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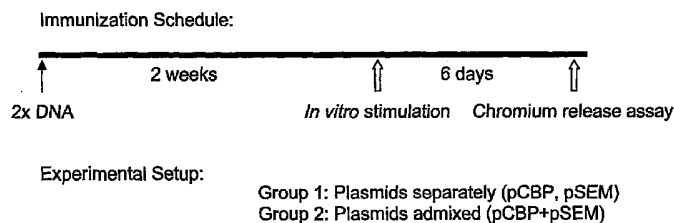
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(54) Title: COMBINATIONS OF TUMOR-ASSOCIATED ANTIGENS IN DIAGNOSTICS FOR VARIOUS TYPES OF CANCERS

Schedule of immunization with plasmids (pCBP expressing SSX2 41-49; and pSEM expressing Melan A)

Schedule of immunization



(57) Abstract: Disclosed herein are methods for matching a cancer condition with an appropriate immunotherapeutic agent and/or regimen. Also disclosed are methods for confirming diagnosis of a particular type of cancer. Embodiments of the invention disclosed herein are directed to the use of effective combinations of TuAAs to optimize the match between a patient's cancer condition and available immunotherapies.

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**COMBINATIONS OF TUMOR-ASSOCIATED ANTIGENS IN DIAGNOSTICS
FOR VARIOUS TYPES OF CANCERS**

Cross Reference to Related Applications

[0001] This application claims priority under 35 U.S.C. § 119(e) to U.S. Provisional Application No. 60/580,969, filed on June 17, 2004, entitled COMBINATIONS OF TUMOR-ASSOCIATED ANTIGENS IN DIAGNOSTICS FOR VARIOUS TYPES OF CANCERS; the disclosure of which is incorporated herein by reference in its entirety.

Background of the Invention

Field of the Invention

[0002] Disclosed herein are methods for matching a cancer condition with an appropriate immunotherapeutic agent and/or regimen. Also disclosed are methods for confirming diagnosis of a particular type of cancer.

Description of the Related Art

[0003] The American Cancer Society has estimated that over one million people get cancer each year, and that approximately one out of every two American men and one out of every three American women will have some type of cancer at some point during their lifetime.

[0004] Cancer generally develops when cells in a part of the body begin to grow out of control. Although there are many kinds of cancer, they usually start because of out-of-control growth of abnormal cells.

[0005] Normal body cells grow, divide, and die in an orderly fashion. Cancer cells are different in that they continue to grow and divide. Instead of dying, they outlive normal cells and continue to form new abnormal cells.

[0006] Usual treatment options for cancer include surgery, radiation therapy, and chemotherapy. A fourth branch of treatment is developing, which is referred to as immunotherapy. Immunotherapies attempt to help the immune system recognize cancer cells, and/or to strengthen a response against cancer cells in order to destroy the cancer. Immunotherapies include active and passive immunotherapies. Active immunotherapies attempt to stimulate the body's own immune system to fight the disease. Passive

immunotherapies generally do not rely on the body to attack the disease; instead, they use immune system components (such as antibodies) created outside of the body.

[0007] Despite the various types of treatments, a continuing need exists for additional treatment options that are more closely matched to a patient's cancer condition or type. In addition, there is a need for more accurate diagnostic tools for cancer.

Summary of the Invention

[0008] Embodiments of the invention disclosed herein are directed to the use of a preselected panel of tumor-associated antigens (TuAAs) to match a patient's cancer condition or type with an appropriate immunotherapeutic agent or regimen. In preferred embodiments, the TuAAs are antigens expressed by the cancer cell itself. In alternate embodiments, the TuAAs are antigens associated with non-cancerous components of the tumor, such as tumor-associated neovasculature or other stroma. Methods to determine, diagnose, or confirm a diagnosis of a type of cancer using a preselected panel of antigens is also disclosed. Methods for predicting disease progression in a cancer patient are also disclosed.

[0009] Some embodiments of the invention are directed to methods for matching a patient's cancer condition or type with an immunotherapeutic agent including the steps of assaying the patient's tumor tissue for expression of a preselected panel of antigens and based on the assay results, selecting an immunotherapeutic agent targeting one, or two, or three or more of the antigens expressed by the patient's tumor tissue. The method can further include the step of developing an antigen profile for the tumor and selecting the immunotherapeutic agent based on the profile. In some embodiments the selected agent is an active immunotherapeutic. In some embodiments, the agent comprises an immunogen that includes or encodes at least a portion of at least one of the expressed antigens. In other embodiments the selected agent is a passive immunotherapeutic. In some embodiments the agent comprises a monoclonal antibody.

[0010] Still other embodiments relate to methods for preparing a cancer immunotherapeutic composition wherein an immunotherapeutic is selected on the basis of the expression profile of tumor tissue for at least two tumor-associated antigens (TuAAs) in a preselected panel so that the immunotherapeutic agent comprises or encodes at least a segment of at least one of the expressed TuAAs and wherein the immunotherapeutic agent is optionally combined with pharmaceutically acceptable excipients.

[0011] Embodiments of the invention are also directed to a method of matching a patient's cancer condition with an immunotherapeutic regimen including the steps of assaying the patient's tumor tissue for two or more expressed tumor associated antigens (TuAAs) in a preselected panel of antigens to develop an antigen profile for the tumor and selecting an immunotherapeutic regimen based on the antigen profile. In some embodiments, the regimen comprises administering at least one immunotherapeutic agents targeting two, three, four, or more of the expressed antigens. The agents can be in forms such as, for example, nucleic acid, or polypeptide, or cellular, or humoral, or active, or passive, etc. For embodiments in which the regimen comprises administering two or more immunotherapeutic agents, the agents can be similar in form or different in form. Thus, in some embodiments, the regimen can include both an active immunotherapeutic agent and a passive immunotherapeutic agent.

[0012] In some embodiments, methods for matching a cancer condition in a patient with an immunotherapeutic agent are disclosed. The methods can include the steps of: determining the patient's class I MHC type; assaying the patient's tumor tissue for two or more expressed tumor-associated antigens (TuAAs) in a preselected panel; assaying the patient's tumor tissue for the expression of MHC class I or β 2-microglobulin; selecting an immunotherapeutic agent for administration to the patient based on the assays, wherein the immunotherapeutic agent comprises or encodes an epitope restricted by the patient's class I MHC type, for each of two or more antigens expressed by the tumor. In some embodiments, antigen expression is detected on neoplastic cells, or tumor-associated stromal cells, or both. In some embodiments, the two or more antigens expressed by the tumor include an antigen expressed by a neoplastic cell and an antigen expressed by a tumor-associated stromal cell.

[0013] Other embodiments are directed to determining, establishing, or confirming the diagnosis of a type of cancer including the steps of assaying a patient's tumor tissue to detect one or more expressed polypeptides in a preselected panel, wherein the panel comprises two, or three, or four or more TuAAs and at least one lineage specific marker; and confirming the cancer diagnosis based on the assay. In one embodiment, the panel comprises at least two, or three, or four or more TuAAs selected from the group consisting of NY-ESO-1, CEA, PSA, PSMA, tyrosinase, melan-A/MART-1, an SSX protein, and a MAGE protein. In some embodiments, the lineage specific marker is a TuAA; in other embodiments the lineage specific marker is not a TuAA. For melanoma,

the lineage specific marker can be, for example, tyrosinase, melan-A/MART-1, or gp100. For breast cancer, the lineage specific marker can be, for example, mammaglobin or prolactin-inducible protein (Brst2). For colon cancer, the lineage specific marker can be CEA. For lung cancer, the lineage specific antigen can be, for example, thyroid transcription factor 1 (TTF1). For prostate cancer, the lineage specific marker can be, for example, PSA or PSMA.

[0014] Yet other embodiments relate to methods of determining or confirming the occurrence of cancer comprising the step of determining the expression profile of tumor tissue for at least one polypeptide wherein the polypeptide is part of a preselected panel comprising at least two TuAAs and at least one lineage marker.

[0015] The preselected panel of TuAAs can include, for example, but not limited to, cancer testis antigens, tissue specific antigens, oncofetal antigens, differentiation antigens, growth factors, growth factor receptors, adhesion factors, signal transduction proteins, transcription factors, oncogene products, tumor suppressor gene products, microbial agents, and the like. In some embodiments, the preselected panel comprises two, or three, or more antigens selected from the group consisting of an SSX protein, SSX-2, SSX-4, a MAGE protein, MAGE-1, MAGE-3, PRAME, NY-ESO-1, LAGE, PSMA, PSCA, SCP-1, melan-A/MART-1 and tyrosinase. In some embodiments, the cancer is carcinoma. The carcinoma can be, for example, breast, colorectal, prostate, pancreatic, lung, ovarian, renal cell, or melanocyte.

[0016] The tumor tissue assayed can include primary tumor tissue or metastatic tumor tissue. Antigen expression can be detected on neoplastic cells, or tumor-associated stromal cells, or both. In some embodiments, the preselected panel includes an antigen expressed by a neoplastic cell and an antigen expressed by a tumor-associated stromal cell. The stromal cells can be neovasculature. The neovasculature associated antigen can be PSMA and the neoplastic cell antigen can be NY-ESO-1, SSX-2, LAGE, or PRAME.

[0017] Antigen expression can be detected, directly or indirectly. For example, the assay can detect the absence, presence and/or abundance of mRNA, polypeptide, mature protein, peptide, or MHC-peptide complex. In some embodiments, the assay detects the condition of the TuAAs, such as processing state, differential splicing, mutation from germline, variation from consensus sequence in human population, cellular localization, subcellular localization, co-expression with other markers, and the like. Examples of useful assays include RT-PCR, transcript determination, protein determination, epitope

determination, or any combination thereof. In some embodiments, the assay comprises reverse transcription polymerase chain reaction (RT-PCR), real-time PCR, quantitative PCR, northern hybridization, autoradiography, chemiluminescent detection, autofluorography, flow cytometry, gene chip expression profiling, immunohistochemistry, western hybridization, radioimmunoassay, or in situ hybridization, individually or in any combination thereof. In some embodiments, at least two assaying steps are carried out at different time points during the course of disease and comparative information is obtained from the assaying steps. The obtained information can be used to implement, modify or withdraw a therapy.

[0018] In one embodiment, the tumor is melanoma and the preselected panel of antigens comprises at least two, or three, or four or more TuAAs selected from the group consisting of tyrosinase, melan-A/MART-1, NY-ESO-1, PRAME, an SSX protein, and a MAGE protein. The SSX protein can be SSX-2 or SSX-4. The MAGE protein can be MAGE-1 or MAGE-3.

[0019] In another embodiment, the tumor is breast cancer and the preselected panel of antigens comprises at least two, or three, or four or more TuAAs selected from the group consisting of NY-ESO-1, C35, Her2/Neu, an SSX protein, and a MAGE protein. The SSX protein can be SSX-2 or SSX-4. The MAGE protein can be MAGE-1 or MAGE-3.

[0020] In yet another embodiment, the tumor is colorectal cancer and the preselected panel of antigens comprises at least two, or three, or four or more TuAAs selected from the group consisting of CEA, an SSX protein, PRAME, NY-ESO-1, LAGE, PSCA, SCP-1, PSMA, and a MAGE protein. The SSX protein can be SSX-2 or SSX-4. The MAGE protein can be MAGE-1 or MAGE-3.

[0021] In yet a further embodiment, the tumor is ovarian cancer and the preselected panel of antigens comprises at least two, or three or four or more TuAAs selected from the group consisting of an SSX protein, PRAME, NY-ESO-1, PSMA, Her2/neu, C35, PSCA, SCP-1, CEA, LAGE, and a MAGE protein. The SSX protein can be SSX-2 or SSX-4. The MAGE protein can be MAGE-1 or MAGE-3. The ovarian cancer can be, for example, serous carcinoma, non-serous carcinoma, mucinous (cell) carcinoma, clear cell carcinoma, and the like.

[0022] In still another embodiment, the tumor is lung cancer and the preselected panel of antigens comprises at least two, or three, or four or more TuAAs selected from the

group consisting of PSMA, NY-ESO-1, SSX-2, and a MAGE protein. The cancer can be, for example, non-small cell lung cancer. The MAGE protein can be MAGE-1 or MAGE-3.

[0023] In a further embodiment, the tumor is prostate cancer and the preselected panel of antigens comprises at least two, or three, or four or more TuAAs selected from the group consisting of NY-ESO-1, PSA, PSCA, PSMA, an SSX protein, and a MAGE protein. The SSX protein can be SSX-2 or SSX-4. The MAGE protein can be MAGE-1 or MAGE-3.

