415		
Ser	Pro	Phe	Pro	Pro	His	His	Pro	Ala	Leu	Asp	Ser	Ala	Trp	Thr	Ala	
				420				425					430			
Ala	Ala	Ala	Ala	Ala	Ala	Ala	Ala	Phe	Pro	Ser	Leu	Pro	Pro	Pro	Pro	
			435				440					445				
Gly	Ser	Ala	Ser	Leu	Pro	Pro	Ser	Gly	Ala	Pro	Leu	Gly	Leu	Ser	Thr	
		450				455					460					
Phe	Leu	Gly	Ala	Ala	Val	Phe	Arg	His	Pro	Ala	Phe	Ile	Ser	Pro	Ala	

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465	470	475	480
Phe Gly Arg Leu Phe Ser Thr Met Ala Pro Leu Thr Ser Ala Ser Thr			
	485	490	495
Ala Ala Ala Leu Leu Arg Gln Pro Thr Pro Ala Val Glu Gly Ala Val			
	500	505	510
Ala Ser Gly Ala Leu Ala Asp Pro Ala Thr Ala Ala Ala Asp Arg Arg			
	515	520	525
Ala Ser Ser Ile Ala Ala Leu Arg Leu Lys Ala Lys Glu His Ala Ala			
	530	535	540
Gln Leu Thr Gln Leu Asn Ile Leu Pro Gly Thr Ser Thr Gly Lys Glu			
545	550	555	560
Val Cys			

<210> SEQ ID NO 13
 <211> LENGTH: 501
 <212> TYPE: PRT
 <213> ORGANISM: Human

<400> SEQUENCE: 13

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

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260							265					270				
Val	His	Glu	Glu	Lys	Met	Thr	Asn	Gly	Gln	Gln	Ala	Pro	Asp	Asn	Ser	
		275					280					285				
Leu	Ser	Thr	Val	Pro	Pro	Gly	Cys	Ile	Asn	Leu	Ser	Gly	Ala	Gly	Ile	
		290				295					300					
Ser	Cys	Arg	Ser	Thr	Arg	Asp	Leu	Tyr	Ala	Thr	Val	Ile	His	Asp	Ile	
305					310					315					320	
Gln	Glu	Glu	Glu	Met	Glu	Asn	Asp	Gln	Thr	Pro	Pro	Asp	Gly	Phe	Leu	
				325					330					335		
Ser	Asn	Ser	Asp	Ser	Pro	Glu	Leu	Ile	Asn	Met	Thr	Gly	His	Cys	Met	
			340					345					350			
Pro	Pro	Asn	Ala	Leu	Asp	Ser	Phe	Ser	His	Asp	Phe	Thr	Ser	Leu	Ser	
		355					360					365				
Lys	Asp	Glu	Leu	Leu	Tyr	Lys	Pro	Asp	Ser	Asn	Glu	Phe	Ala	Val	Gly	
	370					375					380					
Thr	Lys	Asn	Tyr	Ser	Val	Ser	Ala	Gly	Asp	Pro	Pro	Val	Thr	Val	Met	
385					390					395					400	
Ser	Leu	Val	Glu	Thr	Val	Pro	Asn	Thr	Pro	Gln	Ile	Ser	Pro	Ala	Met	
				405					410					415		
Ala	Lys	Lys	Ile	Asn	Asp	Asp	Ile	Lys	Tyr	Gln	Leu	Met	Lys	Glu	Val	
			420					425					430			
Arg	Arg	Phe	Gly	Gln	Asn	Tyr	Glu	Arg	Ile	Phe	Ile	Leu	Leu	Glu	Glu	
		435					440					445				
Val	Gln	Gly	Ser	Met	Lys	Val	Lys	Arg	Gln	Phe	Val	Glu	Phe	Thr	Ile	
	450					455					460					
Lys	Glu	Ala	Ala	Arg	Phe	Lys	Lys	Val	Val	Leu	Ile	Gln	Gln	Leu	Glu	
465					470					475					480	
Lys	Ala	Leu	Lys	Glu	Ile	Asp	Ser	His	Cys	His	Leu	Arg	Lys	Val	Lys	
				485					490					495		
His	Met	Arg	Lys	Arg												
			500													
<210> SEQ ID NO 14																
<211> LENGTH: 636																
<212> TYPE: PRT																
<213> ORGANISM: Human																
<400> SEQUENCE: 14																
Met	Ser	Phe	Leu	Ile	Lys	Gly	Ala	Gln	Lys	His	Gly	Phe	Ile	Cys	Gln	
1				5					10					15		
Thr	His	Lys	Glu	Leu	Phe	Lys	Arg	Cys	Ile	Leu	Lys	Ser	Ser	Lys	Thr	
			20					25					30			
Phe	Asn	Gly	Gln	Lys	Met	Ile	Ser	Ser	Gln	Ala	Ser	Ser	Pro	Val	Asn	
		35					40					45				
Ser	Lys	Asn	Met	Asp	Ser	Phe	Asn	Tyr	Ile	Ile	Val	Gly	Ala	Gly	Ser	
	50					55					60					
Ala	Gly	Cys	Val	Leu	Ala	Asn	Arg	Leu	Thr	Glu	Asn	Pro	His	Asn	Thr	
65					70					75					80	
Val	Lys	Leu	Leu	Glu	Ala	Gly	Pro	Lys	Asp	Thr	Val	Leu	Gly	Ser	Lys	
				85					90					95		
Gln	Leu	Ser	Trp	Lys	Ile	His	Met	Pro	Ala	Ala	Leu	Thr	Tyr	Asn	Leu	
			100					105					110			

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Cys	Asp	Glu	Lys	Tyr	Asn	Trp	Tyr	Tyr	His	Thr	Thr	Pro	Gln	Lys	His
		115					120					125			
Met	Asp	Asn	Arg	Ile	Leu	Tyr	Trp	Pro	Arg	Gly	Arg	Val	Trp	Gly	Gly
	130					135					140				
Ser	Ser	Ser	Leu	Asn	Ala	Met	Val	Tyr	Ile	Arg	Gly	His	Ala	Glu	Asp
	145			150						155				160	
Tyr	Asn	Arg	Trp	Ser	Lys	Glu	Gly	Ala	Val	Gly	Trp	Asp	Tyr	Glu	Phe
			165						170					175	
Cys	Leu	Pro	Tyr	Phe	Lys	Lys	Ala	Gln	Thr	His	Glu	Leu	Gly	Ala	Asp
			180					185					190		
Leu	Tyr	Arg	Gly	Gly	Asp	Gly	Pro	Leu	His	Val	Ser	Arg	Gly	Lys	Thr
		195					200					205			
Lys	Asn	Pro	Leu	His	Cys	Ala	Phe	Leu	Asp	Ala	Ala	Gln	Gln	Ala	Gly
	210					215					220				
Tyr	Pro	Phe	Thr	Asp	Asp	Met	Asn	Gly	Phe	Gln	Gln	Glu	Gly	Phe	Gly
	225				230					235					240
Trp	Met	Asp	Met	Thr	Ile	Tyr	Glu	Asp	Phe	Pro	Arg	Ala	Val	Tyr	His
			245						250					255	
Thr	Glu	Ile	Ser	Tyr	Ile	Ile	Cys	Ile	Gly	Tyr	Cys	Tyr	Asn	Lys	Asn
		260					265						270		
Val	Tyr	Phe	Val	Gly	Lys	Arg	Trp	Asn	Thr	Ala	Ser	Ala	Tyr	Leu	Arg
		275					280					285			
Pro	Ala	Leu	Ser	Arg	Pro	Asn	Leu	Ser	Ala	Glu	Val	Ser	Thr	Leu	Val
	290					295					300				
Thr	Lys	Val	Leu	Phe	Glu	Gly	Thr	Lys	Ala	Ile	Gly	Ile	Glu	Tyr	Ile
	305				310					315					320
Lys	Asn	Gly	Glu	Lys	Lys	Lys	Val	Phe	Ala	Ser	Lys	Glu	Val	Ile	Leu
			325						330					335	
Ser	Gly	Gly	Ala	Ile	Asn	Ser	Pro	Gln	Leu	Leu	Met	Leu	Ser	Gly	Val
			340					345					350		
Gly	Val	Gly	Gln	Asn	Leu	Gln	Asp	His	Leu	Glu	Val	Tyr	Ile	Gln	Gln
		355					360					365			
Lys	Cys	Thr	Gln	Pro	Leu	Thr	Leu	Tyr	Lys	Ser	Gln	Lys	Pro	Leu	Gln
	370					375					380				
Met	Ile	Lys	Ile	Gly	Leu	Glu	Trp	Phe	Trp	Lys	Ser	Thr	Gly	Asp	Gly
	385				390					395					400
Ala	Thr	Ala	His	Leu	Glu	Thr	Gly	Gly	Phe	Ile	Arg	Ser	Arg	Pro	Gly
			405						410					415	
Ile	Ser	His	Pro	Asp	Ile	Gln	Phe	His	Phe	Leu	Pro	Ser	Gln	Val	Ile
			420				425						430		
Asp	His	Gly	Arg	Val	Ala	Ser	Gln	Leu	Glu	Ala	Tyr	Gln	Val	His	Ile
		435					440					445			
Gly	Pro	Met	Arg	Ser	Thr	Ser	Val	Gly	Lys	Leu	Lys	Leu	Lys	Ser	Ser
	450					455					460				
Asp	Pro	Thr	Glu	His	Pro	Ile	Leu	Glu	Pro	Asn	Tyr	Leu	Ser	Thr	Glu
	465				470					475					480
Met	Asp	Val	Trp	Glu	Phe	Arg	Gln	Cys	Val	Lys	Leu	Ala	Arg	Glu	Ile
			485						490					495	
Phe	Ala	Gln	Lys	Ala	Phe	Glu	Glu	Phe	Arg	Gly	Pro	Glu	Ile	Gln	Pro
			500					505					510		
Gly	Glu	His	Ile	Gln	Ser	Asp	Lys	Glu	Ile	Asp	Ala	Phe	Ile	Arg	Gln

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515					520					525					
Lys	Ser	Asp	Ser	Ala	Tyr	His	Pro	Ser	Cys	Thr	Cys	Lys	Met	Gly	Gln
530					535					540					
Asn	Ser	Asp	Pro	Met	Ala	Val	Val	Asn	Pro	Glu	Thr	Lys	Val	Ile	Gly
545					550					555					560
Thr	Glu	Asn	Leu	Arg	Val	Val	Asp	Ala	Ser	Ile	Met	Pro	Ser	Ile	Val
				565					570					575	
Ser	Gly	Asn	Leu	Asn	Ala	Pro	Thr	Ile	Met	Ile	Ala	Glu	Lys	Ala	Ala
				580					585					590	
Asp	Ile	Ile	Leu	Gly	Leu	Pro	Pro	Leu	Gln	Glu	Lys	Asn	Val	Pro	Val
				595					600					605	
Tyr	Lys	Pro	Lys	Thr	Leu	Glu	Thr	Gln	His	Asn	Pro	Asp	Lys	Val	Ala
				610					615					620	
Trp	Gln	Asn	Lys	Ser	Ile	Tyr	Pro	Met	Leu	Ile	Lys				
625					630					635					

<210> SEQ ID NO 15
 <211> LENGTH: 140
 <212> TYPE: PRT
 <213> ORGANISM: Human

<400> SEQUENCE: 15

Leu	Leu	Tyr	Lys	Pro	Val	Asp	Arg	Val	Thr	Arg	Ser	Thr	Leu	Val	Leu
1				5					10				15		
His	Asp	Leu	Leu	Lys	His	Thr	Pro	Ala	Ser	His	Pro	Asp	His	Pro	Leu
				20				25					30		
Leu	Gln	Asp	Ala	Leu	Arg	Ile	Ser	Gln	Asn	Phe	Leu	Ser	Ser	Ile	Asn
				35				40					45		
Glu	Glu	Ile	Thr	Pro	Arg	Arg	Gln	Ser	Met	Thr	Val	Lys	Lys	Gly	Glu
				50				55					60		
Gly	Glu	Asp	Arg	Met	Lys	Ala	Ser	Ser	Thr	Arg	Lys	Arg	Leu	Leu	Leu
				65				70					80		
Met	Glu	Glu	Ala	Leu	Gln	Arg	Pro	Val	Ala	Ser	Asp	Phe	Glu	Pro	Gln
				85				90					95		
Gly	Leu	Ser	Glu	Ala	Ala	Arg	Trp	Asn	Ser	Lys	Glu	Asn	Leu	Leu	Ala
				100				105					110		
Gly	Pro	Ser	Glu	Asn	Asp	Pro	Asn	Leu	Phe	Val	Ala	Leu	Tyr	Asp	Phe
				115				120					125		
Val	Ala	Ser	Gly	Asp	Asn	Thr	Leu	Ser	Ile	Thr	Lys				
				130				135					140		