[0024] In another embodiment, the tumor is pancreatic cancer and the panel of antigens comprises at least two, or three, or four or more TuAAs selected from the group consisting of PSMA, PRAME, NY-ESO, LAGE, PSCA, and a MAGE protein and an SSX protein. The SSX protein can be SSX-2 or SSX-4. The MAGE protein can be MAGE-1 or MAGE-3.

[0025] In still another embodiment, the tumor is renal cell carcinoma or renal cancer? and the panel of antigens comprises at least two, or three, or four or more TuAAs selected from the group consisting of PSMA, PRAME, NY-ESO, LAGE, PSCA, SCP-1, a MAGE protein, and an SSX protein. The SSX protein can be SSX-2 or SSX-4. The MAGE protein can be MAGE-1 or MAGE-3.

[0026] Another embodiment relates to a method of marketing cancer immunotherapeutics comprising establishing a relationship with a cancer diagnostics laboratory, wherein the laboratory includes TuAA expression in its standard panel of tests, and wherein the TuAAs assayed for correspond to the immunogens of the immunotherapeutics to be marketed, and sending a report with each patient's test results identifying immunotherapeutics comprising immunogens that correspond to the TuAAs expressed by the patient's tumor. In some embodiments, the relationship comprises contract services. In some embodiments, the relationship is a partnership.

Brief Description of the Drawings

[0027] Figure 1 is a timeline depicting the schedule of immunization with two plasmid (pCBP expressing SSX-2 41-49 and pSEM expressing Melan A).

[0028] Figure 2 is a bar graph that shows CTL activity obtained using the protocol in Figure 1.

[0029] Figure 3 is a timeline depicting the schedule of immunization of an entrain-and-amplify immunization protocol using plasmids and peptides representing two epitopes.

[0030] Figure 4 is a table showing *in vivo* clearance of epitope-pulsed cells in mice immunized according to the protocol of Figure 3.

[0031] Figures 5A and 5B are timelines depicting immunization protocols for inducing strong multivalent responses. Figure 5A shows the use of peptides for boosting restores multivalent immune responses even if plasmids and peptides are used as mixtures. Figure 5B shows segregation of plasmid and peptide components allows induction of multivalent immune responses.

Detailed Description of the Preferred Embodiment

[0032] The frequency of expression of many tumor-associated antigens (TuAAs) in various types of cancers is known. However, the frequency of appearance of some antigens, and especially certain combinations of TuAAs in various types of cancers has not been reported. Accurate measurement of the presence of TuAAs in tumor tissues aids in determining which TuAAs will be useful for the treatment of a particular type of cancer.

[0033] Many attempts to develop immunotherapies for cancer have targeted a single antigen. This can be problematic for two distinct reasons. Firstly, the expression of any particular TuAA in cancer can be mosaic with the antigen expression ranging from high in some cells within a tumor mass to completely absent in others. Moreover, the TuAA may be expressed in some lesions but not others. By directing an immune response against more than a single antigen, if properly selected, the number of tumor cells that can be recognized is maximized. Secondly, some tumors lose expression of a TuAA following immunization, giving rise to a resistant population. If the immune response is directed against more than one TuAA it becomes much more difficult for a resistant tumor to arise because it must then simultaneously lose expression of each of the antigens in order to escape. Thus, in treating cancer with immunotherapy, it can be advantageous to use a combination of TuAAs both due to more complete coverage of the population of tumor cells, and because there will be less chance of tumor escape through loss of expression of the TuAAs. In preferred embodiments, this multivalent attack technique is employed when a tumor is positive for two, three, four or more TuAAs of the combination used.

[0034] Multivalent attack can offer another advantage in increasing the sensitivity of the tumor to attack. If more than a single antigen on a tumor cell is targeted, the effective concentration of antitumor agent is increased. In addition, attack on stroma associated with the tumor, such as vasculature, can increase the accessibility of the tumor

cells to the agent(s) targeting them. Thus, even an antigen that is also expressed on some normal tissue can receive greater consideration as a target antigen, if the other antigens to be targeted in a multivalent attack are not also expressed by that tissue.

Definitions

[0035] Unless otherwise clear from the context of the use of a term herein, the following listed terms shall generally have the indicated meanings for purposes of this description.

[0036] PROFESSIONAL ANTIGEN-PRESENTING CELL (pAPC) – a cell that possesses T cell costimulatory molecules and is able to induce a T cell response. Well characterized pAPCs include dendritic cells, B cells, and macrophages.

[0037] PERIPHERAL CELL – a cell that is not a pAPC.

[0038] HOUSEKEEPING PROTEASOME – a proteasome normally active in peripheral cells, and generally not present or not strongly active in pAPCs.

[0039] IMMUNOPROTEASOME – a proteasome normally active in pAPCs; the immunoproteasome is also active in some peripheral cells in infected tissues or following exposure to interferon.

[0040] EPITOPE – a molecule or substance capable of stimulating an immune response. In preferred embodiments, epitopes according to this definition include but are not necessarily limited to a polypeptide and a nucleic acid encoding a polypeptide, wherein the polypeptide is capable of stimulating an immune response. In other preferred embodiments, epitopes according to this definition include but are not necessarily limited to peptides presented on the surface of cells, the peptides being non-covalently bound to the binding cleft of class I MHC, such that they can interact with T cell receptors (TCR). Epitopes presented by class I MHC may be in immature or mature form. “Mature” refers to an MHC epitope in distinction to any precursor (“immature”) that may include or consist essentially of a housekeeping epitope, but also includes other sequences in a primary translation product that are removed by processing, including without limitation, alone or in any combination, proteasomal digestion, N-terminal trimming, or the action of exogenous enzymatic activities. Thus, a mature epitope may be provided embedded in a somewhat longer polypeptide, the immunological potential of which is due, at least in part, to the embedded epitope; likewise, the mature epitope can be provided in its ultimate form that can bind in the MHC binding cleft to be recognized by TCR.

[0041] MHC EPITOPE – a polypeptide having a known or predicted binding affinity for a mammalian class I or class II major histocompatibility complex (MHC) molecule.

[0042] HOUSEKEEPING EPITOPE – In a preferred embodiment, a housekeeping epitope is defined as a polypeptide fragment that is an MHC epitope, and that is displayed on a cell in which housekeeping proteasomes are predominantly active. In another preferred embodiment, a housekeeping epitope is defined as a polypeptide containing a housekeeping epitope according to the foregoing definition, that is flanked by one to several additional amino acids. In another preferred embodiment, a housekeeping epitope is defined as a nucleic acid that encodes a housekeeping epitope according to the foregoing definitions. Exemplary housekeeping epitopes are provided in U.S. Application Nos. 10/117,937, filed on April 4, 2002 (Pub. No. 20030220239 A1), and 10/657,022, and in PCT Application No. PCT/US2003/027706 (Pub. No. WO04022709A2), filed 9/5/2003; and U.S. Provisional Application Nos. 60/282,211, filed on April 6, 2001; 60/337,017, filed on November 7, 2001; 60/363210 filed 3/7/02; and 60/409,123, filed on September 5, 2002. Each of the listed applications is entitled “EPITOPE SEQUENCES.” Each of the applications mentioned in this paragraph is incorporated herein by reference in its entirety.

[0043] IMMUNE EPITOPE – In a preferred embodiment, an immune epitope is defined as a polypeptide fragment that is an MHC epitope, and that is displayed on a cell in which immunoproteasomes are predominantly active. In another preferred embodiment, an immune epitope is defined as a polypeptide containing an immune epitope according to the foregoing definition, that is flanked by one to several additional amino acids. In another preferred embodiment, an immune epitope is defined as a polypeptide including an epitope cluster sequence, having at least two polypeptide sequences having a known or predicted affinity for a class I MHC. In yet another preferred embodiment, an immune epitope is defined as a nucleic acid that encodes an immune epitope according to any of the foregoing definitions.

[0044] TARGET CELL – In a preferred embodiment, a target cell is a cell associated with a pathogenic condition that can be acted upon by the components of the immune system, for example, a cell infected with a virus or other intracellular parasite, or a neoplastic cell. In another embodiment, a target cell is a cell to be targeted by the vaccines and methods of the invention. Examples of target cells according to this definition include but are not necessarily limited to: a neoplastic cell and a cell harboring an intracellular

parasite, such as, for example, a virus, a bacterium, or a protozoan. Target cells can also include cells that are targeted by CTL as a part of an assay to determine or confirm proper epitope liberation and processing by a cell expressing immunoproteasome, to determine T cell specificity or immunogenicity for a desired epitope. Such cells can be transformed to express the liberation sequence, or the cells can simply be pulsed with peptide/epitope.

[0045] TARGET-ASSOCIATED ANTIGEN (TAA) – a protein or polypeptide present in a target cell.

[0046] TUMOR-ASSOCIATED ANTIGEN (TuAA) – a TAA, wherein the target cell is a neoplastic cell. In alternate embodiments, a TuAA is an antigen associated with non-cancerous cells of the tumor such as tumor neovasculature or other stromal cells within the tumor microenvironment.

[0047] HLA EPITOPE – a polypeptide having a known or predicted binding affinity for a human class I or class II HLA complex molecule.

[0048] ANTIBODY – a natural immunoglobulin (Ig), poly- or monoclonal, or any molecule composed in whole or in part of an Ig binding domain, whether derived biochemically, or by use of recombinant DNA, or by any other means. Examples include *inter alia*, F(ab), single chain Fv, and Ig variable region-phage coat protein fusions.

[0049] SUBSTANTIAL SIMILARITY – this term is used to refer to sequences that differ from a reference sequence in an inconsequential way as judged by examination of the sequence. Nucleic acid sequences encoding the same amino acid sequence are substantially similar despite differences in degenerate positions or minor differences in length or composition of any non-coding regions. Amino acid sequences differing only by conservative substitution or minor length variations are substantially similar. Additionally, amino acid sequences comprising housekeeping epitopes that differ in the number of N-terminal flanking residues, or immune epitopes and epitope clusters that differ in the number of flanking residues at either terminus, are substantially similar. Nucleic acids that encode substantially similar amino acid sequences are themselves also substantially similar.

[0050] FUNCTIONAL SIMILARITY – this term is used to refer to sequences that differ from a reference sequence in an inconsequential way as judged by examination of a biological or biochemical property, although the sequences may not be substantially similar. For example, two nucleic acids can be useful as hybridization probes for the same sequence but encode differing amino acid sequences. Two peptides that induce cross-reactive CTL responses are functionally similar even if they differ by non-conservative

amino acid substitutions (and thus may not be within the substantial similarity definition). Pairs of antibodies, or TCRs, that recognize the same epitope can be functionally similar to each other despite whatever structural differences exist. Testing for functional similarity of immunogenicity can be conducted by immunizing with the “altered” antigen and testing the ability of an elicited response, including but not limited to an antibody response, a CTL response, cytokine production, and the like, to recognize the target antigen. Accordingly, two sequences may be designed to differ in certain respects while retaining the same function. Such designed sequence variants of disclosed or claimed sequences are among the embodiments of the present invention.

[0051] EXPRESSION CASSETTE – a polynucleotide sequence encoding a polypeptide, operably linked to a promoter and other transcription and translation control elements, including but not limited to enhancers, termination codons, internal ribosome entry sites, and polyadenylation sites. The cassette can also include sequences that facilitate moving it from one host molecule to another.

[0052] EMBEDDED EPITOPE – in some embodiments, an embedded epitope is an epitope that is wholly contained within a longer polypeptide; in other embodiments, the term also can include an epitope in which only the N-terminus or the C-terminus is embedded such that the epitope is not wholly in an interior position with respect to the longer polypeptide.

[0053] MATURE EPITOPE – a peptide with no additional sequence beyond that present when the epitope is bound in the MHC peptide-binding cleft.

[0054] EPITOPE CLUSTER – a polypeptide, or a nucleic acid sequence encoding it, that is a segment of a protein sequence, including a native protein sequence, comprising two or more known or predicted epitopes with binding affinity for a shared MHC restriction element. In preferred embodiments, the density of epitopes within the cluster is greater than the density of all known or predicted epitopes with binding affinity for the shared MHC restriction element within the complete protein sequence. Epitope clusters are disclosed and more fully defined in U.S. Patent Application No. 09/561,571 entitled “EPITOPE CLUSTERS,” which is incorporated herein by reference in its entirety.

[0055] LIBERATION SEQUENCE – a designed or engineered sequence comprising or encoding a housekeeping epitope embedded in a larger sequence that provides a context allowing the housekeeping epitope to be liberated by processing

activities including, for example, immunoproteasome activity, N terminal trimming, and/or other processes or activities, alone or in any combination.

[0056] CTLp – CTL precursors are T cells that can be induced to exhibit cytolytic activity. Secondary *in vitro* lytic activity, by which CTLp are generally observed, can arise from any combination of naïve, effector, and memory CTL *in vivo*.

[0057] MEMORY T CELL – A T cell, regardless of its location in the body, that has been previously activated by antigen, but is in a quiescent physiologic state requiring re-exposure to antigen in order to gain effector function. Phenotypically they are generally CD62L⁻ CD44^{hi} CD107α⁻ IGNgamma⁻ LTβ⁻ TNF-α⁻ and is in G0 of the cell cycle.

[0058] EFFECTOR T CELL – A T cell that, upon encountering antigen antigen, readily exhibits effector function. Effector T cells are generally capable of exiting the lymphatic system and entering the immunological periphery. Phenotypically they are generally CD62L⁻ CD44^{hi} CD107α⁺ IGNgamma⁺ LTβ⁺ TNF-α⁺ and actively cycling.

[0059] EFFECTOR FUNCTION – Generally, T cell activation generally, including acquisition of cytolytic activity and/or cytokine secretion.

[0060] INDUCING a T cell response – Includes in many embodiments the process of generating a T cell response from naïve, or in some contexts, quiescent cells; activating T cells.

[0061] AMPLIFYING a T cell response – Includes in many embodiments the process or increasing the number of cells, the number of activated cells, the level of activity, rate of proliferation, or similar parameter of T cells involved in a specific response.

[0062] ENTRAINMENT – Includes in many embodiments an induction that confers particular stability on the immune profile of the induced lineage of T cells.

[0063] TOLL-LIKE RECEPTOR (TLR) – Toll-like receptors (TLRs) are a family of pattern recognition receptors that are activated by specific components of microbes and certain host molecules. As part of the innate immune system, they contribute to the first line of defense against many pathogens, but also play a role in adaptive immunity.

[0064] TOLL-LIKE RECEPTOR (TLR) LIGAND – Any molecule capable of binding and activating a toll-like receptor. Examples include, without limitation: poly I:C A synthetic, double-stranded RNA known for inducing interferon. The polymer is made of one strand each of polyinosinic acid and polycytidylic acid, double-stranded RNA, unmethylated CpG oligodeoxyribonucleotide or other immunostimulatory sequences

(ISSs), lipopolysaccharide (LPS), β -glucans, and imidazoquinolines, as well as derivatives and analogues thereof.

[0065] IMMUNOPOTENTIATING ADJUVANTS – Adjuvants that activate pAPC or T cells including, for example: TLR ligands, endocytic-Pattern Recognition Receptor (PRR) ligands, quillaja saponins, tucaresol, cytokines, and the like. Some preferred adjuvants are disclosed in Marciani, D.J. *Drug Discovery Today* 8:934-943, 2003, which is incorporated herein by reference in its entirety.

[0066] IMMUNOSTIMULATORY SEQUENCE (ISS) – Generally an oligodeoxyribonucleotide containing an unmethylated CpG sequence. The CpG may also be embedded in bacterially produced DNA, particularly plasmids. Further embodiments include various analogues; among preferred embodiments are molecules with one or more phosphorothioate bonds or non-physiologic bases.

[0067] VACCINE – In preferred embodiments a vaccine can be an immunogenic composition providing or aiding in prevention of disease. In other embodiments, a vaccine is a composition that can provide or aid in a cure of a disease. In others, a vaccine composition can provide or aid in amelioration of a disease. Further embodiments of a vaccine immunogenic composition can be used as therapeutic and/or prophylactic agents.

[0068] IMMUNIZATION – a process to induce partial or complete protection against a disease. Alternatively, a process to induce or amplify an immune system response to an antigen. In the second definition it can connote a protective immune response, particularly proinflammatory or active immunity, but can also include a regulatory response. Thus in some embodiments immunization is distinguished from tolerization (a process by which the immune system avoids producing proinflammatory or active immunity) while in other embodiments this term includes tolerization.

[0069] ENCODE – an open-ended term such that a nucleic acid encoding a particular amino acid sequence can consist of codons specifying that (poly)peptide, but can also comprise additional sequences either translatable, or for the control of transcription, translation, or replication, or to facilitate manipulation of some host nucleic acid construct.

[0070] COVERAGE – the fraction or proportion of tumor cells expressing a particular TuAA or at least one TuAA from a set of selected TuAAs.

[0071] REDUNDANCY – the degree to which a population of tumor cells, or some subset of them, express more than one of a selected set of TuAAs.

[0072] CO-TARGETING – in preferred embodiments, co-targeting involves inducing and/or amplifying an immune response against a target cell, while also inducing an immune response against at least one other agent in the vicinity and/or *milieu* of a tumor. In some embodiments, agents within the vicinity and/or *milieu* of the tumor include, but are not limited to, cancer cells, stromal cells, including those associated with neovasculature, endothelial cells, fibroblasts, inflammatory cells, epithelial cells, autocrine factors, and paracrine factors. In some embodiments, neoplastic cells and stromal cells are specifically targeted. In other embodiments, an immune response is induced and/or amplified against neovasculature and other non-transformed, non-lymphoid cells within the tumor microenvironment. In still other embodiments, an immune response is induced against cancer cells and autocrine and/or paracrine factors produced by cells in the tumor microenvironment.

Cancer Immunotherapy and Diagnosis

[0073] Cancer immunotherapy has been strongly influenced by work on melanoma and prostate cancer, as they have been among the earliest and most widely approached targets in the field. Many of the antigens used in the various attempts to develop therapeutic vaccines for these cancers have been differentiation markers, that is antigens specific to that cell type. As a result, the existing paradigm is to develop immunotherapeutics for a particular type of cancer. Patients are then treated with the agent simply because they have been diagnosed with a particular type of cancer. In some instances, a patient's tumor is first evaluated for expression of a particular target antigen. However, many of the TuAAs now known, even some initially classified as differentiation markers, are expressed in many types of cancer. As such it can be useful to classify tumors by the TuAAs that they express rather than, or in addition to, their tissue of origin. Thus, in some embodiments, a single immunotherapeutic, preferably multivalent, can be used to treat a wide variety of tumor types. This is not to say that any particular antigen or combination of antigens will be uniformly useful across all, or even many, tumor types. To the contrary, expression frequency can vary considerably from type to type. Moreover, among the widely expressed TuAAs it is common that they are expressed in only a fraction of any particular tumor type. Indeed, this is part of the impetus to apply immunotherapeutics based on these antigens to various tumor types. Nonetheless, both individual antigens, and combinations of them, will have definable frequencies associated with particular tumor types. Thus, immunotherapeutics designed according to the more

favorable frequencies observed can be more effective and/or efficient when applied to those particular tumor types.

[0074] Despite the prevalence of certain TuAAs, or combinations of them, in particular tumor types, it is not always sufficient to simply treat patients having a particular type of tumor with an immunotherapeutic targeting a prevalent antigen or antigens expressed by that tumor type. Preferably, patients' tumor tissue should be screened for the expression of TuAAs for which there is a corresponding immunotherapeutic available, whether marketed or in clinical trials. As the number and variety of cancer immunotherapies grow it will be increasingly advantageous to screen any particular patient's tumor tissue for expression of a variety of TuAAs that can be expressed by that tumor type so as to afford the clinician the widest choice in matching a cancer condition with available immunotherapies.

[0075] Although much of this disclosure focuses on agents that actively induce immunity mediated by class I MHC restricted T cells, the matching procedures described are equally applicable with immunotherapies of all kinds, active or passive, cellular or humoral, or any combination thereof. The methods claimed herein are adapted to this developing environment where there is a substantial number of immunotherapies targeting various antigens. The methods embodied herein optimize the matching between a particular patient's cancer type or condition to available immunotherapeutics. This is in contrast to existing practice that is designed to simply qualify a patient as eligible (or ineligible) for treatment with one particular agent.

[0076] Preferably, a panel of TuAAs that are expressed with relatively high frequency in a particular tumor type is assembled and assays established. Accordingly, one embodiment of the invention described herein includes assembly of the panel and establishment of appropriate assays. It can be advantageous to include a TuAA that is widely expressed in a variety of tumor types in the panel.

[0077] The methods disclosed herein can begin with an assay of a tumor tissue of the corresponding presumptive type for expression of a preselected panel of antigens. In some embodiments, a panel of TuAAs assembled for one tumor type can be used to screen other tumor types that can express at least some of the same antigens. In some embodiments, an expression profile is developed using the assay results. Selection of an appropriate immunotherapeutic can be based on how well the composition of the immunotherapeutic, such as immunogens (or effector agents in the case of passive

immunotherapy), corresponds to the detected antigens of the panel. The panel can include more antigens than are likely to be targeted by any immunotherapeutic of well-defined composition, or detected in any one tissue sample.

[0078] Thus, it is not necessary that an immunotherapeutic agent comprise immunogens corresponding to every antigen in the panel. Nor is it required that the panel antigens all be the target of some set of immunotherapeutic agents that could reasonably be combined in a regimen of immunotherapy. Also, although advantageous, it is not required that there is a perfect match between the composition of the immunotherapeutic(s) and the expression profile of the tumor. Heterogeneity of antigen expression by a patient's tumor is common. Thus, there is a significant possibility of an antigen, undetectable in a tissue sample, nonetheless being expressed at another site. This is especially true for the antigens most commonly expressed by the particular tumor type. Thus, a multivalent immunotherapeutic in which one, some, or all of the constituent immunogens correspond to TuAAs expressed by an assayed portion of a patient's tumor can be used to treat that patient according to the judgment of the clinician. Similarly the patient can be treated with a combination of multi- and monovalent agents to optimize the match between the expression profile and the antigens targeted. Passive immunotherapeutics in particular are often monovalent, but the skilled clinician will nonetheless understand how they can be combined with additional passive or active immunotherapeutics into a useful immunotherapeutic regimen. Passive immunotherapies currently known in the art include: trastuzumab (HERCEPTIN®) which targets the TuAA HER2/Neu; bevacizumab (AVASTIN®) which targets VEGF (vascular endothelial growth factor) to inhibit vascularization of tumors; cetuximab (ERBITUX™) which targets the antigen epidermal growth factor receptor (EGFR, HER1, c-erbB-1); and panitumumab which also targets the antigen epidermal growth factor receptor. Additionally there are several mono- and multivalent active immunotherapeutic in development. These include APC8015 (PROVENGE®) which targets prostatic acid phosphatase; APC8024 which targets HER2/Neu; MKC1106 which targets PRAME, PSMA, SSX-2, and NY-ESO-1; pSEM (SYNCHROVAX™ SEM) which targets Melan-A; MKC1207 which targets Melan-A and tyrosinase; pTA2M (SYNCHROTOPE® TA2M) which targets tyrosinase; DCVAX®-prostate which targets PSMA; ALVAC(2)-gp100M which targets gp100; ALVAC MAGE 1,3 which targets MAGE-1 and MAGE-3; ALVAC CEA which target CEA; the NY-ESO-

1/ISCOMATRIXTM vaccine which targets NY-ESO-1; PANVACTM-VF which targets CEA; and MUC-1; and PROSTVAC[®]-VF which targets PSA.

[0079] Diagnosis of cancer type can be challenging, leading to uncertainty. Similar screening assays can be used to establish or confirm the diagnosis of tumor type by including a lineage specific marker in the panel. The marker can itself be a TuAA, as in tyrosinase for melanoma and PSA for prostate, for example. Alternatively, the marker can be any antigen that is reasonably specific to the cell type in question and the expression of which is maintained in neoplastic cells, for example, mammaglobin for breast tissue.

Assay Technology

[0080] Many technologies to carry out the assay steps of the invention are known in the art. Generally, any reliable method of detecting specific proteins or mRNAs can be adapted. Preference is given to techniques based on characteristics such as the ability to assay large numbers of samples and/or provide results quickly or that the assay is inexpensive to practice, or some optimum of these parameters. Tumor tissue to assay can be obtained as bulk tissue through surgery or in cellular form from blood, bone marrow, cell aspirates, peritoneal lavage, plural aspirates, or bronchial washes, and the like.

[0081] The assaying step can include a determination of at least one of presence, absence, abundance or condition of a TuAA in the panel. In some embodiments, the determination includes analysis of at least one of: mRNA, peptide, polypeptide, mature protein, and MHC-peptide complex. In some embodiments, the determination includes analysis of at least one of: processing state of a polypeptide, differential splicing of a nucleic acid, mutation of a nucleic acid in comparison with a germline sequence, variation of a nucleic acid or polypeptide sequence from a consensus sequence in a population, cellular localization, subcellular localization, and co-expression with a marker.