<210> SEQ ID NO 16
 <211> LENGTH: 109
 <212> TYPE: PRT
 <213> ORGANISM: Human

<400> SEQUENCE: 16

Met	Leu	Met	Ala	Gln	Glu	Ala	Leu	Ala	Phe	Leu	Met	Ala	Gln	Gly	Ala
1				5					10				15		
Met	Leu	Ala	Ala	Gln	Glu	Arg	Arg	Val	Pro	Arg	Ala	Ala	Glu	Val	Pro
				20				25					30		
Gly	Ala	Gln	Gly	Gln	Gln	Gly	Pro	Arg	Gly	Arg	Glu	Glu	Ala	Pro	Arg
				35				40					45		
Gly	Val	Arg	Met	Ala	Val	Pro	Leu	Leu	Arg	Arg	Met	Glu	Gly	Ala	Pro

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50	55	60
Ala Gly Pro Gly Gly Arg Thr Ala Ala Cys Phe Ser Cys Thr Ser Arg		
65	70	75 80
Cys Leu Ser Arg Arg Pro Trp Lys Arg Ser Trp Ser Ala Gly Ser Cys		
	85	90 95
Pro Gly Met Pro His Leu Ser Pro Asp Gln Gly Arg Phe		
	100	105

<210> SEQ ID NO 17
 <211> LENGTH: 222
 <212> TYPE: PRT
 <213> ORGANISM: Human

<400> SEQUENCE: 17

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

<210> SEQ ID NO 18
 <211> LENGTH: 702
 <212> TYPE: PRT
 <213> ORGANISM: Human

<400> SEQUENCE: 18

Met Glu Ser Pro Ser Ala Pro Pro His Arg Trp Cys Ile Pro Trp Gln		
1	5	10 15
Arg Leu Leu Leu Thr Ala Ser Leu Leu Thr Phe Trp Asn Pro Pro Thr		
	20	25 30
Thr Ala Lys Leu Thr Ile Glu Ser Thr Pro Phe Asn Val Ala Glu Gly		

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35					40					45					
Lys 50	Glu	Val	Leu	Leu	Leu 55	Val	His	Asn	Leu	Pro 60	Gln	His	Leu	Phe	Gly
Tyr 65	Ser	Trp	Tyr	Lys	Gly 70	Glu	Arg	Val	Asp	Gly 75	Asn	Arg	Gln	Ile	Ile 80
Gly	Tyr	Val	Ile	Gly 85	Thr	Gln	Gln	Ala	Thr 90	Pro	Gly	Pro	Ala	Tyr 95	Ser
Gly	Arg	Glu	Ile 100	Ile	Tyr	Pro	Asn	Ala 105	Ser	Leu	Leu	Ile	Gln 110	Asn	Ile
Ile	Gln	Asn 115	Asp	Thr	Gly	Phe	Tyr 120	Thr	Leu	His	Val	Ile 125	Lys	Ser	Asp
Leu 130	Val	Asn	Glu	Glu	Ala	Thr 135	Gly	Gln	Phe	Arg	Val 140	Tyr	Pro	Glu	Leu
Pro 145	Lys	Pro	Ser	Ile	Ser 150	Ser	Asn	Asn	Ser	Lys 155	Pro	Val	Glu	Asp	Lys 160
Asp	Ala	Val	Ala	Phe 165	Thr	Cys	Glu	Pro	Glu 170	Thr	Gln	Asp	Ala	Thr 175	Tyr
Leu	Trp	Trp	Val 180	Asn	Asn	Gln	Ser	Leu 185	Pro	Val	Ser	Pro	Arg 190	Leu	Gln
Leu	Ser	Asn 195	Gly	Asn	Arg	Thr	Leu 200	Thr	Leu	Phe	Asn	Val 205	Thr	Arg	Asn
Asp	Thr 210	Ala	Ser	Tyr	Lys 215	Cys	Glu	Thr	Gln	Asn	Pro 220	Val	Ser	Ala	Arg
Arg 225	Ser	Asp	Ser	Val	Ile 230	Leu	Asn	Val	Leu	Tyr 235	Gly	Pro	Asp	Ala	Pro 240
Thr	Ile	Ser	Pro	Leu 245	Asn	Thr	Ser	Tyr	Arg 250	Ser	Gly	Glu	Asn	Leu 255	Asn
Leu	Ser	Cys	His 260	Ala	Ala	Ser	Asn	Pro 265	Pro	Ala	Gln	Tyr	Ser 270	Trp	Phe
Val	Asn	Gly 275	Thr	Phe	Gln	Gln	Ser 280	Thr	Gln	Glu	Leu	Phe 285	Ile	Pro	Asn
Ile	Thr 290	Val	Asn	Asn	Ser	Gly 295	Ser	Tyr	Thr	Cys	Gln 300	Ala	His	Asn	Ser
Asp 305	Thr	Gly	Leu	Asn	Arg 310	Thr	Thr	Val	Thr	Thr 315	Ile	Thr	Val	Tyr	Ala 320
Glu	Pro	Pro	Lys 325	Pro	Phe	Ile	Thr	Ser	Asn	Asn 330	Ser	Asn	Pro	Val 335	Glu
Asp	Glu	Asp	Ala 340	Val	Ala	Leu	Thr	Cys 345	Glu	Pro	Glu	Ile	Gln 350	Asn	Thr
Thr	Tyr	Leu 355	Trp	Trp	Val	Asn	Asn 360	Gln	Ser	Leu	Pro	Val 365	Ser	Pro	Arg
Leu 370	Gln	Leu	Ser	Asn	Asp 375	Asn	Arg	Thr	Leu	Thr	Leu	Leu	Ser	Val	Thr
Arg 385	Asn	Asp	Val	Gly	Pro 390	Tyr	Glu	Cys	Gly	Ile 395	Gln	Asn	Glu	Leu	Ser
Val	Asp	His	Ser	Asp 405	Pro	Val	Ile	Leu	Asn	Val 410	Leu	Tyr	Gly	Pro 415	Asp
Asp	Pro	Thr	Ile 420	Ser	Pro	Ser	Tyr	Thr	Tyr	Tyr 425	Arg	Pro	Gly	Val 430	Asn
Leu	Ser	Leu	Ser	Cys	His	Ala	Ala 440	Ser	Asn	Pro	Pro	Ala 445	Gln	Tyr	Ser

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

<210> SEQ ID NO 19
 <211> LENGTH: 278
 <212> TYPE: PRT
 <213> ORGANISM: Human

<400> SEQUENCE: 19

Met Asp Phe Ser Arg Asn Leu Tyr Asp Ile Gly Glu Gln Leu Asp Ser
 1 5 10 15
 Glu Asp Leu Ala Ser Leu Lys Phe Leu Ser Leu Asp Tyr Ile Pro Gln
 20 25 30
 Arg Lys Gln Glu Pro Ile Lys Asp Ala Leu Met Leu Phe Gln Arg Leu
 35 40 45
 Gln Glu Lys Arg Met Leu Glu Glu Ser Asn Leu Ser Phe Leu Lys Glu
 50 55 60
 Leu Leu Phe Arg Ile Asn Arg Leu Asp Leu Leu Ile Thr Tyr Leu Asn
 65 70 75 80
 Thr Arg Lys Glu Glu Met Glu Arg Glu Leu Gln Thr Pro Gly Arg Ala
 85 90 95
 Gln Ile Ser Ala Tyr Arg Val Met Leu Tyr Gln Ile Ser Glu Glu Val

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<210> SEQ ID NO 20
<211> LENGTH: 303
<212> TYPE: PRT
<213> ORGANISM: Human

<400> SEQUENCE: 20

Met Ala Thr Ser Arg Tyr Glu Pro Val Ala Glu Ile Gly Val Gly Ala
1          5          10          15
Tyr Gly Thr Val Tyr Lys Ala Arg Asp Pro His Ser Gly His Phe Val
          20          25          30
Ala Leu Lys Ser Val Arg Val Pro Asn Gly Gly Gly Gly Gly Gly
          35          40          45
Leu Pro Ile Asn Thr Val Arg Glu Val Ala Leu Leu Arg Arg Leu Glu
          50          55          60
Ala Phe Glu His Pro Asn Val Val Arg Leu Met Asp Val Cys Ala Thr
          65          70          75          80
Ser Arg Thr Asp Arg Glu Ile Lys Val Thr Leu Val Phe Glu His Val
          85          90          95
Asp Gln Asp Leu Arg Thr Tyr Leu Asp Lys Ala Pro Pro Pro Gly Leu
          100          105          110
Pro Ala Glu Thr Ile Lys Asp Leu Met Arg Gln Phe Leu Arg Gly Leu
          115          120          125
Asp Phe Leu His Ala Asn Cys Ile Val His Arg Asp Leu Lys Pro Glu
          130          135          140
Asn Ile Leu Val Thr Ser Gly Gly Thr Val Lys Leu Ala Asp Phe Gly
          145          150          155          160
Leu Ala Arg Ile Tyr Ser Tyr Gln Met Ala Leu Thr Pro Val Val Val
          165          170          175

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Thr	Leu	Trp	Tyr	Arg	Ala	Pro	Glu	Val	Leu	Leu	Gln	Ser	Thr	Tyr	Ala
			180					185					190		
Thr	Pro	Val	Asp	Met	Trp	Ser	Val	Gly	Cys	Ile	Phe	Ala	Glu	Met	Phe
		195					200					205			
Arg	Arg	Lys	Pro	Leu	Phe	Cys	Gly	Asn	Ser	Glu	Ala	Asp	Gln	Leu	Gly
	210					215					220				
Lys	Ile	Phe	Asp	Leu	Ile	Gly	Leu	Pro	Pro	Glu	Asp	Asp	Trp	Pro	Arg
225					230					235					240
Asp	Val	Ser	Leu	Pro	Arg	Gly	Ala	Phe	Pro	Pro	Arg	Gly	Pro	Arg	Pro
				245					250					255	
Val	Gln	Ser	Val	Val	Pro	Glu	Met	Glu	Glu	Ser	Gly	Ala	Gln	Leu	Leu
			260					265					270		
Leu	Glu	Met	Leu	Thr	Phe	Asn	Pro	His	Lys	Arg	Ile	Ser	Ala	Phe	Arg
		275					280					285			
Ala	Leu	Gln	His	Ser	Tyr	Leu	His	Lys	Asp	Glu	Gly	Asn	Pro	Glu	
	290					295					300				

<210> SEQ ID NO 21
 <211> LENGTH: 823
 <212> TYPE: PRT
 <213> ORGANISM: Human

<400> SEQUENCE: 21

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

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Ser	Pro	Asp	Thr	Val	Pro	Leu	Gly	Thr	Gly	Thr	Ser	Ile	Leu	Ser	Lys	
				245					250					255		
Gln	Val	Gln	Asn	Lys	Pro	Lys	Thr	Gly	Arg	Ser	Leu	Leu	Gly	Gly	Pro	
				260					265					270		
Ala	Ala	Leu	Ser	Pro	Leu	Thr	Pro	Ser	Phe	Gly	Ile	Leu	Pro	Leu	Glu	
				275					280					285		
Thr	Pro	Ser	Pro	Gly	Asp	Gly	Ser	Tyr	Leu	Gln	Asn	Tyr	Thr	Asn	Thr	
				290					295					300		
Pro	Pro	Val	Ile	Asp	Val	Pro	Ser	Thr	Gly	Ala	Pro	Ser	Lys	Lys	Ser	
				305					310					315		
Val	Ala	Arg	Ile	Gly	Gln	Thr	Gly	Thr	Lys	Ser	Val	Phe	Ser	Gln	Ser	
				325					330					335		
Gly	Asn	Ser	Arg	Glu	Val	Thr	Pro	Ile	Leu	Ala	Gln	Thr	Gln	Ser	Ser	
				340					345					350		
Gly	Pro	Gln	Thr	Ser	Thr	Thr	Pro	Gln	Val	Leu	Ser	Pro	Thr	Ile	Thr	
				355					360					365		
Ser	Pro	Pro	Asn	Ala	Leu	Pro	Arg	Arg	Ser	Ser	Arg	Leu	Phe	Thr	Ser	
				370					375					380		
Asp	Ser	Ser	Thr	Thr	Lys	Glu	Asn	Ser	Lys	Lys	Leu	Lys	Met	Lys	Phe	
				385					390					395		
Pro	Pro	Lys	Ile	Pro	Asn	Arg	Lys	Thr	Lys	Ser	Lys	Thr	Asn	Lys	Gly	
				405					410					415		
Gly	Ile	Thr	Gln	Pro	Asn	Ile	Asn	Asp	Ser	Leu	Glu	Ile	Thr	Lys	Leu	
				420					425					430		
Asp	Ser	Ser	Ile	Ile	Ser	Glu	Gly	Lys	Ile	Ser	Thr	Ile	Thr	Pro	Gln	
				435					440					445		
Ile	Gln	Ala	Phe	Asn	Leu	Gln	Lys	Ala	Ala	Ala	Gly	Leu	Met	Ser	Leu	
				450					455					460		
Leu	Arg	Glu	Met	Gly	Lys	Gly	Tyr	Leu	Ala	Leu	Cys	Ser	Tyr	Asn	Cys	
				465					470					475		
Lys	Glu	Ala	Ile	Asn	Ile	Leu	Ser	His	Leu	Pro	Ser	His	His	Tyr	Asn	
				485					490					495		
Thr	Gly	Trp	Val	Leu	Cys	Gln	Ile	Gly	Arg	Ala	Tyr	Phe	Glu	Leu	Ser	
				500					505					510		
Glu	Tyr	Met	Gln	Ala	Glu	Arg	Ile	Phe	Ser	Glu	Val	Arg	Arg	Ile	Glu	
				515					520					525		
Asn	Tyr	Arg	Val	Glu	Gly	Met	Glu	Ile	Tyr	Ser	Thr	Thr	Leu	Trp	His	
				530					535					540		
Leu	Gln	Lys	Asp	Val	Ala	Leu	Ser	Val	Leu	Ser	Lys	Asp	Leu	Thr	Asp	
				545					550					555		
Met	Asp	Lys	Asn	Ser	Pro	Glu	Ala	Trp	Cys	Ala	Ala	Gly	Asn	Cys	Phe	
				565					570					575		
Ser	Leu	Gln	Arg	Glu	His	Asp	Ile	Ala	Ile	Lys	Phe	Phe	Gln	Arg	Ala	
				580					585					590		
Ile	Gln	Val	Asp	Pro	Asn	Tyr	Ala	Tyr	Ala	Tyr	Thr	Leu	Leu	Gly	His	
				595					600					605		
Glu	Phe	Val	Leu	Thr	Glu	Glu	Leu	Asp	Lys	Ala	Leu	Ala	Cys	Phe	Arg	
				610					615					620		
Asn	Ala	Ile	Arg	Val	Asn	Pro	Arg	His	Tyr	Asn	Ala	Trp	Tyr	Gly	Leu	
				625					630					635		