[0082] Commonly, detection of specific proteins involves the use of antibodies. Immunohistochemistry (IHC) is broadly applicable, but western hybridization, radioimmunoassay (RIA), and flow cytometry can also be used; collectively protein determinations. TRC-tetramers and antibodies recognizing specific peptide-MHC complexes can also be used. Tumor tissue can be used as target or stimulator in a wide variety of immunological assays (Elispot, T cell hybridoma reactivity, microcytotoxicity, and the like). Such assays are specific for a target epitope, not just the parent antigen, and thus can be referred to as epitope determinations. Detection of specific mRNA can be accomplished using any of several modalities of RT-PCR (reverse transcription-polymerase

chain reaction) and similar nucleic acid amplification techniques (*e.g.*, 3SR), northern hybridization, querying of gene arrays with mRNA or cDNA, and in situ hybridization; collectively transcript determinations. Reagents that detect presentation of particular T cell epitopes from target antigens can also be used. These include, for example, T cell lines and hybridomas, and more preferably, antibodies specific for the peptide-MHC complex and TCR tetramers (see for example Li et al. *Nature Biotech.* 23:349-354, 2005 which is incorporated herein by reference in its entirety).

[0083] PCR techniques are sensitive and generally easy to implement, however they cannot detect the mosaicism of antigen expression within a sample. IHC (and other in situ techniques), though potentially more labor intensive, allow spatial variation of expression within a sample to be observed. Thus, distinctions between co-expression of antigens within the same cells versus co-expression within different cells within the same sample can be made. Both situations can be desirable, the former providing for greater redundancy of targeting and reduced likelihood of antigen-loss escape mutants arising, the latter revealing how a greater proportion of the total tumor tissue can be directly targeted. Such information is also relevant to the use of antigens with more complex expression patterns. For example, PSMA, which can be expressed by prostate cells and tumor neovasculature, can be used as a prostate lineage marker if its expression can be associated specifically with the neoplastic cells, either through use of an in situ detection methodology or microdissection before assaying expression.

[0084] In preferred embodiments of the invention the immunotherapeutic agent induces a T cell response, especially including a class I MHC-restricted T cell response. Thus, it can be advantageous to confirm MHC expression by the tumor tissue. Reagents for detection of MHC, including for PCR and antibody based methods, are widely known in the art. Class-, locus- and type-specific reagents are in common usage. Class I expression can also be assessed by detection of β 2-microglobulin. Class- and locus-specific reagents offer the advantage of a broadly applicable uniform procedure. Type-specific reagents allow for simultaneous confirmation of expression and MHC type. Antibody-based techniques can offer the advantage of directly detecting protein expression at the cell surface, which is of clinical relevance, in contrast to RT-PCR and the like, from which surface expression can only be inferred. TCR tetramer-based assays allow simultaneous confirmation of both MHC and target antigen (indeed, even target epitope) expression and are inherently type specific.

Panel Design

[0085] Several modalities of the disclosed methods are envisioned. The first is concerned primarily with identifying antigens that are available to be targeted in a particular patient's tumor tissue. Thus, in some embodiments, the panel of antigens assayed for in practicing the method disclosed herein is assembled from more commonly expressed TuAAs for which targeting immunotherapeutics are available (marketed or in development). Antigens can be included in a panel on a prospective basis, for example, due to common or highly specific expression in one or another subset of tumors, or in anticipation of the development of a corresponding therapeutic product. Thus, the same research observations that indicate an antigen would be a good target for immunotherapy (e.g., specificity, prevalence, and level of expression; presentation for T cell based products or surface expression for antibody based products; and that by inclusion in a multivalent immunotherapeutic redundancy or breadth of targeting can be increased) also can justify inclusion of that antigen in the diagnostic panels of the invention.

[0086] An antigen whose expression is specific to a particular tumor type, such as tyrosinase in melanoma, is suitable for panels used in screening that tumor type. An antigen that is expressed in a variety of tumor types, even if not highly prevalent in any particular one, can be suitable for inclusion in panels used to screen that variety of tumor types or in panels used as a general screen, e.g., not tied to an individual tumor type. In some embodiments, the panel of antigens specifically excludes markers from complex expression profiles associated with cancer, and the like, that are not appropriate targets of immunotherapy.

[0087] The histologic origin of a tumor is generally of clinical interest, for example, in designing a treatment strategy or confirming that an apparent recurrence is related to the presumptive original cancer. To this end lineage markers can be included in the panels of antigens.

Marketing of Cancer Immunotherapeutics

[0088] Embodiments of the invention disclosed herein relate to methods for identifying patients that can benefit from particular cancer immunotherapies which can also be useful in the identification of candidates for participation in clinical trials of such products and in marketing the vaccines. Much diagnostic work for cancer is carried out in centralized labs. Whether for recruitment or marketing, an arrangement is made with one or more of these laboratories. The arrangement can entail a fee-for-service contract or a

partnership or joint venture. The laboratory includes TuAA expression profiling assays, as described herein, in their standard panel of tests carried out on submitted tumor samples and the results are reported along with those of the other tests. When a tumor sample is identified as positive for one of more antigens corresponding to constituent immunogens of a vaccine a notice is included in the same communication as the test report alerting the doctor (or patient if the results of the test are reported directly to the patient) to the availability of a clinical trial the patient may be eligible for or a product that the patient may benefit from.

Tumor Associated Antigens

[0089] Examples of TuAAs useful in embodiments disclosed herein include tyrosinase (SEQ. ID NO. 1), melan-A, (SEQ. ID NO. 2), SSX-2, (SEQ. ID NO.3), PSMA (prostate-specific membrane antigen) (SEQ. ID NO. 4), MAGE-1 (SEQ. ID NO. 5), MAGE-3 (SEQ. ID NO. 6), NY-ESO-1 (SEQ. ID NO. 7), PRAME (SEQ ID NO.8), Her2/Neu (SEQ ID NO. 9), PSA (SEQ ID NO. 10), C35 (SEQ ID NO. 11), SSX-4 (SEQ ID NO. 12), gp100 (SEQ ID NO. 13), thyroid transcription factor 1 (TTF1) (SEQ ID NO. 14), mammaglobin (SEQ ID NO. 15), prolactin-inducible protein (Brst2) (SEQ ID NO. 16), mesothelin, isoform 1 (SEQ ID NO. 17), mesothelin, isoform 2 (SEQ ID NO. 18), PSCA (SEQ ID NO. 19) and SCP-1 (SEQ ID NO. 20). The natural coding sequences for these 20 proteins, or any segments within them, can be determined from their cDNA or complete coding (cds) sequences, SEQ. ID NOS. 21-40, respectively. The sequences described in Table 1 are provided in the Sequence Listing filed herewith.

Table 1. SEQ. ID NOS.

SEQ. ID NO.	IDENTITY	ACCESSION NUMBER**
1	Tyrosinase protein	P14679
2	Melan-A protein	Q16655
3	SSX-2 protein	NP_003138
4	PSMA protein	NP_004467
5	MAGE-1 protein	P43355
6	MAGE-3 protein	P43357
7	NY-ESO-1 protein	P78358
8	PRAME protein	NP_006106
9	Her2/Neu protein	P04626
10	PSA protein	NP_001639

11	C35 protein	NP_115715
12	SSX-4 protein	NP_783856
13	gp100 protein	NP_008859
14	TTF1 protein	NP_003308
15	mammaglobin protein	NP_002402
16	Brst2 protein	NP_002643
17	Mesothelin, isoform 1, protein	NP_005814
18	Mesothelin, isoform 2, protein	NP_037536
19	PSCA protein	NP_005663
20	SCP-1 protein	Q15431
21	Tyrosinase cDNA	NM_000372
22	Melan-A cDNA	U06452
23	SSX-2 cDNA	NM_003147
24	PSMA cDNA	NM_004476
25	MAGE-1 cds	M77481
26	MAGE-3 cds	U03735
27	NY-ESO-1 cDNA	U87459
28	PRAME cDNA	NM_006115
29	Her2/Neu cDNA	M11730
30	PSA cDNA	NM_001648
31	C35 cDNA	NM_032339
32	SSX-4 cDNA	NM_175729
33	gp100 cDNA	NM_006928
34	TTF1 cDNA	NM_003317
35	mammaglobin cDNA	NM_002411
36	Brst2 cDNA	NM_002652
37	Mesothelin, isoform 1, cDNA	NM_005823
38	Mesothelin, isoform 2, cDNA	NM_013404
39	PSCA cDNA	NM_005672
40	SCP-1 cDNA	NM_003176

**All accession numbers used here and throughout can be accessed through the NCBI databases, for example, through the Entrez seek and retrieval system on the world wide web.

[0090] Tyrosinase is a melanin biosynthetic enzyme that is considered one of the most specific markers of melanocytic differentiation. Tyrosinase is expressed in few cell types, primarily in melanocytes, and high levels are often found in melanomas. The usefulness of tyrosinase as a TuAA is taught in U.S. Patent 5,747,271 entitled "METHOD FOR IDENTIFYING INDIVIDUALS SUFFERING FROM A CELLULAR ABNORMALITY SOME OF WHOSE ABNORMAL CELLS PRESENT COMPLEXES

OF HLA-A2/TYROSINASE DERIVED PEPTIDES, AND METHODS FOR TREATING SAID INDIVIDUALS” which is hereby incorporated by reference in its entirety.

[0091] GP100, also known as PMel17, is another melanin biosynthetic protein expressed at high levels in melanomas. GP100 as a TuAA is disclosed in U.S. Patent 5,844,075 entitled “MELANOMA ANTIGENS AND THEIR USE IN DIAGNOSTIC AND THERAPEUTIC methods,” which is hereby incorporated by reference in its entirety.

[0092] Melan-A, also known as MART-1 (Melanoma Antigen Recognized by T cells), is another melanin biosynthetic protein expressed at high levels in melanomas. The usefulness of Melan-A/MART-1 as a TuAA is taught in U.S. Patent Nos. 5,874,560 and 5,994,523 both entitled “MELANOMA ANTIGENS AND THEIR USE IN DIAGNOSTIC AND THERAPEUTIC METHODS,” as well as U.S. Patent No. 5,620,886, entitled “ISOLATED NUCLEIC ACID SEQUENCE CODING FOR A TUMOR REJECTION ANTIGEN PRECURSOR PROCESSED TO AT LEAST ONE TUMOR REJECTION ANTIGEN PRESENTED BY HLA-A2,” each of which is hereby incorporated by reference in its entirety.

[0093] SSX-2, also known as Hom-Mel-40, is a member of a family of highly conserved cancer-testis (CT) antigens (Gure, A.O. et al. *Int. J. Cancer* 72:965-971, 1997, which is hereby incorporated by reference in its entirety). Its identification as a TuAA is taught in U.S. Patent 6,025,191 entitled “ISOLATED NUCLEIC ACID MOLECULES WHICH ENCODE A MELANOMA SPECIFIC ANTIGEN AND USES THEREOF,” which is hereby incorporated by reference in its entirety. Cancer-testis antigens are found in a variety of tumors, but are generally absent from normal adult tissues except testis. Expression of different members of the SSX family has been found in various tumor cell lines. Due to the high degree of sequence identity among SSX family members, similar epitopes from more than one member of the family will be generated and able to bind to an MHC molecule, so that some vaccines directed against one member of this family can cross-react and be effective against other members of this family.

[0094] MAGE-1 (melanoma-associated antigen-1), MAGE-2 (melanoma-associated antigen-2), and MAGE-3 (melanoma-associated antigen-3) are members of another family of cancer-testis antigens originally discovered in melanoma but found in a variety of tumors. The identification of MAGE proteins as TuAAs is taught in U.S. Patent 5,342,774, entitled “NUCLEOTIDE SEQUENCE ENCODING THE TUMOR REJECTION ANTIGEN PRECURSOR, MAGE-1,” which is hereby incorporated by

reference in its entirety, and in numerous subsequent patents. Currently there are 17 entries for (human) MAGE in the SWISS Protein database. There is extensive similarity among these proteins, such that in many cases, an epitope from one can induce a cross-reactive response to other members of the family. A few members of the MAGE family have not been observed in tumors, most notably MAGE-H1 and MAGE-D1, which are expressed in testes and brain, and bone marrow stromal cells, respectively. The possibility of cross-reactivity on normal tissue is ameliorated by the fact that they are among the least similar to the other MAGE proteins.

[0095] GAGE-1 is a member of the GAGE family of cancer testis antigens (Van den Eynde, B., et al., *J. Exp. Med.* 182: 689-698, 1995; U.S. Patent Nos. 5,610,013; 5,648,226; 5,858,689; 6,013,481; and 6,069,001, each of which is hereby incorporated by reference in its entirety). The PubGene database currently lists 12 distinct accessible members, some of which are synonymously known as PAGE or XAGE. GAGE-1 through GAGE-8 have a very high degree of sequence identity, so most epitopes can be shared among multiple members of the family.

[0096] BAGE is a cancer-testis antigen commonly expressed in melanoma, particularly metastatic melanoma, as well as in carcinomas of the lung, breast, bladder, and squamous cells of the head and neck. Its usefulness as a TuAA is taught in U.S. Patent Nos. 5,683,88, entitled "TUMOR REJECTION ANTIGENS WHICH CORRESPOND TO AMINO ACID SEQUENCES IN TUMOR REJECTION ANTIGEN PRECURSOR BAGE, AND USES THEREOF" and 5,571,711, entitled "ISOLATED NUCLEIC ACID MOLECULES CODING FOR BAGE TUMOR REJECTION ANTIGEN PRECURSORS," each of which is hereby incorporated by reference in its entirety.

[0097] NY-ESO-1, also known as CTAG-1 (Cancer-Testis Antigen-1) and CAG-3 (Cancer Antigen-3), is a cancer-testis antigen found in a wide variety of tumors. NY-ESO-1 as a TuAA is disclosed in U.S. Patent 5,804,381, entitled "ISOLATED NUCLEIC ACID MOLECULE ENCODING AN ESOPHAGEAL CANCER ASSOCIATED ANTIGEN, THE ANTIGEN ITSELF, AND USES THEREOF," which is hereby incorporated by reference in its entirety. A paralogous locus encoding antigens with extensive sequence identity, LAGE-1a/s and LAGE-1b/L, has been disclosed in publicly available assemblies of the human genome, and has been concluded to arise through alternate splicing. Additionally, CT-2 (or CTAG-2, Cancer-Testis Antigen-2) appears to be either an allele, a mutant, or a sequencing discrepancy of LAGE-1b/L. Due to the extensive

sequence identity, many epitopes from NY-ESO-1 can also induce immunity to tumors expressing these other antigens. NY-ESO-1 and LAGE are virtually identical through amino acid 70. From amino acid 71 through 134 the longest run of identity between the two proteins is 6 residues, but potentially cross-reactive sequences are present. From amino acid 135 through 180, NY-ESO and LAGE-1a/s are identical except for a single residue, but LAGE-1b/L is unrelated due to the alternate splice. The CAMEL and LAGE-2 antigens appear to derive from the LAGE-1 mRNA, but from alternate reading frames, thus giving rise to unrelated protein sequences. More recently, GenBank Accession AF277315.5, Homo sapiens chromosome X clone RP5-865E18, RP5-1087L19, complete sequence, reports three independent loci in this region which are labeled as LAGE1 (corresponding to CTAG-2 in the genome assemblies), LAGE2-A and LAGE2-B (both corresponding to CTAG-1 in the genome assemblies).

[0098] PRAME, also known as MAPE, DAGE, and OIP4, was originally observed as a melanoma antigen. Subsequently, it has been recognized as a cancer-testis (CT) antigen, but unlike many CT antigens, such as, MAGE, GAGE and BAGE, PRAME is expressed in acute myeloid leukemias. PRAME is a member of the MAPE family, which consists largely of hypothetical proteins with which it shares limited sequence similarity. The usefulness of PRAME as a TuAA is taught in U.S. Patent 5,830,753, entitled "ISOLATED NUCLEIC ACID MOLECULES CODING FOR TUMOR REJECTION ANTIGEN PRECURSOR DAGE AND USES THEREOF," which is hereby incorporated by reference in its entirety.

[0099] PSMA (prostate-specific membranes antigen), a TuAA described in U.S. Patent 5,538,866 entitled "PROSTATE-SPECIFIC MEMBRANES ANTIGEN" which is hereby incorporated by reference in its entirety, is expressed by normal prostate epithelium and, at a higher level, in prostatic cancer. Additionally expression has also been observed in ovarian carcinoma. It has also been found in the neovasculature of non-prostatic tumors. PSMA can thus form the basis for vaccines directed to both prostate and ovarian cancer and to the neovasculature of other tumors. This later concept is more fully described in a provisional U.S. Patent Application No. 60/274,063, entitled "ANTI-NEOVASCULAR VACCINES FOR CANCER," filed March 7, 2001, and U.S. Application No. 10/094,699 (Pub. No. 20030046714 A1), filed on March 7, 2002, entitled "ANTI-NEOVASCULAR PREPARATIONS FOR CANCER," each of which is hereby incorporated by reference in its entirety. Briefly, as tumors grow they recruit ingrowth of new blood vessels. This is

understood to be necessary to sustain growth as the centers of unvascularized tumors are generally necrotic and angiogenesis inhibitors have been reported to cause tumor regression. Such new blood vessels, or neovasculature, express antigens not found in established vessels, and thus can be specifically targeted. By inducing CTL against neovascular antigens the vessels can be disrupted, interrupting the flow of nutrients to, and removal of wastes from, tumors, leading to regression.

[0100] Alternate splicing of the PSMA mRNA leads to a protein with an apparent start at Met₅₈, thereby deleting the putative membrane anchor region of PSMA as described in U.S. Patent 5,935,818, entitled "ISOLATED NUCLEIC ACID MOLECULE ENCODING ALTERNATIVELY SPLICED PROSTATE-SPECIFIC MEMBRANES ANTIGEN AND USES THEREOF," which is hereby incorporated by reference in its entirety. A protein termed PSMA-like protein, Genbank accession number AF261715, is nearly identical to amino acids 309-750 of PSMA, but has a different expression profile. Thus, the most preferred epitopes are those with an N-terminus located from amino acid 58 to 308.

[0101] PSA (prostate specific antigen) is a peptidase of the kallikrein family and a differentiation antigen of the prostate. Expression in breast tissue has also been reported. Alternate names include gamma-seminoprotein, kallikrein 3, semingelase, seminin, and P-30 antigen. PSA has a high degree of sequence identity with the various alternate splicing products prostatic/glandular kallikrein-1 and -2, as well as kallikrein 4, which is also expressed in prostate and breast tissue. Other kallikreins generally share less sequence identity and have different expression profiles. Nonetheless, cross-reactivity that might be provoked by any particular epitope, along with the likelihood that that epitope would be liberated by processing in non-target tissues (most generally by the housekeeping proteasome), should be considered in designing a vaccine.

[0102] PSCA (prostate stem cell antigen) and also known as SCAH-2, is a differentiation antigen preferentially expressed in prostate epithelial cells, and overexpressed in prostate cancers. Lower level expression is seen in some normal tissues including neuroendocrine cells of the digestive tract and collecting ducts of the kidney. PSCA is described in U.S. Patent 5,856,136, entitled "HUMAN STEM CELL ANTIGENS," which is hereby incorporated by reference in its entirety.

[0103] Synaptonemal complex protein 1 (SCP-1), also known as HOM-TES-14, is a meiosis-associated protein and also a cancer-testis antigen (Tureci, O., et al. Proc. Natl.

Acad. Sci. USA 95:5211-5216, 1998, which is hereby incorporated by reference in its entirety). As a cancer antigen its expression is not cell-cycle regulated and it is found frequently in gliomas, breast, renal cell, and ovarian carcinomas. It has some similarity to myosins, but with few enough identities that cross-reactive epitopes are not an immediate prospect.

[0104] The ED-B domain of fibronectin is also a potential target. Fibronectin is subject to developmentally regulated alternative splicing, with the ED-B domain being encoded by a single exon that is used primarily in oncofetal tissues (Matsuura, H. and S. Hakomori *Proc. Natl. Acad. Sci. USA* 82:6517-6521, 1985; Carnemolla, B. et al. *J. Cell Biol.* 108:1139-1148, 1989; Loidon-Rosa, B. et al. *Cancer Res.* 50:1608-1612, 1990; Nicolo, G. et al. *Cell Differ. Dev.* 32:401-408, 1990; Borsi, L. et al. *Exp. Cell Res.* 199:98-105, 1992; Oyama, F. et al. *Cancer Res.* 53:2005-2011, 1993; Mandel, U. et al. *APMIS* 102:695-702, 1994; Farnoud, M.R. et al. *Int. J. Cancer* 61:27-34, 1995; Pujuguet, P. et al. *Am. J. Pathol.* 148:579-592, 1996; Gabler, U. et al. *Heart* 75:358-362, 1996; Chevalier, X. *Br. J. Rheumatol.* 35:407-415, 1996; Midulla, M. *Cancer Res.* 60:164-169, 2000, each of which is hereby incorporated by reference in its entirety).

[0105] The ED-B domain is also expressed in fibronectin of the neovasculature (Kaczmarek, J. et al. *Int. J. Cancer* 59:11-16, 1994; Castellani, P. et al. *Int. J. Cancer* 59:612-618, 1994; Neri, D. et al. *Nat. Biotech.* 15:1271-1275, 1997; Karelina, T.V. and A.Z. Eisen *Cancer Detect. Prev.* 22:438-444, 1998; Tarli, L. et al. *Blood* 94:192-198, 1999; Castellani, P. et al. *Acta Neurochir. (Wien)* 142:277-282, 2000, each of which is hereby incorporated by reference in its entirety). As an oncofetal domain, the ED-B domain is commonly found in the fibronectin expressed by neoplastic cells in addition to being expressed by the neovasculature. Thus, CTL-inducing vaccines targeting the ED-B domain can exhibit two mechanisms of action: direct lysis of tumor cells, and disruption of the tumor's blood supply through destruction of the tumor-associated neovasculature. As CTL activity can decay rapidly after withdrawal of vaccine, interference with normal angiogenesis can be minimal. The design and testing of vaccines targeted to neovasculature is described in Provisional U.S. Patent Application No. 60/274,063, entitled "ANTI-NEOVASCULATURE VACCINES FOR CANCER," filed on March 7, 2001, and in U.S. Patent Application No. 10/094,699, (Pub. No. 20030046714 A1), entitled "ANTI-NEOVASCULATURE PREPARATIONS FOR CANCER," filed on March 7, 2002, each of which is hereby incorporated by reference in its entirety. A tumor cell line is disclosed

in Provisional U.S. Application No. 60/363,131, filed on March 7, 2002, entitled "HLA-TRANSGENIC MURINE TUMOR CELL LINE," which is hereby incorporated by reference in its entirety.

[0106] Carcinoembryonic antigen (CEA) is a paradigmatic oncofetal protein first described in 1965 (Gold and Freedman, *J. Exp. Med.* 121: 439-462, 1965, which is hereby incorporated by reference in its entirety). Fuller references can be found in the Online Mendelian Inheritance in Man; record *114890. It has officially been renamed carcinoembryonic antigen-related cell adhesion molecule 5 (CEACAM5). Its expression is most strongly associated with adenocarcinomas of the epithelial lining of the digestive tract and in fetal colon. CEA is a member of the immunoglobulin supergene family and the defining member of the CEA subfamily.

[0107] Survivin, also known as Baculoviral IAP Repeat-Containing Protein 5 (BIRC5), is another protein with an oncofetal pattern of expression. It is a member of the inhibitor of apoptosis protein (IAP) gene family. It is widely over-expressed in cancers (Ambrosini, G. et al., *Nat. Med.* 3:917-921, 1997; Velculescu V.E. et al., *Nat. Genet.* 23:387-388, 1999, which is hereby incorporated by reference in its entirety) and its function as an inhibitor of apoptosis is believed to contribute to the malignant phenotype.

[0108] HER2/NEU is an oncogene related to the epidermal growth factor receptor (van de Vijver, et al., *New Eng. J. Med.* 319:1239-1245, 1988, which is hereby incorporated by reference in its entirety), and apparently identical to the c-ERBB2 oncogene (Di Fiore, et al., *Science* 237: 178-182, 1987, which is hereby incorporated by reference in its entirety). The over-expression of ERBB2 has been implicated in the neoplastic transformation of prostate cancer. As with HER2, it is amplified and over-expressed in 25-30% of breast cancers among other tumors where expression level is correlated with the aggressiveness of the tumor (Slamon, et al., *New Eng. J. Med.* 344:783-792, 2001, which is hereby incorporated by reference in its entirety). A more detailed description is available in the Online Mendelian Inheritance in Man; record *164870.