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<210> SEQ ID NO 22
<211> LENGTH: 382
<212> TYPE: PRT
<213> ORGANISM: Human

<400> SEQUENCE: 22

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

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

<210> SEQ ID NO 23
 <211> LENGTH: 257
 <212> TYPE: PRT
 <213> ORGANISM: Human

<400> SEQUENCE: 23

Met Pro Phe Ile Ser His His Tyr Pro His Asp His Ser Cys Arg Trp
 1 5 10 15
 Val Glu Pro Phe Ile Gly Gly Gly Ala Val Phe Leu Asn Met Phe Ala
 20 25 30
 Gln Asn Ala Leu Leu Ala Asp Ser Asn Pro Asp Leu Ile Asn Leu Tyr
 35 40 45
 Arg Thr Ile Gln Arg Gln Lys Thr Asn Phe Ile Asn Gln Val Gln Asn
 50 55 60
 Leu Ala Asp Lys Thr Phe Val Glu Lys Asp Tyr Tyr Glu Met Arg Asp
 65 70 75 80
 Arg Phe Asn Lys Thr Cys Ile Ser Gly Gln Pro Leu Gln Arg Ala Ala
 85 90 95
 Leu Phe Tyr Ser Leu Asn Arg Leu Gly Tyr Asn Gly Met Cys Arg Tyr
 100 105 110
 Asn Ser Glu Arg Ile Tyr Ser Val Pro Trp Gly Lys His Thr Glu Leu
 115 120 125
 Lys Leu Asp Phe Asn Lys Ile Asp Tyr Leu Ser Phe Arg Leu Ser Gly
 130 135 140
 Ile Glu Leu Ile Thr Ala Gly Phe Glu Glu Thr Leu Ala Ala Thr Gly

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145	150	155	160
Glu Gly Asp Gln Ile Tyr Cys Asp Pro Pro Tyr Asp Lys Thr Ser Lys			
	165	170	175
Thr Ser Phe Val Ser Tyr Asp Gly Lys Pro Phe Ser Gln Ser Asp His			
	180	185	190
Val Leu Leu Ala Asn Met Leu Val Asp Ala His Arg Lys Gly Ala Ala			
	195	200	205
Val Ala Ile Ser Asn Ser Leu Thr Pro Phe Thr Leu Gly Leu Tyr Glu			
	210	215	220
Glu Arg Gly Phe Val Ile His Arg Leu Ser Ala Tyr Arg Ser Val Gly			
	225	230	235
Ser Lys Pro Asn Thr Arg Lys Thr Glu Thr Glu Ile Leu Ala Val Leu			
	245	250	255

Lys

<210> SEQ ID NO 24
 <211> LENGTH: 288
 <212> TYPE: PRT
 <213> ORGANISM: Human

<400> SEQUENCE: 24

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

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245					250					255					
Ile	Glu	Thr	Val	Ser	Ala	Thr	Arg	Ser	Ile	Asn	Ser	Asn	Ala	Leu	Lys
			260					265					270		
Arg	Gly	Lys	Ile	Asn	Glu	Val	Leu	Val	Leu	Asn	Tyr	Val	Pro	Lys	Leu
		275					280					285			
<210> SEQ ID NO 25 <211> LENGTH: 395 <212> TYPE: PRT <213> ORGANISM: Human <400> SEQUENCE: 25															
Gly	Pro	Gly	Cys	Asn	Thr	Lys	Lys	Pro	Asn	Leu	Asp	Ala	Glu	Leu	Asp
1				5					10					15	
Gln	Leu	Leu	Gln	Gly	His	Tyr	Ile	Lys	Gly	Tyr	Pro	Lys	Gln	Tyr	Thr
			20					25					30		
Tyr	Phe	Leu	Glu	Asp	Gly	Lys	Val	Lys	Val	Ser	Arg	Pro	Glu	Gly	Val
		35					40					45			
Lys	Ile	Ile	Pro	Pro	Gln	Ser	Asp	Arg	Gln	Lys	Ile	Val	Leu	Gln	Ala
	50					55					60				
His	Asn	Leu	Ala	His	Thr	Gly	Arg	Glu	Ala	Thr	Leu	Leu	Lys	Ile	Ala
	65					70					75			80	
Asn	Leu	Tyr	Trp	Trp	Pro	Asn	Met	Arg	Lys	Asp	Val	Val	Lys	Gln	Leu
			85					90						95	
Gly	Arg	Cys	Gln	Gln	Cys	Leu	Ile	Thr	Asn	Ala	Ser	Asn	Lys	Ala	Ser
			100					105					110		
Gly	Pro	Ile	Leu	Arg	Pro	Asp	Arg	Pro	Gln	Lys	Pro	Phe	Asp	Lys	Phe
		115					120					125			
Phe	Ile	Asp	Tyr	Ile	Gly	Pro	Leu	Pro	Pro	Ser	Gln	Gly	Tyr	Leu	Tyr
	130					135					140				
Val	Leu	Val	Val	Val	Asp	Gly	Met	Thr	Gly	Phe	Thr	Trp	Leu	Tyr	Pro
	145					150					155				160
Thr	Lys	Ala	Pro	Ser	Thr	Ser	Ala	Thr	Val	Lys	Ser	Leu	Asn	Val	Leu
			165						170					175	
Thr	Ser	Ile	Ala	Ile	Pro	Lys	Val	Ile	His	Ser	Asp	Gln	Gly	Ala	Ala
		180						185					190		
Phe	Thr	Ser	Ser	Thr	Phe	Ala	Glu	Trp	Ala	Lys	Glu	Arg	Gly	Ile	His
		195					200					205			
Leu	Glu	Phe	Ser	Thr	Pro	Tyr	His	Pro	Gln	Ser	Ser	Gly	Lys	Val	Glu
	210					215					220				
Arg	Lys	Asn	Ser	Asp	Ile	Lys	Arg	Leu	Leu	Thr	Lys	Leu	Leu	Val	Gly
	225					230					235				240
Arg	Pro	Thr	Lys	Trp	Tyr	Asp	Leu	Leu	Pro	Val	Val	Gln	Leu	Ala	Leu
			245					250					255		
Asn	Asn	Thr	Tyr	Ser	Pro	Val	Leu	Lys	Tyr	Thr	Pro	His	Gln	Leu	Leu
		260						265					270		
Phe	Gly	Ile	Asp	Ser	Asn	Thr	Pro	Phe	Ala	Asn	Gln	Asp	Thr	Leu	Asp
		275					280					285			
Leu	Thr	Arg	Glu	Glu	Glu	Leu	Ser	Leu	Leu	Gln	Glu	Ile	Arg	Thr	Ser
	290					295					300				
Leu	Tyr	His	Pro	Ser	Thr	Pro	Pro	Ala	Ser	Ser	Arg	Ser	Trp	Ser	Pro
	305					310					315				320

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Val	Val	Gly	Gln	Leu	Val	Gln	Glu	Arg	Val	Ala	Arg	Pro	Ala	Ser	Leu
				325					330					335	
Arg	Pro	Arg	Trp	His	Lys	Pro	Ser	Thr	Val	Leu	Lys	Val	Leu	Asn	Pro
			340					345					350		
Arg	Thr	Val	Val	Ile	Leu	Asp	His	Leu	Gly	Asn	Asn	Arg	Thr	Val	Ser
		355					360					365			
Ile	Asp	Asn	Leu	Lys	Pro	Thr	Ser	His	Gln	Asn	Gly	Thr	Thr	Asn	Asp
	370					375					380				
Thr	Ala	Thr	Met	Asp	His	Leu	Glu	Lys	Asn	Glu					
385					390					395					

<210> SEQ ID NO 26
 <211> LENGTH: 395
 <212> TYPE: PRT
 <213> ORGANISM: Human

<400> SEQUENCE: 26

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

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Leu Thr Arg Glu Glu Glu Leu Ser Leu Leu Gln Glu Ile Arg Thr Ser
 290 295 300
 Leu Tyr His Pro Ser Thr Pro Pro Ala Ser Ser Arg Ser Trp Ser Pro
 305 310 315 320
 Val Val Gly Gln Leu Val Gln Glu Arg Val Ala Arg Pro Ala Ser Leu
 325 330 335
 Arg Pro Arg Trp His Lys Pro Ser Thr Val Leu Lys Val Leu Asn Pro
 340 345 350
 Arg Thr Val Val Ile Leu Asp His Leu Gly Asn Asn Arg Thr Val Ser
 355 360 365
 Ile Asp Asn Leu Lys Pro Thr Ser His Gln Asn Gly Thr Thr Asn Asp
 370 375 380
 Thr Ala Thr Met Asp His Leu Glu Lys Asn Glu
 385 390 395

<210> SEQ ID NO 27
 <211> LENGTH: 407
 <212> TYPE: PRT
 <213> ORGANISM: Human

<400> SEQUENCE: 27

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

-continued

245										250										255											
Gly	Gly	Asn	Lys	Phe	Val	Tyr	Leu	Pro	Ser	Tyr	Val	Leu	Lys	Phe	Ala																
			260					265							270																
Ser	Gly	Lys	Ala	Leu	Asn	Lys	Asp	Lys	Asp	Phe	Lys	Val	Asn	Gly	Arg																
		275					280						285																		
Val	Thr	Asn	Cys	Thr	Phe	Leu	Lys	Ser	Arg	Ser	Ser	Phe	Asn	Gly	Ala																
	290					295					300																				
Lys	Leu	Pro	Leu	Ala	Val	Thr	Glu	Lys	His	Gly	Phe	Ser	Asn	Val	Met																
305					310						315				320																
Thr	Asn	Ile	Leu	Ala	Met	Lys	Glu	Glu	Lys	Met	Leu	Lys	Gly	Thr	Gly																
			325						330					335																	
Gln	Gly	Gly	Phe	Trp	Phe	Glu	Gly	His	Glu	Asp	Met	Lys	Phe	Lys	Gln																
			340					345					350																		
Ser	Glu	Phe	Ile	Lys	Lys	Tyr	Asn	Lys	Asp	Thr	Glu	Phe	Gln	Glu	Met																
	355						360					365																			
Phe	Asp	Glu	Val	Ser	Ser	Glu	Phe	Trp	Gln	Gly	Arg	Leu	Glu	Asp	Arg																
370						375					380																				
Phe	Gly	Asp	Glu	Tyr	Asp	Ser	Val	Glu	Lys	Ser	Lys	Gly	Asn	Asp	Phe																
385					390				395					400																	
Asp	Asp	Asp	Asp	Asp	Asp	Glu																									
					405																										