[0109] MESOTHELIN is an antigen originally found in mesotheliomas but also known to be upregulated in many pancreatic and ovarian cancers. Its use as a vaccine target, as well as useful epitopes, is described in Thomas, A.M. et al., *J. Exp. Med.* 200:297-306, 2004, which is hereby incorporated by reference in its entirety

[0110] Further examples of tumor-associated antigens include MelanA (MART-1), gp100 (Pmel 17), tyrosinase, TRP-1, TRP-2, MAGE-1, MAGE-3, BAGE, GAGE-1,

GAGE-2, p15(58), CEA, RAGE, NY-ESO (LAGE), SCP-1, Hom/Mel-40, PRAME, p53, H-Ras, HER-2/neu, BCR-ABL, E2A-PRL, H4-RET, IGH-IGK, MYL-RAR, Epstein Barr virus antigens, EBNA, human papillomavirus (HPV) antigens E6 and E7, TSP-180, MAGE-4, MAGE-5, MAGE-6, p185erbB2, p180erbB-3, c-met, nm-23H1, PSA, TAG-72-4, CA 19-9, CA 72-4, CAM 17.1, NuMa, K-ras, β -Catenin, CDK4, Mum-1, p16, TAGE, PSMA, PSCA, CT7, telomerase, 43-9F, 5T4, 791Tgp72, alpha-fetoprotein, β -HCG, BCA225, BTAA, CA 125, CA 15-3 (CA 27.29\BCAA), CA 195, CA 242, CA-50, CAM43, CD68\KP1, CO-029, FGF-5, G250, Ga733 (EpCAM), HTgp-175, M344, MA-50, MG7-Ag, MOV18, NB/70K, NY-CO-1, RCAS1, SDCCAG16, TA-90 (Mac-2 binding protein/cyclophilin C-associated protein), TAAL6, TAG72, TLP, TPS, and the like.

[0111] Additional tumor-associated antigens are described in Chen, YT, "Identification of human tumor antigens by serological expression cloning: an online review on SEREX" *Cancer Immun.* 2004 [updated 2004 Mar 10; cited 2004 Apr 1] at world wide web cancerimmunotherapy.org/SEREX/; and Renkvist, N. et al., "A listing of tumor antigens recognized by T cells," *Cancer Immunology Immunotherapy*, 50:3-15 (2001), each of which is hereby incorporated by reference in its entirety.

[0112] Table 2, adapted from Scanlan et al., "The cancer/testis genes: Review, standardization, and commentary," *Cancer Immunity* 4:1 (January 23, 2004), which is hereby incorporated by reference in its entirety, provides a listing of CT Antigens. Table 3 provides the frequency of mRNA expression in various tumor types for the CT antigens in Table 2. Scanlan et al., "The cancer/testis genes: Review, standardization, and commentary," *Cancer Immunity* 4:1 (January 23, 2004), which is hereby incorporated by reference in its entirety.

Table 2
Listing of CT genes

CT Identifier	Transcript/Transcript family	Family Members/CT Identifier (Synonyms)
CT1	MAGEA	MAGEA1/CT1.1, MAGEA2/CT1.2, MAGEA3/CT1.3, MAGEA4/CT1.4, MAGEA5/CT1.5, MAGEA6/CT1.6, MAGEA7/CT1.7, MAGEA8/CT1.8,

		MAGEA9/CT.9, MAGEA10/CT1.10, MAGEA11/CT1.11, MAGEA12/CT1.12
CT2	BAGE	BAGE/CT2.1, BAGE2/CT2.2, BAGE3/CT2.3, BAGE4/CT2.4, BAGE5/CT2.5
CT3	MAGEB	MAGEB1/CT3.1, MAGEB2/CT3.2, MAGEB5/CT3.3, MAGEB6/CT3.4
CT4	GAGE1	GAGE1/CT4.1, GAGE2/CT4.2, GAGE3/CT4.3, GAGE4/CT4.4, GAGE5/CT4.5, GAGE6/CT4.6, GAGE7/CT4.7, GAGE8/CT4.8
CT5	SSX	SSX1/CT5.1, SSX2/CT5.2a, SSX2/CT5.2b, SSX3/CT5.3, SSX4/CT5.4
CT6	NY-ESO-1	NY-ESO-1/CT6.1, LAGE-1a/CT6.2a, LAGE-1b/CT6.2b
CT7	MAGEC1	MAGEC1/CT7.1, MAGEC3/CT7.2
CT8	SYCP1	SYCP1/CT8
CT9	BRDT	BRDT/CT9
CT10	MAGEE1	MAGEE1/CT10
CT11	CTp11/SPANX	SPANXA1/CT11.1, SPANXB1/CT11.2, SPANXC/CT11.3, SPANXD/CT11.4
CT12	XAGE-1/GAGED	XAGE-1a/CT12.1a, XAGE-1b/CT12.1b, XAGE-1c/CT12.1c, XAGE-1d/CT12.1d, XAGE-2/CT12.2, XAGE-3a/CT12.3a, XAGE-3b/CT12.3b, XAGE-4/CT12.4
CT13	HAGE	HAGE/CT13
CT14	SAGE	SAGE/CT14

CT15	ADAM2	ADAM2/CT15
CT16	PAGE-5	PAGE-5/CT16.1, CT16.2
CT17	LIP1	LIP1/CT17
CT18	NA88	NA88/CT12
CT19	IL13RA1	IL13RA1/CT19
CT20	TSP50	TSP50/CT20
CT21	CTAGE-1	CTAGE-1/CT21.1, CTAGE-2/CT21.2
CT22	SPA17	SPA17/CT22
CT23	OY-TES-1	OY-TES-1/CT23
CT24	CSAGE	CSAGE/CT24.1, TRAG3/CT24.2
CT25	MMA1/DSCR8	MMA-1a/CT25.1a, MMA-1b/CT25.1b
CT26	CAGE	CAGE/CT26
CT27	BORIS	BORIS/CT27
CT28	HOM-TES-85	HOM-TES-85/CT28
CT29	AF15q14/ D40	D40/CT29
CT30	E2F-like/HCA661	HCA661/CT30
CT31	PLU-1	PLU-1/CT31
CT32	LDHC	LDHC/CT32
CT33	MORC	MORC/CT33

CT34	SGY-1	SGY-1/CT34
CT35	SPO11	SPO11/CT35
CT36	TPX1	TPX-1/CT36
CT37	NY-SAR-35	NY-SAR-35/CT37
CT38	FTHL17	FTHL17/CT38
CT39	NXF2	NXF2/CT39
CT40	TAF7L	TAF7L/CT40
CT41	TDRD1	TDRD1/CT41.1, NY-CO-45/CT41.2
CT42	TEX15	TEX15/CT42
CT43	FATE	FATE/CT43
CT44	TPTE	TPTE/CT44
---	PRAME	(MAPE, DAGE)

Table 3.

CT Family (Member)	Frequency (%) of Expression in Tumor Type																Ref
	Blad	Brn	Brst	Col	Eso	Gas	H/N	Liver	Leuk/ Lymph	Lung (NSCLC)	Mel	Ov	Pancr	Pros	Renal	Sarc	
MAGEA1/CT1.1	22	-	18	2	53	29	28	80	0	49	48	28	-	15	0	14	44
BAGE1/CT2.1	15	-	10	0	-	-	8	-	0	4	26	15	-	0	0	6	44
MAGEB1/CT3.1	0	0	17	0	-	0	0	-	0	14	22	-	-	0	0	9	45
GAGE/CT4.1	12	-	9	0	-	-	19	38 ^b	1	19	28	31	-	10	0	25	44
SSX2/CT5.2	44	6	7	12	-	-	35	9 ^b	36	16	35	-	-	40	5	50	46
NY-ESO-1/CT6.1	80	0	30	0	-	0	-	29	0	17	34	25	0	25	9	0	8
MAGEC1/CT7.1	44	-	30	10	-	-	36	-	-	33	70	-	-	-	-	60	20
SYCP1/CT8	-	47	20	0	-	7	-	28 ^b	0	7	14	0	-	0	8	0	9
BRDT/CT9	0	-	0	0	8	-	8	-	-	25	0	-	-	-	0	-	16
MAGEE1/CT10	44	-	38	0	-	-	36	-	-	24	50	-	-	-	-	0	12
SPANXC/CT11.3	9	-	25	22	0	-	-	-	-	33	70	-	0	-	-	-	14

XAGE-1a/CT12.1a	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
HAGE/CT13	24	37	5	31	27	-	-	-	20	9	32.	17	-	-	22	6	20	13	47
SAGE/CT14	12	0	5	0	20	-	17	-	-	4	22	4	-	-	0	5	5	13	
ADAM2/CT15	-	-	0	0	-	-	-	-	-	-	0	0	0	-	-	12	-	17	
PAGE-5/CT16	-	-	5	11	-	-	-	-	-	-	39	22	0	-	-	44	-	17	
LIP1/CT17	-	-	5	0	-	-	-	-	-	-	0	0	0	-	-	25	-	17	
NA88/CT18	-	-	-	-	-	-	-	-	-	-	-	11	-	-	-	-	-	48	
TSP50/CT20	-	-	28	-	-	-	-	-	-	-	-	-	-	-	-	-	-	49	
CTAGE-1/CT21.1	-	-	-	-	-	-	-	-	-	35	-	-	-	-	-	-	-	50	
SPA17/CT22	-	-	-	-	-	-	-	-	-	26	-	-	-	-	-	-	-	51	
OYTES1/CT23	28	-	40	15	-	0	-	40	-	-	20	-	-	-	-	0	-	52	
MMA1a/CT25.1a	-	-	0	0	0	-	-	-	-	-	40	26	-	0	-	-	18	15	
CAGE/CT26	-	-	-	-	-	89	-	-	-	-	100	-	-	-	-	-	-	53	
HOMTES85/CT28	-	35	0	10	-	-	-	19	-	-	28	36	32	-	0	-	-	54	

D40/CT29	-	20	-	13	-	0	-	-	-	41	-	36	27	-	-	55
HCA661/CT30	0	-	-	-	-	0	0	29	-	-	20	-	-	-	-	56
PLU-1/CT31	-	-	86	-	-	-	-	-	-	-	-	-	-	-	-	27
LDHC/CT32	-	-	35	15	-	-	-	-	-	47	44	42	-	37	57	18
MORC/CT33	-	-	0	0	-	-	-	-	-	18	18	14	-	0	0	18
SGY-1/CT34	-	-	20	0	-	-	-	-	-	12	25	57	-	12	0	18
SPO11/CT35	-	-	0	0	-	-	-	-	-	0	6	0	-	0	0	18
TPX1/CT36	-	-	15	0	-	-	-	-	-	-	6	14	-	37	14	18
NYSAR35/CT37	42	-	23	0	8	-	-	-	-	17	6	8	-	-	0	57
FTHL17/CT38	22	-	14	0	0	-	10	-	0	25	0	-	-	0	0	58
NXF2/CT39	19	-	0	11	12	-	5	-	0	15	55	-	-	14	0	58
TAF7L/CT40	10	-	0	0	0	-	10	-	0	9	21	-	-	0	0	58
TDRD1/CT41.1	28	-	37	0	10	-	22	-	5	5	0	-	-	38	0	58
TEX15/CT42	21	-	0	0	20	-	11	-	0	21	27	-	-	12	33	58

FATE/CT43	-	-	-	-	21	-	7	-	66	-	0	-	-	-	-	-	-	-	19
TPTE/CT44	-	-	-	-	0	-	0	-	39	-	36	-	-	-	-	-	-	-	19

^a Abbreviations: Blad, bladder; Brn, brain; Brst, breast; Col, colon; Gas, gastric; H/N, head and neck; Leuk, leukemia; Lymph, lymphoma; NSCLC, non-small cell lung carcinoma; Mel, melanoma; Ov, ovarian; Pancr, pancreatic; Pros, prostate; Sarc, sarcoma; Ref, reference.

^b Reference 59.

[0113] Additional antigens associated with tumor neovasculature include VEGFR2 (vascular endothelial growth factor receptor 2) described in U.S. Patent No. 6,342,221, which is hereby incorporated by reference in its entirety; and Tie-2, an endothelium specific receptor tyrosine kinase which is described in WO9943801, which is hereby incorporated by reference in its entirety.

[0114] In addition to the disruption of blood flow to tumors that can be achieved using anti-neovasculature agents such as those recited above, co-targeting molecules expressed on cancer cells as well as molecules expressed on underlying non-transformed stromal cells (including neovasculature as well as interstitial tissue, for example) can also improve the effectiveness of multivalent immunotherapeutics in limiting tumor growth and promoting cancer regression by other mechanisms. Stroma encompasses neovasculature as well as fibroblasts, and in general, all non-transformed, non-lymphoid cells within a tumor microenvironment. For example, immune mediated attack of the endothelial cells (via cytotoxic T lymphocytes (CTLs) or antibody dependent cytotoxic cells (ADCC)) can result in neovasculature permeabilization and initiation of inflammatory events that result in recruitment and translocation of immune effectors, such as CTLs, targeting the neoplastic cells within primary tumor and metastatic lesions. Compared to strategies targeting only cancer cells, methods to co-target associated stromal tissue improve the efficacy of the former. Similarly, compared to strategies targeting neovasculature only, methods to co-target cancer cells improve the overall therapeutic effect by attacking lesions, including those of limited size and vascularization, especially those adversely located within vital organs. With regard to neovasculature, co-targeting VEGFRs (such as II), CD55 and PSMA as well as other molecules expressed by neovasculature, can be accomplished by generating CTL or antibodies with capability to initiate ADCC or complement activated cell injury. Alternatively, initial endothelial injury can be brought about through passive immunotherapy using available anti-angiogenic antibodies.