<210> SEQ ID NO 28
 <211> LENGTH: 661
 <212> TYPE: PRT
 <213> ORGANISM: Human
 <400> SEQUENCE: 28

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

-continued

Gly	Ser	Arg	Ser	Tyr	Val	Pro	Leu	Ala	His	Ser	Ser	Ser	Ala	Phe	Thr
	195						200					205			
Ile	Thr	Asp	Gln	Val	Pro	Phe	Ser	Val	Ser	Val	Ser	Gln	Leu	Arg	Ala
	210					215					220				
Leu	Asp	Gly	Gly	Asn	Lys	His	Phe	Leu	Arg	Asn	Gln	Pro	Leu	Thr	Phe
225				230					235						240
Ala	Leu	Gln	Leu	His	Asp	Pro	Ser	Gly	Tyr	Leu	Ala	Glu	Ala	Asp	Leu
				245					250					255	
Ser	Tyr	Thr	Trp	Asp	Phe	Gly	Asp	Ser	Ser	Gly	Thr	Leu	Ile	Ser	Arg
			260					265					270		
Ala	Leu	Val	Val	Thr	His	Thr	Tyr	Leu	Glu	Pro	Gly	Pro	Val	Thr	Ala
		275					280					285			
Gln	Val	Val	Leu	Gln	Ala	Ala	Ile	Pro	Leu	Thr	Ser	Cys	Gly	Ser	Ser
	290					295					300				
Pro	Val	Pro	Gly	Thr	Thr	Asp	Gly	His	Arg	Pro	Thr	Ala	Glu	Ala	Pro
305					310					315					320
Asn	Thr	Thr	Ala	Gly	Gln	Val	Pro	Thr	Thr	Glu	Val	Val	Gly	Thr	Thr
				325					330					335	
Pro	Gly	Gln	Ala	Pro	Thr	Ala	Glu	Pro	Ser	Gly	Thr	Thr	Ser	Val	Gln
			340					345					350		
Val	Pro	Thr	Thr	Glu	Val	Ile	Ser	Thr	Ala	Pro	Val	Gln	Met	Pro	Thr
			355				360					365			
Ala	Glu	Ser	Thr	Gly	Met	Thr	Pro	Glu	Lys	Val	Pro	Val	Ser	Glu	Val
	370					375					380				
Met	Gly	Thr	Thr	Leu	Ala	Glu	Met	Ser	Thr	Pro	Glu	Ala	Thr	Gly	Met
385					390					395					400
Thr	Pro	Ala	Glu	Val	Ser	Ile	Val	Val	Leu	Ser	Gly	Thr	Thr	Ala	Ala
				405					410					415	
Gln	Val	Thr	Thr	Thr	Glu	Trp	Val	Glu	Thr	Thr	Ala	Arg	Glu	Leu	Pro
				420				425					430		
Ile	Pro	Glu	Pro	Glu	Gly	Pro	Asp	Ala	Ser	Ser	Ile	Met	Ser	Thr	Glu
		435					440					445			
Ser	Ile	Thr	Gly	Ser	Leu	Gly	Pro	Leu	Leu	Asp	Gly	Thr	Ala	Thr	Leu
	450					455					460				
Arg	Leu	Val	Lys	Arg	Gln	Val	Pro	Leu	Asp	Cys	Val	Leu	Tyr	Arg	Tyr
465					470					475					480
Gly	Ser	Phe	Ser	Val	Thr	Leu	Asp	Ile	Val	Gln	Gly	Ile	Glu	Ser	Ala
				485					490					495	
Glu	Ile	Leu	Gln	Ala	Val	Pro	Ser	Gly	Glu	Gly	Asp	Ala	Phe	Glu	Leu
			500					505					510		
Thr	Val	Ser	Cys	Gln	Gly	Gly	Leu	Pro	Lys	Glu	Ala	Cys	Met	Glu	Ile
			515				520					525			
Ser	Ser	Pro	Gly	Cys	Gln	Pro	Pro	Ala	Gln	Arg	Leu	Cys	Gln	Pro	Val
		530				535					540				
Leu	Pro	Ser	Pro	Ala	Cys	Gln	Leu	Val	Leu	His	Gln	Ile	Leu	Lys	Gly
545					550					555					560
Gly	Ser	Gly	Thr	Tyr	Cys	Leu	Asn	Val	Ser	Leu	Ala	Asp	Thr	Asn	Ser
				565					570					575	
Leu	Ala	Val	Val	Ser	Thr	Gln	Leu	Ile	Met	Pro	Gly	Gln	Glu	Ala	Gly
			580					585					590		
Leu	Gly	Gln	Val	Pro	Leu	Ile	Val	Gly	Ile	Leu	Leu	Val	Leu	Met	Ala

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595	600	605
Val Val Leu Ala Ser Leu Ile Tyr Arg Arg Arg Leu Met Lys Gln Asp		
610	615	620
Phe Ser Val Pro Gln Leu Pro His Ser Ser Ser His Trp Leu Arg Leu		
625	630	635
Pro Arg Ile Phe Cys Ser Cys Pro Ile Gly Glu Asn Ser Pro Leu Leu		
	645	650
Ser Gly Gln Gln Val		
660		
<210> SEQ ID NO 29		
<211> LENGTH: 648		
<212> TYPE: PRT		
<213> ORGANISM: Human		
<400> SEQUENCE: 29		
Met Ser His His Gly Gly Ala Pro Lys Ala Ser Thr Trp Val Val Ala		
1	5	10
Ser Arg Arg Ser Ser Thr Val Ser Arg Ala Pro Glu Arg Arg Pro Ala		
	20	25
Glu Glu Leu Asn Arg Thr Gly Pro Glu Gly Tyr Ser Val Gly Arg Gly		
	35	40
Gly Arg Trp Arg Gly Thr Ser Arg Pro Pro Glu Ala Val Ala Ala Gly		
	50	55
His Glu Glu Leu Pro Leu Cys Phe Ala Leu Lys Ser His Phe Val Gly		
	65	70
Ala Val Ile Gly Arg Gly Gly Ser Lys Ile Lys Asn Ile Gln Ser Thr		
	85	90
Thr Asn Thr Thr Ile Gln Ile Ile Gln Glu Gln Pro Glu Ser Leu Val		
	100	105
Lys Ile Phe Gly Ser Lys Ala Met Gln Thr Lys Ala Lys Ala Val Ile		
	115	120
Asp Asn Phe Val Lys Lys Leu Glu Glu Asn Tyr Asn Ser Glu Cys Gly		
	130	135
Ile Asp Thr Ala Phe Gln Pro Ser Val Gly Lys Asp Gly Ser Thr Asp		
	145	150
Asn Asn Val Val Ala Gly Asp Arg Pro Leu Ile Asp Trp Asp Gln Ile		
	165	170
Arg Glu Glu Gly Leu Lys Trp Gln Lys Thr Lys Trp Ala Asp Leu Pro		
	180	185
Pro Ile Lys Lys Asn Phe Tyr Lys Glu Ser Thr Ala Thr Ser Ala Met		
	195	200
Ser Lys Val Glu Ala Asp Ser Trp Arg Lys Glu Asn Phe Asn Ile Thr		
	210	215
Trp Asp Asp Leu Lys Asp Gly Glu Lys Arg Pro Ile Pro Asn Pro Thr		
	225	230
Cys Thr Phe Asp Asp Ala Phe Gln Cys Tyr Pro Glu Val Met Glu Asn		
	245	250
Ile Lys Lys Ala Gly Phe Gln Lys Pro Thr Pro Ile Gln Ser Gln Ala		
	260	265
Trp Pro Ile Val Leu Gln Gly Ile Asp Leu Ile Gly Val Ala Gln Thr		
	275	280

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Gly	Thr	Gly	Lys	Thr	Leu	Cys	Tyr	Leu	Met	Pro	Gly	Phe	Ile	His	Leu
290						295					300				
Val	Leu	Gln	Pro	Ser	Leu	Lys	Gly	Gln	Arg	Asn	Arg	Pro	Gly	Met	Leu
305					310					315					320
Val	Leu	Thr	Pro	Thr	Arg	Glu	Leu	Ala	Leu	Gln	Val	Glu	Gly	Glu	Cys
				325					330					335	
Cys	Lys	Tyr	Ser	Tyr	Lys	Gly	Leu	Arg	Ser	Val	Cys	Val	Tyr	Gly	Gly
			340					345					350		
Gly	Asn	Arg	Asp	Glu	Gln	Ile	Glu	Glu	Leu	Lys	Lys	Gly	Val	Asp	Ile
			355				360					365			
Ile	Ile	Ala	Thr	Pro	Gly	Arg	Leu	Asn	Asp	Leu	Gln	Met	Ser	Asn	Phe
370						375					380				
Val	Asn	Leu	Lys	Asn	Ile	Thr	Tyr	Leu	Val	Leu	Asp	Glu	Ala	Asp	Lys
385					390					395					400
Met	Leu	Asp	Met	Gly	Phe	Glu	Pro	Gln	Ile	Met	Lys	Ile	Leu	Leu	Asp
			405					410						415	
Val	Arg	Pro	Asp	Arg	Gln	Thr	Val	Met	Thr	Ser	Ala	Thr	Trp	Pro	His
			420				425						430		
Ser	Val	His	Arg	Leu	Ala	Gln	Ser	Tyr	Leu	Lys	Glu	Pro	Met	Ile	Val
		435					440					445			
Tyr	Val	Gly	Thr	Leu	Asp	Leu	Val	Ala	Val	Ser	Ser	Val	Lys	Gln	Asn
450						455					460				
Ile	Ile	Val	Thr	Thr	Glu	Glu	Glu	Lys	Trp	Ser	His	Met	Gln	Thr	Phe
465					470					475					480
Leu	Gln	Ser	Met	Ser	Ser	Thr	Asp	Lys	Val	Ile	Val	Phe	Val	Ser	Arg
			485					490						495	
Lys	Ala	Val	Ala	Asp	His	Leu	Ser	Ser	Asp	Leu	Ile	Leu	Gly	Asn	Ile
			500					505					510		
Ser	Val	Glu	Ser	Leu	His	Gly	Asp	Arg	Glu	Gln	Arg	Asp	Arg	Glu	Lys
		515					520					525			
Ala	Leu	Glu	Asn	Phe	Lys	Thr	Gly	Lys	Val	Arg	Ile	Leu	Ile	Ala	Thr
530						535					540				
Asp	Leu	Ala	Ser	Arg	Gly	Leu	Asp	Val	His	Asp	Val	Thr	His	Val	Tyr
545					550					555					560
Asn	Phe	Asp	Phe	Pro	Arg	Asn	Ile	Glu	Glu	Tyr	Val	His	Arg	Ile	Gly
			565					570						575	
Arg	Thr	Gly	Arg	Ala	Gly	Arg	Thr	Gly	Val	Ser	Ile	Thr	Thr	Leu	Thr
			580					585					590		
Arg	Asn	Asp	Trp	Arg	Val	Ala	Ser	Glu	Leu	Ile	Asn	Ile	Leu	Glu	Arg
		595					600					605			
Ala	Asn	Gln	Ser	Ile	Pro	Glu	Glu	Leu	Val	Ser	Met	Ala	Glu	Arg	Phe
610						615					620				
Lys	Ala	His	Gln	Gln	Lys	Arg	Glu	Met	Glu	Arg	Lys	Met	Glu	Arg	Pro
625					630					635					640
Gln	Gly	Arg	Pro	Lys	Lys	Phe	His								
				645											

<210> SEQ ID NO 30

<211> LENGTH: 1240

<212> TYPE: PRT

<213> ORGANISM: Human

<400> SEQUENCE: 30

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Met	Pro	Arg	Gly	Ser	Trp	Lys	Pro	Gln	Val	Cys	Thr	Gly	Thr	Asp	Met	1	5	10	15
Lys	Leu	Arg	Leu	Pro	Ala	Ser	Pro	Glu	Thr	His	Leu	Asp	Met	Leu	Arg	20	25	30	
His	Leu	Tyr	Gln	Gly	Cys	Gln	Val	Val	Gln	Gly	Asn	Leu	Glu	Leu	Thr	35	40	45	
Tyr	Leu	Pro	Thr	Asn	Ala	Ser	Leu	Ser	Phe	Leu	Gln	Asp	Ile	Gln	Glu	50	55	60	
Val	Gln	Gly	Tyr	Val	Leu	Ile	Ala	His	Asn	Gln	Val	Arg	Gln	Val	Pro	65	70	75	80
Leu	Gln	Arg	Leu	Arg	Ile	Val	Arg	Gly	Thr	Gln	Leu	Phe	Glu	Asp	Asn	85	90	95	
Tyr	Ala	Leu	Ala	Val	Leu	Asp	Asn	Gly	Asp	Pro	Leu	Asn	Asn	Thr	Thr	100	105	110	
Pro	Val	Thr	Gly	Ala	Ser	Pro	Gly	Gly	Leu	Arg	Glu	Leu	Gln	Leu	Arg	115	120	125	
Ser	Leu	Thr	Glu	Ile	Leu	Lys	Gly	Gly	Val	Leu	Ile	Gln	Arg	Asn	Pro	130	135	140	
Gln	Leu	Cys	Tyr	Gln	Asp	Thr	Ile	Leu	Trp	Lys	Asp	Ile	Phe	His	Lys	145	150	155	160
Asn	Asn	Gln	Leu	Ala	Leu	Thr	Leu	Ile	Asp	Thr	Asn	Arg	Ser	Arg	Ala	165	170	175	
Cys	His	Pro	Cys	Ser	Pro	Met	Cys	Lys	Gly	Ser	Arg	Cys	Trp	Gly	Glu	180	185	190	
Ser	Ser	Glu	Asp	Cys	Gln	Ser	Leu	Thr	Arg	Thr	Val	Cys	Ala	Gly	Gly	195	200	205	
Cys	Ala	Arg	Cys	Lys	Gly	Pro	Leu	Pro	Thr	Asp	Cys	Cys	His	Glu	Gln	210	215	220	
Cys	Ala	Ala	Gly	Cys	Thr	Gly	Pro	Lys	His	Ser	Asp	Cys	Leu	Ala	Cys	225	230	235	240
Leu	His	Phe	Asn	His	Ser	Gly	Ile	Cys	Glu	Leu	His	Cys	Pro	Ala	Leu	245	250	255	
Val	Thr	Tyr	Asn	Thr	Asp	Thr	Phe	Glu	Ser	Met	Pro	Asn	Pro	Glu	Gly	260	265	270	
Arg	Tyr	Thr	Phe	Gly	Ala	Ser	Cys	Val	Thr	Ala	Cys	Pro	Tyr	Asn	Tyr	275	280	285	
Leu	Ser	Thr	Asp	Val	Gly	Ser	Cys	Thr	Leu	Val	Cys	Pro	Leu	His	Asn	290	295	300	
Gln	Glu	Val	Thr	Ala	Glu	Asp	Gly	Thr	Gln	Arg	Cys	Glu	Lys	Cys	Ser	305	310	315	320
Lys	Pro	Cys	Ala	Arg	Val	Cys	Tyr	Gly	Leu	Gly	Met	Glu	His	Leu	Arg	325	330	335	
Glu	Val	Arg	Ala	Val	Thr	Ser	Ala	Asn	Ile	Gln	Glu	Phe	Ala	Gly	Cys	340	345	350	
Lys	Lys	Ile	Phe	Gly	Ser	Leu	Ala	Phe	Leu	Pro	Glu	Ser	Phe	Asp	Gly	355	360	365	
Asp	Pro	Ala	Ser	Asn	Thr	Ala	Pro	Leu	Gln	Pro	Glu	Gln	Leu	Gln	Val	370	375	380	
Phe	Glu	Thr	Leu	Glu	Glu	Ile	Thr	Gly	Tyr	Leu	Tyr	Ile	Ser	Ala	Trp	385	390	395	400

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Pro	Asp	Ser	Leu	Pro	Asp	Leu	Ser	Val	Phe	Gln	Asn	Leu	Gln	Val	Ile	405	410	415	
Arg	Gly	Arg	Ile	Leu	His	Asn	Gly	Ala	Tyr	Ser	Leu	Thr	Leu	Gln	Gly	420	425	430	
Leu	Gly	Ile	Ser	Trp	Leu	Gly	Leu	Arg	Ser	Leu	Arg	Glu	Leu	Gly	Ser	435	440	445	
Gly	Leu	Ala	Leu	Ile	His	His	Asn	Thr	His	Leu	Cys	Phe	Val	His	Thr	450	455	460	
Val	Pro	Trp	Asp	Gln	Leu	Phe	Arg	Asn	Pro	His	Gln	Ala	Leu	Leu	His	465	470	475	480
Thr	Ala	Asn	Arg	Pro	Glu	Asp	Glu	Cys	Val	Gly	Glu	Gly	Leu	Ala	Cys	485	490	495	
His	Gln	Leu	Cys	Ala	Arg	Gly	His	Cys	Trp	Gly	Pro	Gly	Pro	Thr	Gln	500	505	510	
Cys	Val	Asn	Cys	Ser	Gln	Phe	Leu	Arg	Gly	Gln	Glu	Cys	Val	Glu	Glu	515	520	525	
Cys	Arg	Val	Leu	Gln	Gly	Leu	Pro	Arg	Glu	Tyr	Val	Asn	Ala	Arg	His	530	535	540	
Cys	Leu	Pro	Cys	His	Pro	Glu	Cys	Gln	Pro	Gln	Asn	Gly	Ser	Val	Thr	545	550	555	560
Cys	Phe	Gly	Pro	Glu	Ala	Asp	Gln	Cys	Val	Ala	Cys	Ala	His	Tyr	Lys	565	570	575	
Asp	Pro	Pro	Phe	Cys	Val	Ala	Arg	Cys	Pro	Ser	Gly	Val	Lys	Pro	Asp	580	585	590	
Leu	Ser	Tyr	Met	Pro	Ile	Trp	Lys	Phe	Pro	Asp	Glu	Glu	Gly	Ala	Cys	595	600	605	
Gln	Pro	Cys	Pro	Ile	Asn	Cys	Thr	His	Ser	Cys	Val	Asp	Leu	Asp	Asp	610	615	620	
Lys	Gly	Cys	Pro	Ala	Glu	Gln	Arg	Ala	Ser	Pro	Leu	Thr	Ser	Ile	Ile	625	630	635	640
Ser	Ala	Val	Val	Gly	Ile	Leu	Leu	Val	Val	Val	Leu	Gly	Val	Val	Phe	645	650	655	
Gly	Ile	Leu	Ile	Lys	Arg	Arg	Gln	Gln	Lys	Ile	Arg	Lys	Tyr	Thr	Met	660	665	670	
Arg	Arg	Leu	Leu	Gln	Glu	Thr	Glu	Leu	Val	Glu	Pro	Leu	Thr	Pro	Ser	675	680	685	
Gly	Ala	Met	Pro	Asn	Gln	Ala	Gln	Met	Arg	Ile	Leu	Lys	Glu	Thr	Glu	690	695	700	
Leu	Arg	Lys	Val	Lys	Val	Leu	Gly	Ser	Gly	Ala	Phe	Gly	Thr	Val	Tyr	705	710	715	720
Lys	Gly	Ile	Trp	Ile	Pro	Asp	Gly	Glu	Asn	Val	Lys	Ile	Pro	Val	Ala	725	730	735	
Ile	Lys	Val	Leu	Arg	Glu	Asn	Thr	Ser	Pro	Lys	Ala	Asn	Lys	Glu	Ile	740	745	750	
Leu	Asp	Glu	Ala	Tyr	Val	Met	Ala	Gly	Val	Gly	Ser	Pro	Tyr	Val	Ser	755	760	765	
Arg	Leu	Leu	Gly	Ile	Cys	Leu	Thr	Ser	Thr	Val	Gln	Leu	Val	Thr	Gln	770	775	780	
Leu	Met	Pro	Tyr	Gly	Cys	Leu	Leu	Asp	His	Val	Arg	Glu	Asn	Arg	Gly	785	790	795	800
Arg	Leu	Gly	Ser	Gln	Asp	Leu	Leu	Asn	Trp	Cys	Met	Gln	Ile	Ala	Lys				

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805								810				815					
Gly	Met	Ser	Tyr	Leu	Glu	Asp	Val	Arg	Leu	Val	His	Arg	Asp	Leu	Ala		
820								825				830					
Ala	Arg	Asn	Val	Leu	Val	Lys	Ser	Pro	Asn	His	Val	Lys	Ile	Thr	Asp		
835								840				845					
Phe	Gly	Leu	Ala	Arg	Leu	Leu	Asp	Ile	Asp	Glu	Thr	Glu	Tyr	His	Ala		
850								855				860					
Asp	Gly	Gly	Lys	Val	Pro	Ile	Lys	Trp	Met	Ala	Leu	Glu	Ser	Ile	Leu		
865								870				875				880	
Arg	Arg	Arg	Phe	Thr	His	Gln	Ser	Asp	Val	Trp	Ser	Tyr	Gly	Val	Thr		
885								890				895					
Val	Trp	Glu	Leu	Met	Thr	Phe	Gly	Ala	Lys	Pro	Tyr	Asp	Gly	Ile	Pro		
900								905				910					
Ala	Arg	Glu	Ile	Pro	Asp	Leu	Leu	Glu	Lys	Gly	Glu	Arg	Leu	Pro	Gln		
915								920				925					
Pro	Pro	Ile	Cys	Thr	Ile	Asp	Val	Tyr	Met	Ile	Met	Val	Lys	Cys	Trp		
930								935				940					
Met	Ile	Asp	Ser	Glu	Cys	Arg	Pro	Arg	Phe	Arg	Glu	Leu	Val	Ser	Glu		
945								950				955				960	
Phe	Ser	Arg	Met	Ala	Arg	Asp	Pro	Gln	Arg	Phe	Val	Val	Ile	Gln	Asn		
965								970				975					
Glu	Asp	Leu	Gly	Pro	Ala	Ser	Pro	Leu	Asp	Ser	Thr	Phe	Tyr	Arg	Ser		
980								985				990					
Leu	Leu	Glu	Asp	Asp	Asp	Met	Gly	Asp	Leu	Val	Asp	Ala	Glu	Glu	Tyr		
995								1000				1005					
Leu	Val	Pro	Gln	Gln	Gly	Phe	Phe	Cys	Pro	Asp	Pro	Ala	Pro	Gly			
1010								1015				1020					
Ala	Gly	Gly	Met	Val	His	His	Arg	His	Arg	Ser	Ser	Ser	Thr	Arg			
1025								1030				1035					
Ser	Gly	Gly	Gly	Asp	Leu	Thr	Leu	Gly	Leu	Glu	Pro	Ser	Glu	Glu			
1040								1045				1050					
Glu	Ala	Pro	Arg	Ser	Pro	Leu	Ala	Pro	Ser	Glu	Gly	Ala	Gly	Ser			
1055								1060				1065					
Asp	Val	Phe	Asp	Gly	Asp	Leu	Gly	Met	Gly	Ala	Ala	Lys	Gly	Leu			
1070								1075				1080					
Gln	Ser	Leu	Pro	Thr	His	Asp	Pro	Ser	Pro	Leu	Gln	Arg	Tyr	Ser			
1085								1090				1095					
Glu	Asp	Pro	Thr	Val	Pro	Leu	Pro	Ser	Glu	Thr	Asp	Gly	Tyr	Val			
1100								1105				1110					
Ala	Pro	Leu	Thr	Cys	Ser	Pro	Gln	Pro	Glu	Tyr	Val	Asn	Gln	Pro			
1115								1120				1125					
Asp	Val	Arg	Pro	Gln	Pro	Pro	Ser	Pro	Arg	Glu	Gly	Pro	Leu	Pro			
1130								1135				1140					
Ala	Ala	Arg	Pro	Ala	Gly	Ala	Thr	Leu	Glu	Arg	Pro	Lys	Thr	Leu			
1145								1150				1155					
Ser	Pro	Gly	Lys	Asn	Gly	Val	Val	Lys	Asp	Val	Phe	Ala	Phe	Gly			
1160								1165				1170					
Gly	Ala	Val	Glu	Asn	Pro	Glu	Tyr	Leu	Thr	Pro	Gln	Gly	Gly	Ala			
1175								1180				1185					
Ala	Pro	Gln	Pro	His	Pro	Pro	Pro	Ala	Phe	Ser	Pro	Ala	Phe	Asp			
1190								1195				1200					

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Asn Leu Tyr Tyr Trp Asp Gln Asp Pro Pro Glu Arg Gly Ala Pro
1205                      1210                      1215

Pro Ser Thr Phe Lys Gly Thr Pro Thr Ala Glu Asn Pro Glu Tyr
1220                      1225                      1230

Leu Gly Leu Asp Val Pro Val
1235                      1240

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<210> SEQ ID NO 31
<211> LENGTH: 44
<212> TYPE: PRT
<213> ORGANISM: Human

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<400> SEQUENCE: 31

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Met Asn His Pro Gly Leu Phe Leu Phe Leu Gly Leu Thr Phe Ala Val
1                      5                      10                      15

Gln Leu Leu Leu Leu Val Phe Leu Leu Phe Phe Phe Leu Val Trp Trp
                20                      25                      30

Asp Gln Phe Gly Cys Arg Cys Asp Gly Phe Ile Leu
35                      40

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<210> SEQ ID NO 32
<211> LENGTH: 580
<212> TYPE: PRT
<213> ORGANISM: Human

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<400> SEQUENCE: 32

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Met Ala Gly Thr Val Arg Thr Ala Cys Leu Val Val Ala Met Leu Leu
1                      5                      10                      15

Ser Leu Asp Phe Pro Gly Gln Ala Gln Pro Pro Pro Pro Pro Asp
20                      25                      30

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

Leu Lys Trp Val Pro Glu Thr Pro Val Pro Gly Ser Asp Leu Gln Val
50                      55                      60

Cys Leu Pro Lys Gly Pro Thr Cys Cys Ser Arg Lys Met Glu Glu Lys
65                      70                      75                      80

Tyr Gln Leu Thr Ala Arg Leu Asn Met Glu Gln Leu Leu Gln Ser Ala
85                      90                      95

Ser Met Glu Leu Lys Phe Leu Ile Ile Gln Asn Ala Ala Val Phe Gln
100                     105                     110

Glu Ala Phe Glu Ile Val Val Arg His Ala Lys Asn Tyr Thr Asn Ala
115                     120                     125