[0115] In addition or alternatively, co-targeting target-associated antigens, together with growth, metastasis, or survival promoting factors produced by cancer cells or non-transformed cells that are found in the extracellular compartment (diffusing or associated with the extracellular matrix), can also result in a more substantial therapeutic effect. By co-

targeting antigens expressed within or on cancer cells as well as factors that exert autocrine or paracrine effects (growth, survival, and/or invasiveness), the pathogenic process can be slowed or disrupted to significant degree. Co-targeting autocrine or paracrine factors (such as, but not limited to, NF-kB activating molecules - CXCL1, CXCL8, CCL2; or growth factors such as, but not limited to, chorionic-gonadotropic hormone and gastrin) can be carried out by co-induction of neutralizing antibodies or secondarily, by CTLs recognizing cells that produce such factors.

[0116] Overall, co-targeting multiple elements of biological importance for tumor growth and metastasis can limit progression of the malignant process by impacting the processes of clonal selection, immune evasion and escape. Thus, co-targeting stroma-associated antigens provides an additional mode of attack in that such activities are inhibited and/or disrupted.

[0117] One of skill in the art will appreciate that any other antigen or protein associated with vascular or other tumor-associated stromal cells can be a target for the immunogenic compositions, including those that are presently known and those yet to be identified.

Compositions

[0118] Immunogenic compositions, including, for example, vaccines, can be prepared using whole antigen or an epitopic peptide. Peptide immunogens can be readily prepared using standard peptide synthesis means known in the art, for example. Immunogens can be prepared commercially by one of numerous companies that do chemical synthesis. An example such a company is American Peptides, Inc., where the distributor is CLINALFA AG (Laufelfingen, Switzerland). The antigens or immunogens can be prepared in accordance with GMP standards and purity can be assessed by analytical HPLC. The product can be characterized by amino-acid analysis and tested for sterility and the absence of pyrogens.

[0119] The immunogenic compositions can also include adjuvants or other biological response modifiers (BRMs). Particularly advantageous methods of using adjuvants and BRMs are disclosed in U.S. provisional patent application 60/640727, entitled, "METHODS TO TRIGGER, MAINTAIN AND MANIPULATE IMMUNE RESPONSES BY TARGETED ADMINISTRATION OF BIOLOGICAL RESPONSE MODIFIERS INTO

LYMPHOID ORGANS,” filed 12/29/2004 and which is hereby incorporated by reference in its entirety.

[0120] An antigen can be delivered to an animal’s system either directly or indirectly. For example, a polypeptide can be delivered directly as the polypeptide, or it can be delivered indirectly, for example, using a DNA construct or vector, or a recombinant virus that codes for the desired antigen. Any vector driving expression in a professional antigen presenting cell can be suitable for this purpose. In indirect delivery, the antigen is expressed in the cell, then presented by the MHC Class I on the surface of the cell to stimulate a CTL response. Expression of a secreted form of the antigen can be useful to induce an antibody response recognizing antigens that are membrane proteins.

[0121] In a preferred embodiment, an encoded antigen can be delivered in the form of a naked plasmid expression vector. Particularly useful constructs are disclosed in U.S. Patent Application No. 09/561,572, filed April 28, 2000, entitled “EXPRESSION VECTORS ENCODING EPITOPES OF TARGET-ASSOCIATED ANTIGENS;” U.S. Patent Application No. 10/292,413, filed November 17, 2002 (Pub. No. 20030228634 A1), entitled “EXPRESSION VECTORS ENCODING EPITOPES OF TARGET-ASSOCIATED ANTIGENS AND METHODS FOR THEIR DESIGN;” U.S. Patent Application No. 10/225,568, filed August 20, 2002 (Pub No. 200-0138808); PCT Application No. PCT/US2003/026231, filed August 19, 2003 (Pub. No. WO 2004/018666); U.S. Patent No. 6,709,844, entitled “AVOIDANCE OF UNDESIRABLE REPLICATION INTERMEDIATES IN PLASMID PROPAGATION,” and in U.S. Patent Application No. 10/026,066, filed December 7, 2001 (Pub. No. 20030215425 A1), entitled “EPITOPE SYNCHRONIZATION IN ANTIGEN PRESENTING CELLS,” each of which is hereby incorporated by reference in its entirety. Additional methodology, compositions, peptides, and peptide analogues are disclosed in U.S. Provisional Application Nos. 60/581,001, filed June 17, 2004, and ___/___ (Attorney Docket No. 038A), filed on even date as the instant application, both entitled “SSX-2 PEPTIDE ANALOGS;” U.S. Provisional Application Nos. 60/580,962, filed June 17, 2004, and ___/___ (Attorney Docket No. 039A), filed on even date as the instant application, both entitled “NY-ESO PEPTIDE ANALOGS;” U.S. Patent Application No. 09/999,186, filed November 7, 2001, entitled “METHODS OF

COMMERCIALIZING AN ANTIGEN"; U.S. Provisional Application No. 60/640,402, filed on December 29, 2004, entitled, "METHODS TO ELICIT, ENHANCE AND SUSTAIN IMMUNE RESPONSES AGAINST MHC CLASS I- RESTRICTED EPITOPES, FOR PROPHYLACTIC OR THERAPEUTIC PURPOSES"; and U.S. Provisional Application No. 60/640,821, filed on December 29, 2004, entitled "METHODS TO BYPASS CD4+ CELLS IN THE INDUCTION OF AN IMMUNE RESPONSE," each of which is hereby incorporated by reference in its entirety. The feasibility of and general procedures related to the use of naked DNA for immunization are described in U.S. Patent No. 5,589,466, entitled "INDUCTION OF A PROTECTIVE IMMUNE RESPONSE IN A MAMMAL BY INJECTING A DNA SEQUENCE" and in U.S. Patent No. 5,679,647, entitled "METHODS AND DEVICES FOR IMMUNIZING A HOST AGAINST TUMOR-ASSOCIATED ANTIGENS THROUGH ADMINISTRATIONS OF NAKED POLYNUCLEOTIDES WHICH ENCODE TUMOR-ASSOCIATED ANTIGENIC PEPTIDES," each of which is hereby incorporated by reference in its entirety. The former teaches only intramuscular or intradermal injection while the latter teaches only administration to skin or mucosa.

[0122] In a preferred embodiment, the antigen can be administered directly to the lymphatic system. Intranodal administration for the generation of CTL is taught in U.S. Patent Application Nos. 09/380,534, filed September 1, 1999 and 09/776,232, filed on February 2, 2001 (Pub. No. 20020007173 A1), and in PCT Application No. PCTUS98/14289, filed on July 10, 1998 (Pub. No. WO9902183A2) each entitled "A METHOD OF INDUCING A CTL RESPONSE," each of which is hereby incorporated by reference in its entirety. Single bolus injection intra lymph node (i.ln.) required only 0.1% of the dose required in order to obtain a similar level of CTL response by intramuscular (i.m.) injection. Therefore a protective response can be established against systemic viral infection with a single bolus delivered i.ln., but not with a dose nearing the practical limit delivered i.m. Repeated bolus injections i.m. failed to establish a protective response against a peripheral virus infection or transplanted tumor, whereas lower doses administered i.ln. were completely effective. Particularly useful intranodal immunization protocols are taught in Provisional U.S. Patent Application No. 60/479,393, filed June 17, 2003, and U.S. Patent Application No. 10/871,708, filed June 17, 2004, both entitled "METHODS TO CONTROL MAGNITUDE

AND QUALITY THE MHC CLASS I-RESTRICTED IMMUNE RESPONSE,” and in U.S. Patent Application No. 10/871,707, filed on June 17, 2004, (Pub. No. 20050079152 A1), and Provisional U.S. Patent Application No. 60/640,402, filed on December 29, 2004, both entitled “METHODS TO ELICIT, ENHANCE AND SUSTAIN IMMUNE RESPONSES AGAINST MHC CLASS I-RESTRICTED EPITOPES, FOR PROPHYLACTIC OR THERAPEUTIC PURPOSE”, each of which is hereby incorporated by reference in its entirety.

[0123] A class of epitopes that can be advantageous in anti-cancer immunogenic compositions are housekeeping epitopes. These are produced through the action of the housekeeping (or standard) proteasome. Housekeeping epitopes can be liberated from the translation product of expression vectors through proteolytic processing by the immunoproteasome of professional antigen presenting cells (pAPC). In one embodiment of the invention, sequences flanking the housekeeping epitope(s) can be altered to promote cleavage by the immunoproteasome at the desired location(s). Housekeeping epitopes, their uses, and identification are described in U.S. Patent Application Nos. 09/560,465 filed on April 28, 2000, and U.S. Patent Application No. 10/026,066 (Pub. No. 20030215425 A1), filed on December 7, 2001, entitled “EPITOPE SYNCHRONIZATION IN ANTIGEN PRESENTING CELLS,” and U.S. Patent No. 6,861,234, entitled “METHOD OF EPITOPE DISCOVERY,” each of which is hereby incorporated by reference in its entirety.

[0124] Examples of housekeeping epitopes are disclosed in Provisional U.S. Patent Applications Nos. 60/282,211, filed on April 6, 2001; 60/337,017, filed on November 7, 2001; 60/363210 filed March 7, 2002; and 60/409,123, filed on September 5, 2002; U.S. Patent Application No. 10/117,937 (Publication No. 20030220239A1), filed on April 4, 2002; and U.S. Patent Application No. 10/657,022, filed on September 5, 2003 (Pub. No. 20040180354 A1, and PCT Application No. PCT/US2003/027706, filed September 5, 2003 (Pub. No. WO04022709A2) both entitled “EPITOPE SEQUENCES,” each of which is hereby incorporated by reference in its entirety.

[0125] In other embodiments of the invention, the housekeeping epitope(s) can be flanked by arbitrary sequences or by sequences incorporating residues known to be favored in immunoproteasome cleavage sites. As used herein the term “arbitrary sequences” refers to

sequences chosen without reference to the native sequence context of the epitope, their ability to promote processing, or immunological function. In further embodiments of the invention multiple epitopes can be arrayed head-to-tail. These arrays can be made up entirely of housekeeping epitopes. Likewise, the arrays can include alternating housekeeping and immune epitopes. Alternatively, the arrays can include housekeeping epitopes flanked by immune epitopes, whether complete or distally truncated. Further, the arrays can be of any other similar arrangement. There is no restriction on placing a housekeeping epitope at the terminal positions of the array. The vectors can additionally contain authentic protein coding sequences or segments thereof containing epitope clusters as a source of immune epitopes. The term "authentic" refers to natural protein sequences.

[0126] Epitope clusters and their uses are described in U.S. Patent Application Nos. 09/561,571, entitled "EPITOPE CLUSTERS," filed on April 28, 2000; 09/560,465, filed April 28, 2000, 10/005,905, filed on November 7, 2001, and 10/026,066, filed on December 7, 2001, each entitled "EPITOPE SYNCHRONIZATION IN ANTIGEN PRESENTING CELLS," and 10/094,699, filed March 7, 2002, entitled ANTI-NEOVASCULATURE PREPARATIONS FOR CANCER, each of which is hereby incorporated by reference in its entirety.

[0127] In another embodiment of the invention an encoded antigen can be delivered in the form of a viral vector. A wide array of viruses with modified genomes adapted to express interposed reading frames but often no, or at least a reduced number of, viral proteins are known in the art, including without limitation, retroviruses including lentiviruses, adenoviruses, parvoviruses including adeno-associated virus, herpesviruses, and poxviruses including vaccinia virus. Such viral vectors facilitate delivery of the nucleic acid component into the cell allowing for expression. A subset of these vectors, such as retroviruses and parvoviruses, promote integration of their nucleic acid component into the host genome, whereas others do not.

[0128] Bacteria can also serve as vectors, that is they can be used to deliver a nucleic acid molecule capable of causing expression of an antigen. For example, a strain of *Listeria monocytogenes* has been devised that effects its own lysis upon entering the cytosol of macrophages (its normal target), thereby releasing plasmid from which antigen is

subsequently expressed (Dietrich, G. et al., *Biotechnology* 16:181-185, 1998, which is hereby incorporated by reference in its entirety). *Shigella flexneri* and *Escherichia coli* have been similarly used (Sizemore, D.R. et al., *Science* 270:299-302, 1995, and Courvalin, P. et al., *Life Sci.* 318:1207-1212, 1995, respectively, each of which is hereby incorporated by reference in its entirety).