Met Phe Lys Asn Asn Tyr Pro Ser Leu Thr Pro Gln Ala Phe Glu Phe
130                     135                     140

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

Ile Asn Val Asp Asp Met Val Asn Glu Leu Phe Asp Ser Leu Phe Pro
165                     170                     175

Val Ile Tyr Thr Gln Leu Met Asn Pro Gly Leu Pro Asp Ser Ala Leu
180                     185                     190

Asp Ile Asn Glu Cys Leu Arg Gly Ala Arg Arg Asp Leu Lys Val Phe
195                     200                     205

Gly Asn Phe Pro Lys Leu Ile Met Thr Gln Val Ser Lys Ser Leu Gln
210                     215                     220

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Val	Thr	Arg	Ile	Phe	Leu	Gln	Ala	Leu	Asn	Leu	Gly	Ile	Glu	Val	Ile
225					230					235					240
Asn	Thr	Thr	Asp	His	Leu	Lys	Phe	Ser	Lys	Asp	Cys	Gly	Arg	Met	Leu
				245					250					255	
Thr	Arg	Met	Trp	Tyr	Cys	Ser	Tyr	Cys	Gln	Gly	Leu	Met	Met	Val	Lys
			260					265						270	
Pro	Cys	Gly	Gly	Tyr	Cys	Asn	Val	Val	Met	Gln	Gly	Cys	Met	Ala	Gly
		275					280					285			
Val	Val	Glu	Ile	Asp	Lys	Tyr	Trp	Arg	Glu	Tyr	Ile	Leu	Ser	Leu	Glu
		290				295					300				
Glu	Leu	Val	Asn	Gly	Met	Tyr	Arg	Ile	Tyr	Asp	Met	Glu	Asn	Val	Leu
305					310					315					320
Leu	Gly	Leu	Phe	Ser	Thr	Ile	His	Asp	Ser	Ile	Gln	Tyr	Val	Gln	Lys
				325					330						335
Asn	Ala	Gly	Lys	Leu	Thr	Thr	Thr	Ile	Gly	Lys	Leu	Cys	Ala	His	Ser
			340						345					350	
Gln	Gln	Arg	Gln	Tyr	Arg	Ser	Ala	Tyr	Tyr	Pro	Glu	Asp	Leu	Phe	Ile
		355					360					365			
Asp	Lys	Lys	Val	Leu	Lys	Val	Ala	His	Val	Glu	His	Glu	Glu	Thr	Leu
		370				375					380				
Ser	Ser	Arg	Arg	Arg	Glu	Leu	Ile	Gln	Lys	Leu	Lys	Ser	Phe	Ile	Ser
385					390					395					400
Phe	Tyr	Ser	Ala	Leu	Pro	Gly	Tyr	Ile	Cys	Ser	His	Ser	Pro	Val	Ala
				405					410						415
Glu	Asn	Asp	Thr	Leu	Cys	Trp	Asn	Gly	Gln	Glu	Leu	Val	Glu	Arg	Tyr
			420					425					430		
Ser	Gln	Lys	Ala	Ala	Arg	Asn	Gly	Met	Lys	Asn	Gln	Phe	Asn	Leu	His
		435					440					445			
Glu	Leu	Lys	Met	Lys	Gly	Pro	Glu	Pro	Val	Val	Ser	Gln	Ile	Ile	Asp
		450				455					460				
Lys	Leu	Lys	His	Ile	Asn	Gln	Leu	Leu	Arg	Thr	Met	Ser	Met	Pro	Lys
465					470					475					480
Gly	Arg	Val	Leu	Asp	Lys	Asn	Leu	Asp	Glu	Glu	Gly	Phe	Glu	Ser	Gly
				485					490					495	
Asp	Cys	Gly	Asp	Asp	Glu	Asp	Glu	Cys	Ile	Gly	Gly	Ser	Gly	Asp	Gly
			500					505					510		
Met	Ile	Lys	Val	Lys	Asn	Gln	Leu	Arg	Phe	Leu	Ala	Glu	Leu	Ala	Tyr
			515				520					525			
Asp	Leu	Asp	Val	Asp	Asp	Ala	Pro	Gly	Asn	Ser	Gln	Gln	Ala	Thr	Pro
			530			535					540				
Lys	Asp	Asn	Glu	Ile	Ser	Thr	Phe	His	Asn	Leu	Gly	Asn	Val	His	Ser
545					550					555					560
Pro	Leu	Lys	Leu	Leu	Thr	Ser	Met	Ala	Ile	Ser	Val	Val	Cys	Phe	Phe
				565					570						575
Phe	Leu	Val	His												
			580												

<210> SEQ ID NO 33

<211> LENGTH: 1069

<212> TYPE: PRT

<213> ORGANISM: Human

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<400> SEQUENCE: 33

Met	Pro	Arg	Ala	Pro	Arg	Cys	Arg	Ala	Val	Arg	Ser	Leu	Leu	Arg	Ser	1	5	10	15
His	Tyr	Arg	Glu	Val	Leu	Pro	Leu	Ala	Thr	Phe	Val	Arg	Arg	Leu	Gly	20	25	30	
Pro	Gln	Gly	Trp	Arg	Leu	Val	Gln	Arg	Gly	Asp	Pro	Ala	Ala	Phe	Arg	35	40	45	
Ala	Leu	Val	Ala	Gln	Cys	Leu	Val	Cys	Val	Pro	Trp	Asp	Ala	Arg	Pro	50	55	60	
Pro	Pro	Ala	Ala	Pro	Ser	Phe	Arg	Gln	Val	Ser	Cys	Leu	Lys	Glu	Leu	65	70	75	80
Val	Ala	Arg	Val	Leu	Gln	Arg	Leu	Cys	Glu	Arg	Gly	Ala	Lys	Asn	Val	85	90	95	
Leu	Ala	Phe	Gly	Phe	Ala	Leu	Leu	Asp	Gly	Ala	Arg	Gly	Gly	Pro	Pro	100	105	110	
Glu	Ala	Phe	Thr	Thr	Ser	Val	Arg	Ser	Tyr	Leu	Pro	Asn	Thr	Val	Thr	115	120	125	
Asp	Ala	Leu	Arg	Gly	Ser	Gly	Ala	Trp	Gly	Leu	Leu	Leu	Arg	Arg	Val	130	135	140	
Gly	Asp	Asp	Val	Leu	Val	His	Leu	Leu	Ala	Arg	Cys	Ala	Leu	Phe	Val	145	150	155	160
Leu	Val	Ala	Pro	Ser	Cys	Ala	Tyr	Gln	Val	Cys	Gly	Pro	Pro	Leu	Tyr	165	170	175	
Gln	Leu	Gly	Ala	Ala	Thr	Gln	Ala	Arg	Pro	Pro	Pro	His	Ala	Ser	Gly	180	185	190	
Pro	Arg	Arg	Arg	Leu	Gly	Cys	Glu	Arg	Ala	Trp	Asn	His	Ser	Val	Arg	195	200	205	
Glu	Ala	Gly	Val	Pro	Leu	Gly	Leu	Pro	Ala	Pro	Gly	Ala	Arg	Arg	Arg	210	215	220	
Gly	Gly	Ser	Ala	Ser	Arg	Ser	Leu	Pro	Leu	Pro	Lys	Arg	Pro	Arg	Arg	225	230	235	240
Gly	Ala	Ala	Pro	Glu	Pro	Glu	Arg	Thr	Pro	Val	Gly	Gln	Gly	Ser	Trp	245	250	255	
Ala	His	Pro	Gly	Arg	Thr	Arg	Gly	Pro	Ser	Asp	Arg	Gly	Phe	Cys	Val	260	265	270	
Val	Ser	Pro	Ala	Arg	Pro	Ala	Glu	Glu	Ala	Thr	Ser	Leu	Glu	Gly	Ala	275	280	285	
Leu	Ser	Gly	Thr	Arg	His	Ser	His	Pro	Ser	Val	Gly	Arg	Gln	His	His	290	295	300	
Ala	Gly	Pro	Pro	Ser	Thr	Ser	Arg	Pro	Pro	Arg	Pro	Trp	Asp	Thr	Pro	305	310	315	320
Cys	Pro	Pro	Val	Tyr	Ala	Glu	Thr	Lys	His	Phe	Leu	Tyr	Ser	Ser	Gly	325	330	335	
Asp	Lys	Glu	Gln	Leu	Arg	Pro	Ser	Phe	Leu	Leu	Ser	Ser	Leu	Arg	Pro	340	345	350	
Ser	Leu	Thr	Gly	Ala	Arg	Arg	Leu	Val	Glu	Thr	Ile	Phe	Leu	Gly	Ser	355	360	365	
Arg	Pro	Trp	Met	Pro	Gly	Thr	Pro	Arg	Arg	Leu	Pro	Arg	Leu	Pro	Gln	370	375	380	
Arg	Tyr	Trp	Gln	Met	Arg	Pro	Leu	Phe	Leu	Glu	Leu	Leu	Gly	Asn	His	385	390	395	400

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Ala	Gln	Cys	Pro	Tyr	Gly	Val	Leu	Leu	Lys	Thr	His	Cys	Pro	Leu	Arg	
				405					410					415		
Ala	Ala	Val	Thr	Pro	Ala	Ala	Gly	Val	Cys	Ala	Arg	Glu	Lys	Pro	Gln	
			420					425					430			
Gly	Ser	Val	Ala	Ala	Pro	Glu	Glu	Glu	Asp	Thr	Asp	Pro	Arg	Arg	Leu	
		435					440					445				
Val	Gln	Leu	Leu	Arg	Gln	His	Ser	Ser	Pro	Trp	Gln	Val	Tyr	Gly	Phe	
	450					455					460					
Val	Arg	Ala	Cys	Leu	Arg	Arg	Leu	Val	Pro	Pro	Gly	Leu	Trp	Gly	Ser	
465					470					475					480	
Arg	His	Asn	Glu	Arg	Arg	Phe	Leu	Arg	Asn	Thr	Lys	Lys	Phe	Ile	Ser	
			485					490						495		
Leu	Gly	Lys	His	Ala	Lys	Leu	Ser	Leu	Gln	Glu	Leu	Thr	Trp	Lys	Met	
			500					505					510			
Ser	Val	Arg	Asp	Cys	Ala	Trp	Leu	Arg	Arg	Ser	Pro	Gly	Val	Gly	Cys	
		515					520					525				
Val	Pro	Ala	Ala	Glu	His	Arg	Leu	Arg	Glu	Glu	Ile	Leu	Ala	Lys	Phe	
	530					535					540					
Leu	His	Trp	Leu	Met	Ser	Val	Tyr	Val	Val	Glu	Leu	Leu	Arg	Ser	Phe	
545					550					555					560	
Phe	Tyr	Val	Thr	Glu	Thr	Thr	Phe	Gln	Lys	Asn	Arg	Leu	Phe	Phe	Tyr	
			565						570					575		
Arg	Lys	Ser	Val	Trp	Ser	Lys	Leu	Gln	Ser	Ile	Gly	Ile	Arg	Gln	His	
			580					585					590			
Leu	Lys	Arg	Val	Gln	Leu	Arg	Glu	Leu	Ser	Glu	Ala	Glu	Val	Arg	Gln	
		595					600					605				
His	Arg	Glu	Ala	Arg	Pro	Ala	Leu	Leu	Thr	Ser	Arg	Leu	Arg	Phe	Ile	
	610					615					620					
Pro	Lys	Pro	Asp	Gly	Leu	Arg	Pro	Ile	Val	Asn	Met	Asp	Tyr	Val	Val	
625					630					635					640	
Gly	Ala	Arg	Thr	Phe	Arg	Arg	Glu	Lys	Arg	Ala	Glu	Arg	Leu	Thr	Ser	
			645					650						655		
Arg	Val	Lys	Ala	Leu	Phe	Ser	Val	Leu	Asn	Tyr	Glu	Arg	Ala	Arg	Arg	
			660					665					670			
Pro	Gly	Leu	Leu	Gly	Ala	Ser	Val	Leu	Gly	Leu	Asp	Asp	Ile	His	Arg	
		675					680					685				
Ala	Trp	Arg	Thr	Phe	Val	Leu	Arg	Val	Arg	Ala	Gln	Asp	Pro	Pro	Pro	
	690					695					700					
Glu	Leu	Tyr	Phe	Val	Lys	Val	Asp	Val	Thr	Gly	Ala	Tyr	Asp	Thr	Ile	
705					710					715					720	
Pro	Gln	Asp	Arg	Leu	Thr	Glu	Val	Ile	Ala	Ser	Ile	Ile	Lys	Pro	Gln	
			725					730						735		
Asn	Thr	Tyr	Cys	Val	Arg	Arg	Tyr	Ala	Val	Val	Gln	Lys	Ala	Ala	His	
			740					745					750			
Gly	His	Val	Arg	Lys	Ala	Phe	Lys	Ser	His	Val	Ser	Thr	Leu	Thr	Asp	
		755					760					765				
Leu	Gln	Pro	Tyr	Met	Arg	Gln	Phe	Val	Ala	His	Leu	Gln	Glu	Thr	Ser	
	770					775					780					
Pro	Leu	Arg	Asp	Ala	Val	Val	Ile	Glu	Gln	Ser	Ser	Ser	Leu	Asn	Glu	
785					790					795				800		

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

Asp

<210> SEQ ID NO 34

<211> LENGTH: 404

<212> TYPE: PRT

<213> ORGANISM: Human

<400> SEQUENCE: 34

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

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

<210> SEQ ID NO 35

<211> LENGTH: 118

<212> TYPE: PRT

<213> ORGANISM: Human

<400> SEQUENCE: 35

Met	Pro	Arg	Glu	Asp	Ala	His	Phe	Ile	Tyr	Gly	Tyr	Pro	Lys	Lys	Gly
1				5					10					15	

His	Gly	His	Ser	Tyr	Thr	Thr	Ala	Glu	Glu	Ala	Ala	Gly	Ile	Gly	Ile
		20					25					30			

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Leu Thr Val Ile Leu Gly Val Leu Leu Leu Ile Gly Cys Trp Tyr Cys
   35                               40                               45

Arg Arg Arg Asn Gly Tyr Arg Ala Leu Met Asp Lys Ser Leu His Val
   50                               55                               60

Gly Thr Gln Cys Ala Leu Thr Arg Arg Cys Pro Gln Glu Gly Phe Asp
   65                               70                               75                               80

His Arg Asp Ser Lys Val Ser Leu Gln Glu Lys Asn Cys Glu Pro Val
   85                               90                               95

Val Pro Asn Ala Pro Pro Ala Tyr Glu Lys Leu Ser Ala Glu Gln Ser
  100                               105                               110

Pro Pro Pro Tyr Ser Pro
  115

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<210> SEQ ID NO 36
<211> LENGTH: 1255
<212> TYPE: PRT
<213> ORGANISM: Human

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<400> SEQUENCE: 36

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Met Thr Pro Gly Thr Gln Ser Pro Phe Phe Leu Leu Leu Leu Thr
  1           5           10           15

Val Leu Thr Val Val Thr Gly Ser Gly His Ala Ser Ser Thr Pro Gly
  20           25           30

Gly Glu Lys Glu Thr Ser Ala Thr Gln Arg Ser Ser Val Pro Ser Ser
  35           40           45

Thr Glu Lys Asn Ala Val Ser Met Thr Ser Ser Val Leu Ser Ser His
  50           55           60

Ser Pro Gly Ser Gly Ser Ser Thr Thr Gln Gly Gln Asp Val Thr Leu
  65           70           75           80

Ala Pro Ala Thr Glu Pro Ala Ser Gly Ser Ala Ala Thr Trp Gly Gln
  85           90           95

Asp Val Thr Ser Val Pro Val Thr Arg Pro Ala Leu Gly Ser Thr Thr
 100           105           110

Pro Pro Ala His Asp Val Thr Ser Ala Pro Asp Asn Lys Pro Ala Pro
 115           120           125

Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr
 130           135           140

Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser
 145           150           155           160

Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His
 165           170           175

Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala
 180           185           190

Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro
 195           200           205

Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr
 210           215           220

Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser
 225           230           235           240

Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His
 245           250           255

Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala
 260           265           270

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Pro	Pro	Ala	His	Gly	Val	Thr	Ser	Ala	Pro	Asp	Thr	Arg	Pro	Ala	Pro
	275						280					285			
Gly	Ser	Thr	Ala	Pro	Pro	Ala	His	Gly	Val	Thr	Ser	Ala	Pro	Asp	Thr
	290					295				300					
Arg	Pro	Ala	Pro	Gly	Ser	Thr	Ala	Pro	Pro	Ala	His	Gly	Val	Thr	Ser
305				310					315					320	
Ala	Pro	Asp	Thr	Arg	Pro	Ala	Pro	Gly	Ser	Thr	Ala	Pro	Pro	Ala	His
		325						330						335	
Gly	Val	Thr	Ser	Ala	Pro	Asp	Thr	Arg	Pro	Ala	Pro	Gly	Ser	Thr	Ala
		340					345						350		
Pro	Pro	Ala	His	Gly	Val	Thr	Ser	Ala	Pro	Asp	Thr	Arg	Pro	Ala	Pro
	355						360					365			
Gly	Ser	Thr	Ala	Pro	Pro	Ala	His	Gly	Val	Thr	Ser	Ala	Pro	Asp	Thr
	370					375				380					
Arg	Pro	Ala	Pro	Gly	Ser	Thr	Ala	Pro	Pro	Ala	His	Gly	Val	Thr	Ser
385				390					395					400	
Ala	Pro	Asp	Thr	Arg	Pro	Ala	Pro	Gly	Ser	Thr	Ala	Pro	Pro	Ala	His
		405						410						415	
Gly	Val	Thr	Ser	Ala	Pro	Asp	Thr	Arg	Pro	Ala	Pro	Gly	Ser	Thr	Ala
		420					425						430		
Pro	Pro	Ala	His	Gly	Val	Thr	Ser	Ala	Pro	Asp	Thr	Arg	Pro	Ala	Pro
	435						440					445			
Gly	Ser	Thr	Ala	Pro	Pro	Ala	His	Gly	Val	Thr	Ser	Ala	Pro	Asp	Thr
	450					455				460					
Arg	Pro	Ala	Pro	Gly	Ser	Thr	Ala	Pro	Pro	Ala	His	Gly	Val	Thr	Ser
465				470					475					480	
Ala	Pro	Asp	Thr	Arg	Pro	Ala	Pro	Gly	Ser	Thr	Ala	Pro	Pro	Ala	His
		485						490						495	
Gly	Val	Thr	Ser	Ala	Pro	Asp	Thr	Arg	Pro	Ala	Pro	Gly	Ser	Thr	Ala
		500					505						510		
Pro	Pro	Ala	His	Gly	Val	Thr	Ser	Ala	Pro	Asp	Thr	Arg	Pro	Ala	Pro
	515						520					525			
Gly	Ser	Thr	Ala	Pro	Pro	Ala	His	Gly	Val	Thr	Ser	Ala	Pro	Asp	Thr
	530					535				540					
Arg	Pro	Ala	Pro	Gly	Ser	Thr	Ala	Pro	Pro	Ala	His	Gly	Val	Thr	Ser
545				550					555					560	
Ala	Pro	Asp	Thr	Arg	Pro	Ala	Pro	Gly	Ser	Thr	Ala	Pro	Pro	Ala	His
		565						570						575	
Gly	Val	Thr	Ser	Ala	Pro	Asp	Thr	Arg	Pro	Ala	Pro	Gly	Ser	Thr	Ala
		580					585						590		
Pro	Pro	Ala	His	Gly	Val	Thr	Ser	Ala	Pro	Asp	Thr	Arg	Pro	Ala	Pro
	595						600					605			
Gly	Ser	Thr	Ala	Pro	Pro	Ala	His	Gly	Val	Thr	Ser	Ala	Pro	Asp	Thr
	610					615				620					
Arg	Pro	Ala	Pro	Gly	Ser	Thr	Ala	Pro	Pro	Ala	His	Gly	Val	Thr	Ser
625				630					635					640	
Ala	Pro	Asp	Thr	Arg	Pro	Ala	Pro	Gly	Ser	Thr	Ala	Pro	Pro	Ala	His
		645						650						655	
Gly	Val	Thr	Ser	Ala	Pro	Asp	Thr	Arg	Pro	Ala	Pro	Gly	Ser	Thr	Ala
	660						665						670		

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Pro	Pro	Ala	His	Gly	Val	Thr	Ser	Ala	Pro	Asp	Thr	Arg	Pro	Ala	Pro	675	680	685
Gly	Ser	Thr	Ala	Pro	Pro	Ala	His	Gly	Val	Thr	Ser	Ala	Pro	Asp	Thr	690	695	700
Arg	Pro	Ala	Pro	Gly	Ser	Thr	Ala	Pro	Pro	Ala	His	Gly	Val	Thr	Ser	705	710	715
Ala	Pro	Asp	Thr	Arg	Pro	Ala	Pro	Gly	Ser	Thr	Ala	Pro	Pro	Ala	His	725	730	735
Gly	Val	Thr	Ser	Ala	Pro	Asp	Thr	Arg	Pro	Ala	Pro	Gly	Ser	Thr	Ala	740	745	750
Pro	Pro	Ala	His	Gly	Val	Thr	Ser	Ala	Pro	Asp	Thr	Arg	Pro	Ala	Pro	755	760	765
Gly	Ser	Thr	Ala	Pro	Pro	Ala	His	Gly	Val	Thr	Ser	Ala	Pro	Asp	Thr	770	775	780
Arg	Pro	Ala	Pro	Gly	Ser	Thr	Ala	Pro	Pro	Ala	His	Gly	Val	Thr	Ser	785	790	795
Ala	Pro	Asp	Thr	Arg	Pro	Ala	Pro	Gly	Ser	Thr	Ala	Pro	Pro	Ala	His	805	810	815
Gly	Val	Thr	Ser	Ala	Pro	Asp	Thr	Arg	Pro	Ala	Pro	Gly	Ser	Thr	Ala	820	825	830
Pro	Pro	Ala	His	Gly	Val	Thr	Ser	Ala	Pro	Asp	Thr	Arg	Pro	Ala	Pro	835	840	845
Gly	Ser	Thr	Ala	Pro	Pro	Ala	His	Gly	Val	Thr	Ser	Ala	Pro	Asp	Thr	850	855	860
Arg	Pro	Ala	Pro	Gly	Ser	Thr	Ala	Pro	Pro	Ala	His	Gly	Val	Thr	Ser	865	870	875
Ala	Pro	Asp	Thr	Arg	Pro	Ala	Pro	Gly	Ser	Thr	Ala	Pro	Pro	Ala	His	885	890	895
Gly	Val	Thr	Ser	Ala	Pro	Asp	Thr	Arg	Pro	Ala	Pro	Gly	Ser	Thr	Ala	900	905	910
Pro	Pro	Ala	His	Gly	Val	Thr	Ser	Ala	Pro	Asp	Thr	Arg	Pro	Ala	Pro	915	920	925
Gly	Ser	Thr	Ala	Pro	Pro	Ala	His	Gly	Val	Thr	Ser	Ala	Pro	Asp	Asn	930	935	940
Arg	Pro	Ala	Leu	Gly	Ser	Thr	Ala	Pro	Pro	Val	His	Asn	Val	Thr	Ser	945	950	955
Ala	Ser	Gly	Ser	Ala	Ser	Gly	Ser	Ala	Ser	Thr	Leu	Val	His	Asn	Gly	965	970	975
Thr	Ser	Ala	Arg	Ala	Thr	Thr	Thr	Pro	Ala	Ser	Lys	Ser	Thr	Pro	Phe	980	985	990
Ser	Ile	Pro	Ser	His	His	Ser	Asp	Thr	Pro	Thr	Thr	Leu	Ala	Ser	His	995	1000	1005
Ser	Thr	Lys	Thr	Asp	Ala	Ser	Ser	Thr	His	His	Ser	Ser	Val	Pro		1010	1015	1020
Pro	Leu	Thr	Ser	Ser	Asn	His	Ser	Thr	Ser	Pro	Gln	Leu	Ser	Thr		1025	1030	1035
Gly	Val	Ser	Phe	Phe	Phe	Leu	Ser	Phe	His	Ile	Ser	Asn	Leu	Gln		1040	1045	1050
Phe	Asn	Ser	Ser	Leu	Glu	Asp	Pro	Ser	Thr	Asp	Tyr	Tyr	Gln	Glu		1055	1060	1065
Leu	Gln	Arg	Asp	Ile	Ser	Glu	Met	Phe	Leu	Gln	Ile	Tyr	Lys	Gln				

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1070	1075	1080
Gly Gly Phe Leu Gly Leu Ser Asn Ile Lys Phe Arg Pro Gly Ser		
1085	1090	1095
Val Val Val Gln Leu Thr Leu Ala Phe Arg Glu Gly Thr Ile Asn		
1100	1105	1110
Val His Asp Val Glu Thr Gln Phe Asn Gln Tyr Lys Thr Glu Ala		
1115	1120	1125
Ala Ser Arg Tyr Asn Leu Thr Ile Ser Asp Val Ser Val Ser Asp		
1130	1135	1140
Val Pro Phe Pro Phe Ser Ala Gln Ser Gly Ala Gly Val Pro Gly		
1145	1150	1155
Trp Gly Ile Ala Leu Leu Val Leu Val Cys Val Leu Val Ala Leu		
1160	1165	1170
Ala Ile Val Tyr Leu Ile Ala Leu Ala Val Cys Gln Cys Arg Arg		
1175	1180	1185
Lys Asn Tyr Gly Gln Leu Asp Ile Phe Pro Ala Arg Asp Thr Tyr		
1190	1195	1200
His Pro Met Ser Glu Tyr Pro Thr Tyr His Thr His Gly Arg Tyr		
1205	1210	1215
Val Pro Pro Ser Ser Thr Asp Arg Ser Pro Tyr Glu Lys Val Ser		
1220	1225	1230
Ala Gly Asn Gly Gly Ser Ser Leu Ser Tyr Thr Asn Pro Ala Val		
1235	1240	1245
Ala Ala Thr Ser Ala Asn Leu		
1250	1255	

<210> SEQ ID NO 37

<211> LENGTH: 317

<212> TYPE: PRT

<213> ORGANISM: Human

<400> SEQUENCE: 37

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Met Pro Ala Leu Gly Ser Pro Arg Arg Leu Leu Gly Ser Leu Asn Cys
1          5          10          15

Thr Pro Pro Ala Thr Leu Pro Leu Thr Leu Ala Pro Asn Arg Thr Gly
          20          25          30

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

Gly Leu Val Ser Leu Val Glu Asn Val Leu Val Val Ala Ala Ile Ala
          50          55          60

Lys Asn Arg Asn Leu His Ser Pro Met Tyr Tyr Phe Ile Cys Cys Leu
          65          70          75          80

Ala Met Ser Asp Leu Leu Val Ser Val Ser Asn Val Leu Glu Thr Ala
          85          90          95

Val Met Leu Leu Leu Glu Ala Gly Val Leu Ala Thr Arg Ala Ala Val
          100         105         110

Val Gln Gln Leu Asp Asn Val Ile Asp Val Leu Ile Cys Ser Ser Met
          115         120         125

Val Ser Ser Leu Cys Phe Leu Gly Ala Ile Ala Val Asp Arg Tyr Ile
          130         135         140

Ser Ile Phe Tyr Ala Leu Arg Tyr His Ser Val Val Thr Leu Pro Arg
          145         150         155         160

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Ala	Trp	Arg	Ile	Ile	Ala	Ala	Ile	Trp	Val	Ala	Ser	Ile	Leu	Thr	Ser	
				165					170					175		
Val	Leu	Ser	Ile	Thr	Tyr	Tyr	Asn	His	Thr	Val	Val	Leu	Leu	Cys	Leu	
			180					185					190			
Val	Gly	Phe	Phe	Ile	Ala	Met	Leu	Ala	Leu	Met	Ala	Val	Leu	Tyr	Val	
		195					200					205				
His	Met	Leu	Ala	Arg	Ala	Cys	Gln	His	Ala	Arg	Gly	Ile	Ala	Arg	Leu	
	210					215					220					
Gln	Lys	Arg	Gln	Arg	Pro	Ile	His	Gln	Gly	Phe	Gly	Leu	Lys	Gly	Ala	
	225				230					235					240	
Ala	Thr	Leu	Thr	Ile	Leu	Leu	Gly	Val	Phe	Phe	Leu	Cys	Trp	Gly	Pro	
			245					250						255		
Phe	Phe	Leu	His	Leu	Ser	Leu	Ile	Val	Leu	Cys	Pro	Gln	His	Pro	Thr	
		260						265					270			
Cys	Gly	Cys	Ile	Phe	Lys	Asn	Phe	Asn	Leu	Phe	Leu	Ala	Leu	Ile	Ile	
		275					280					285				
Cys	Asn	Ala	Ile	Val	Asp	Pro	Leu	Ile	Tyr	Ala	Phe	Arg	Ser	Gln	Glu	
	290					295					300					
Leu	Arg	Lys	Thr	Leu	Gln	Glu	Val	Leu	Gln	Cys	Ser	Trp				
	305				310					315						

<210> SEQ ID NO 38
 <211> LENGTH: 683
 <212> TYPE: PRT
 <213> ORGANISM: Human

<400> SEQUENCE: 38

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

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Val	Val	His	Lys	Arg	Cys	His	His	Leu	Ile	Val	Thr	Ala	Cys	Thr	Cys
210					215					220					
Gln	Asn	Asn	Ile	Asn	Lys	Val	Asp	Ser	Lys	Ile	Ala	Glu	Gln	Arg	Phe
225				230					235						240
Gly	Ile	Asn	Ile	Pro	His	Lys	Phe	Ser	Ile	His	Asn	Tyr	Lys	Val	Pro
			245						250					255	
Thr	Phe	Cys	Asp	His	Cys	Gly	Ser	Leu	Leu	Trp	Gly	Ile	Met	Arg	Gln
			260					265					270		
Gly	Leu	Gln	Cys	Lys	Ile	Cys	Lys	Met	Asn	Val	His	Ile	Arg	Cys	Gln
	275						280					285			
Ala	Asn	Val	Ala	Pro	Asn	Cys	Gly	Val	Asn	Ala	Val	Glu	Leu	Ala	Lys
290					295					300					
Thr	Leu	Ala	Gly	Met	Gly	Leu	Gln	Pro	Gly	Asn	Ile	Ser	Pro	Thr	Ser
305					310					315					320
Lys	Leu	Val	Ser	Arg	Ser	Thr	Leu	Arg	Arg	Gln	Gly	Lys	Glu	Ser	Ser
				325					330					335	
Lys	Glu	Gly	Asn	Gly	Ile	Gly	Val	Asn	Ser	Ser	Asn	Arg	Leu	Gly	Ile
			340					345					350		
Asp	Asn	Phe	Glu	Phe	Ile	Arg	Val	Leu	Gly	Lys	Gly	Ser	Phe	Gly	Lys
		355					360					365			
Val	Met	Leu	Ala	Arg	Val	Lys	Glu	Thr	Gly	Asp	Leu	Tyr	Ala	Val	Lys
370					375						380				
Val	Leu	Lys	Lys	Asp	Val	Ile	Leu	Gln	Asp	Asp	Asp	Val	Glu	Cys	Thr
385					390					395					400
Met	Thr	Glu	Lys	Arg	Ile	Leu	Ser	Leu	Ala	Arg	Asn	His	Pro	Phe	Leu
				405					410					415	
Thr	Gln	Leu	Phe	Cys	Cys	Phe	Gln	Thr	Pro	Asp	Arg	Leu	Phe	Phe	Val
			420					425					430		
Met	Glu	Phe	Val	Asn	Gly	Gly	Asp	Leu	Met	Phe	His	Ile	Gln	Lys	Ser
	435						440					445			
Arg	Arg	Phe	Asp	Glu	Ala	Arg	Ala	Arg	Phe	Tyr	Ala	Ala	Glu	Ile	Ile
	450					455					460				
Ser	Ala	Leu	Met	Phe	Leu	His	Asp	Lys	Gly	Ile	Ile	Tyr	Arg	Asp	Leu
465					470					475					480
Lys	Leu	Asp	Asn	Val	Leu	Leu	Asp	His	Glu	Gly	His	Cys	Lys	Leu	Ala
			485					490						495	
Asp	Phe	Gly	Met	Cys	Lys	Glu	Gly	Ile	Cys	Asn	Gly	Val	Thr	Thr	Ala
			500					505					510		
Thr	Phe	Cys	Gly	Thr	Pro	Asp	Tyr	Ile	Ala	Pro	Glu	Ile	Leu	Gln	Glu
			515				520					525			
Met	Leu	Tyr	Gly	Pro	Ala	Val	Asp	Trp	Trp	Ala	Met	Gly	Val	Leu	Leu
530						535					540				
Tyr	Glu	Met	Leu	Cys	Gly	His	Ala	Pro	Phe	Glu	Ala	Glu	Asn	Glu	Asp
545					550					555					560
Asp	Leu	Phe	Glu	Ala	Ile	Leu	Asn	Asp	Glu	Val	Val	Tyr	Pro	Thr	Trp
				565					570					575	
Leu	His	Glu	Asp	Ala	Thr	Gly	Ile	Leu	Lys	Ser	Phe	Met	Thr	Lys	Asn
			580					585					590		
Pro	Thr	Met	Arg	Leu	Gly	Ser	Leu	Thr	Gln	Gly	Gly	Glu	His	Ala	Ile
			595				600						605		

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Leu	Arg	His	Pro	Phe	Phe	Lys	Glu	Ile	Asp	Trp	Ala	Gln	Leu	Asn	His
610						615					620				
Arg	Gln	Ile	Glu	Pro	Pro	Phe	Arg	Pro	Arg	Ile	Lys	Ser	Arg	Glu	Asp
625					630					635					640
Val	Ser	Asn	Phe	Asp	Pro	Asp	Phe	Ile	Lys	Glu	Glu	Pro	Val	Leu	Thr
			645						650					655	
Pro	Ile	Asp	Glu	Gly	His	Leu	Pro	Met	Ile	Asn	Gln	Asp	Glu	Phe	Arg
		660						665					670		
Asn	Phe	Ser	Tyr	Val	Ser	Pro	Glu	Leu	Gln	Pro					
		675					680								

<210> SEQ ID NO 39
 <211> LENGTH: 376
 <212> TYPE: PRT
 <213> ORGANISM: Human
 <400> SEQUENCE: 39

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

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

1. A method of treating cancer comprising of: a) extracting a blood sample from a cancer patient; b) isolating monocytes from said blood sample; c) transfecting said monocytes from said blood sample with a construct encoding a chimeric antigen receptor; and d) infusing said transfected monocytes into said cancer patient.

2. The method of claim 1, wherein peripheral blood mononuclear cells (PBMC) are purified from said blood sample.

3. The method of claim 2, wherein said purification of said PBMC is performed using a density gradient.

4. The method of claim 3, wherein said density gradient is ficoll.

5. The method of claim 1, wherein said monocytes are isolated from said blood sample by isolation of cells expressing CD14.

6. The method of claim 1, wherein said monocytes are isolated from said blood sample by collection of cells adhering to a plastic vessel after a culture period of at least one hour.

7. The method of claim 5, wherein said CD14 expressing cells are isolated by magnetic activated cell sorting (MACS).

8. The method of claim 5, wherein said CD14 expressing cells are isolated by fluorescent activated cell sorting (FACS).

9. The method of claim 1, wherein said chimeric antigen receptor construct encodes a protein comprising of: a) an antigen binding domain; b) a transmembrane domain; and c) an intracellular domain.

10. The method of claim 9, wherein said antigen binding domain is an antibody or fragment thereof.

11. The method of claim 9, wherein said antigen binding domain is single chain antibody or fragment thereof.

12. The method of claim 9, wherein said antibody domain is a molecular entity possessing affinity towards a tumor antigen or a tumor endothelial antigen.

13. The method of claim 1, wherein said antibody binding domain possesses affinity towards a tumor endothelial cell antigen.

14. The method of claim 13, wherein said tumor endothelial cell antigen is selected from a group of antigens comprising of:

- a) TEM-1;
- b) ROBO-1-8;

- c) VEGFR2;
- d) CD109;
- e) survivin; and
- f) CD93.

15. The method of claim 1, wherein said antibody binding domain possesses affinity towards a tumor antigen.

16. The method of claim 15, wherein said tumor antigens are selected from a group comprising of: CLPP, 707-AP, AFP, ART-4, BAGE, MAGE, GAGE, SAGE, b-catenin/m, bcr-abl, CAMEL, CAP-1, CEA, CASP-8, CDK/4, CDC-27, Cyp-B, DAM-8, DAM-10, ELV-M2, ETV6, G250, Gp100, HAGE, HER-2/neu, EPV-E6, LAGE, hTERT, survivin, iCE, MART-1, tyrosinase, MUC-1, MC1-R, TEL/AML, and WT-1.

17. The method of claim 1, wherein said intracellular domain of said CAR is capable of inducing monocytic differentiation to DC.

18. The method of claim 1, wherein said intracellular domain of said CAR is capable of inducing monocytic differentiation to M1 macrophages.

19. The method of claim 1, wherein said intracellular domain of said CAR is capable of activating a toll like receptor signaling pathway.

20. The method of claim 1, wherein said intracellular domain of said CAR is capable of activating TLR4 signaling.

21. The method of claim 1, wherein said intracellular domain of said CAR is capable of inducing monocytic differentiation to DC.

22. The method of claim 1, wherein said intracellular domain of said CAR contains a signaling portion of the intracellular domain of the TLR-4 protein.

23. The method of claim 1, wherein said intracellular domain of said CAR contains an activator of molecular pathways endowing M1 phenotype is the functional portion of said TLR-4 protein which interacts with MyD88 at a sufficient affinity to trigger said MyD88 signal transduction.

24. The method of claim 1, wherein said intracellular domain of said CAR contains an activator of molecular pathways endowing DC phenotype is the functional portion of said TLR-4 protein which interacts with MyD88 at a sufficient affinity to trigger said MyD88 signal transduction.

25. The method of claim 1, wherein said activator of molecular pathways endowing M1 phenotype is the func-

tional portion of said TLR-4 protein which interacts with TRAM and MAL at a sufficient affinity to trigger said TLR4 signal transduction.

26. The method of claim 1, wherein said activator of molecular pathways endowing DC phenotype is the functional portion of said TLR-4 protein which interacts with TRAM and MAL at a sufficient affinity to trigger said TLR4 signal transduction.

* * * * *