[0129] The use of microbial vectors for nucleic acid delivery can be complicated by the immune reactions the vectors themselves provoke. When prolonged or repeated administration is required, antibody elicited by the earlier treatment can prevent useful quantities of the vector from ever reaching its intended host. However, by direct administration intra lymph node, for example, the combination of proximity to host cells and the much reduced effective dose makes it possible to administer a dose capable of evading or overwhelming an existing antibody titer.

[0130] The word vector has been used, here and elsewhere, in reference to several modalities and variously modified (e.g., expression vector, viral vector, delivery vector, etc.). The underlying principle is that a nucleic acid capable of causing expression of an antigen, rather than the antigen itself, ultimately arrives in an APC. Unless modified, explicitly or by local context, the term vector as used herein is intended to encompass all such possibilities.

[0131] The techniques discussed above are distinct from the approach of modifying the microbial genome, including extra-chromosomal DNA, such that the antigen is produced as a component of the microbe, which is then itself administered as the immunogen. Examples of microbes used in the genomic modification approach include viruses, bacteria, fungi, and protazoa. In embodiments of the invention described herein, the compositions, including the vaccines, can include the already synthesized antigen or a nucleic acid capable of causing an APC to express the antigen *in vivo*. In alternative embodiments, combinations of these two techniques are used. For example, one embodiment contemplates the use of a virus vector as discussed above that also incorporates a target epitope into a capsid or envelope protein.

[0132] Antigens may be used alone or may be delivered in combination with other antigens or with other compounds such as cytokines. Cytokines that are known to enhance immune stimulation of CTL responses, include, for example, GM-CSF, IL-12, IL-2, TNF,

IFN, IL-18, IL-3, IL-4, IL-8, IL-9, IL-13, IL-10, IL-14, IL-15, G-SCF, IFN alpha, IFN beta, IFN gamma, TGF alpha, TGF beta, and the like. Cytokines are known in the art and are readily available in the literature or commercially. Many animal and human tumors have been shown to produce cytokines, such as IL-4, IL-10, TGF-B, that are potent modulators of the immune response and that protect tumors from immune-mediated destruction. The production of IL-4, IL-10 or TGF-B by tumors may achieve this protective effect by suppressing the induction of cellular immunity, including the elaboration of CTL responses. Alternatively, cytokines that support CTL responses can be exogenously added to help in the balance between induction of anti-tumor cell mediated and non-tumor-destructive humoral responses. Several such exogenous cytokines show utility in experimental mouse vaccination models which are known to enhance CTL responses, including GM-CSF, IFN and IL-2. An example of an effective exogenous cytokine that can be used is GM-CSF. GM-CSF is reported to enhance the expression of the so called "co-stimulatory" molecules, such as B7-1 or B7-2 on antigen presenting cells (APC). These co-stimulatory molecules are important players in the variety of interactions that occur during stimulation of CTL by APC. Moreover, GM-CSF is known to induce activation of APCs and to facilitate growth and differentiation of APCs, thereby making these APCs important CTL stimulating cells available both in greater numbers and potency.

[0133] Immunogenic compositions can additionally contain non-target antigens in order to improve the response to the target antigen. Thus co-induction of a helper response, such as Th and/or B cell immunity against non-self or foreign antigens not expressed within the tumoral process or in the body, can result in a substantial improvement in the magnitude and quality of the immune response to the "self" or "self-modified" target antigens expressed within the tumor or underlying stroma. For example, co-initiating a Th immune response against a non-target antigen such as tetanus toxoid can result in the generation of helper cells with bystander effect relative to generation of CTL or B cell responses against the target tumor or self antigens. Any defined sequence expressing or encompassing peptide motifs that bind to at least one class II MHC protein expressed by recipient, where such sequences are non-homologous or contain non-homologous segments relative to self antigens, can be used. Preferably, such sequences are of microbial origin and shown to be immunogenic in

HLA-defined or broader populations. In addition to tetanus toxoid (whole or portions, including, but not limited to, portions that are 90%, 80%, 75%, 70%, 60%, 50%, 40%, 30%, 25%, 20%, 15%, 10%, or 5% of a whole toxoid), further examples include, but are not limited to, sequences derived from HBVcore, influenza hemagglutinin, Plasmodium circumsporozoite antigen, and HTLV-1 envelope protein, and fragments of these sequences that are 90%, 80%, 75%, 70%, 60%, 50%, 40%, 30%, 25%, 20%, 15%, 10%, or 5% of the respective full-length sequences. In some embodiments, the tetanus toxoid portion is 5% to 90% of a whole toxoid, in other embodiments, the portion is 15% to 80% of a whole toxoid, in still other embodiments, the toxoid portion is 25% to 70% of a whole toxoid, in yet other embodiments, the toxoid portion is 35% to 60% of a whole toxoid, in still other embodiments, the toxoid portion is 45% to 55% of a whole toxoid. Similarly, co-administration of a strongly immunogenic B cell epitope (a non-self antigen) with or without a Th epitope (a non-self antigen) with target epitopes (self, tumoral) in a cognate fashion (that is, within the same molecule), can result in improved immune response, or even break of tolerance (T cell) against the therapeutic target, via immune antibody-antigen complexes and bystander T cell help.

Delivery of the Antigen

[0134] While not wanting to be bound by any particular theory, it is thought that T cells do not have a functional memory that is long-lived. Antibody-mediated B-cell memory, on the other hand, appears to have a long-lived effector memory. Thus, delivering an antigen that induces a CTL response is most preferably done over time to keep the patient's immune system appropriately stimulated to attack the target cells. In one approach the presence of antigen is maintained virtually continuously within the lymphatic system to maintain effector CTL function as disclosed in U.S. Patent Application No. 09/776,232 (Pub. No.20020007173 A1), entitled "A METHOD OF INDUCING A CTL RESPONSE," which is hereby expressly incorporated by reference. In another approach T cell memory is repeatedly induced, and re-amplified and reactivated as described in Provisional U.S. Patent Application No. 60/479,393, entitled "METHODS TO CONTROL MAGNITUDE AND QUALITY THE MHC CLASS I-RESTRICTED IMMUNE RESPONSE," filed June 17, 2003, and in U.S. Patent Application No. 10/871,707, entitled "METHODS TO ELICIT,

ENHANCE AND SUSTAIN IMMUNE RESPONSES AGAINST MHC CLASS I-RESTRICTED EPITOPES, FOR PROPHYLACTIC OR THERAPEUTIC PURPOSE” (Pub. No. 2005-0079152 A1), filed June 17, 2004, each of which is hereby incorporated by reference in its entirety. While it has been suggested that antigens and adjuvants can be prepared as biodegradable microspheres or liposomes, none of these preparations have thus far provided a CTL response that is useful for attacking cancer cells or pathogens on a long term basis. Preferably, delivery of the antigen is sustained over the desired period of time at a level sufficient to maintain the antigen level to obtain the desired response. In one embodiment, a reservoir having fluid antigen composition can be used to deliver the antigen such that it reaches the animal's lymphatic system. While much of the following discussion focuses on the use of infusion to deliver the antigen it is also possible to use bolus injections directly into the lymphatic system, the number and frequency of which will depend on the persistence of antigen conferred by the particular form and formulation of antigen used.

[0135] Ultimately antigen finds its way into the lymphatic system in order to most efficiently stimulate CTL. Delivery of antigen can involve infusion into various compartments of the body, including but not limited to subcutaneous, intravenous, intraperitoneal and intralymphatic, the latter being preferred. While each of these points of infusion results in antigen uptake into the lymphatic system, the relative amounts of antigen needed to induce a beneficial CTL response varies according to the site of infusion. In general, direct infusion of antigen into the lymph system is deemed to be the most efficient means of inducing a CTL response, however, any delivery route can be used. Pump systems are capable of delivering material quantities of antigen in a range that is suitable for inducing a CTL response through delivery to all compartments of the body. CTL stimulation following delivery of antigen via the various routes will vary depending on the properties of different antigens, including factors that influence antigen behavior in the body and its rate of equilibration to (or longevity in) the lymph, such as antigen stability in the body fluid, solubility of antigen in body fluid, binding affinity for HLA and potency as a stimulator of CTL.

[0136] In a preferred embodiment, introduction of the antigen is done as directly as possible to the lymphatic system to avoid the destruction of the antigen by metabolism in

the body. When introduction of a fluid antigen composition occurs subcutaneously, larger quantities of antigen are needed to assure enough antigen reaches the lymphatic system. Such subcutaneous injection is contemplated by the invention disclosed herein, depending on factors such as cost, stability of the antigen, how quickly the antigen gets to the lymph system, how well it equilibrates with the lymph, and other factors that the attending doctor or specialist will recognize. Subcutaneous delivery generally can require 100 to 1000 times more antigen than direct delivery to the lymph system. It is preferable, therefore, that the antigen composition is introduced through a device for local administration to the lymphatic system, *e.g.*, the spleen, a lymph node, or a lymph vessel. The device for local administration can be positioned outside the patient or implanted into the patient. In either case, the device can have a reservoir to hold the fluid antigen-containing composition, a pump to transfer the composition, and a transmission channel leading from the reservoir to be directed to the preferred region of administration in the patient's body. In either case it is preferably portable.

[0137] For the device positioned outside the patient's body (the external device), there are numerous devices used for delivering insulin to diabetic patients that are useful in delivering antigen according to the embodiments described herein. Generally these devices can be comprised of a reservoir for holding the antigen composition (instead of insulin), a programmable pump to pump the composition out of the reservoir, a transmission channel or line for transmitting the composition, and a means to introduce the composition into the animal's body to ultimately reach the lymphatic system.

[0138] Preferably, the reservoir for the antigen composition should be large enough for delivery of the desired amount of antigen over time and easily refillable or replaceable without requiring the user to reinsert the means for introducing the antigen composition to the lymph system.

[0139] In preparing the antigen compositions of embodiments of the invention disclosed herein, a composition (preferably aqueous) can be prepared to be compatible with the lymph system and physiologically acceptable to the animal being treated. Relevant considerations include, for example, the physicochemical properties of the antigen, such as the isoelectric point, molecular weight, glycosylation or other post-translational modification, and overall amino acid composition. These properties along with any known behavior of the

drug in different solutions (*e.g.*, different buffers, cofactors, etc.) as well as its *in vivo* behavior can help guide the choice of formulation components. One parameter that impacts all the major degradation pathways is the solution pH. Thus, the initial formulations also assess the pH dependence of the degradation reactions and the mechanism for degradation, which can often be determined from the pH dependence to determine the stability of the protein in each solution. Rapid screening methods usually involve the use of accelerated stability at elevated temperatures (*e.g.*, 40° C) using techniques known in the art.

[0140] In general the antigen compositions useful in embodiments described herein can be suitable for parenteral injection, in very small quantities. As such a composition should be free of contamination and have a pH compatible with the lymphatic system. However, because very small quantities of the antigenic composition will be delivered it need not be the same pH as blood or lymph, and it need not be aqueous-based. The preferable pH range that is compatible is from about 6.7 - 7.3 and can be prepared using water for injection to meet USP specifications (see Remington: The Science and Practice of Pharmacy, Nineteenth Edition; Chapters 86-88, which is hereby incorporated by reference in its entirety). For antigens that are less soluble, a suitable cosolvent or surfactant can be used, such as dimethyl sulfoxide (DMSO) or PLURONIC brand surfactants. Generally, a standard saline solution that is buffered with a physiologically acceptable weak acid and its base conjugate, *e.g.*, a phosphate or citrate buffering system, will be the basis of the antigen composition. In some cases, a small amount of an antioxidant may be useful to stabilize the composition and prevent oxidation. Factors to consider in preparing the antigen compositions can be found in the 1994 American Chemical Society book entitled "Formulation and Delivery of Proteins and Peptides" (Acs Symposium Series, No. 567) by Jeffery L. Cleland and Robert Langer (Editor), which is hereby incorporated by reference in its entirety.

[0141] For nucleic acid encoded antigens similar considerations can apply, although the variety of physico-chemical properties encountered with polypeptides is absent, so that acceptable formulations will have nearly universal applicability. As seen in Examples 6-10, plasmid DNA in standard phosphate buffered saline (PBS) is an acceptable and effective formulation. In some embodiments of the invention, DNA is administered continuously or intermittently at short intervals, from a reservoir worn on, or implanted in,

the patient's body. It is preferable that the DNA be maintained in a soluble, stable form at or near body temperature over a period of time measured minimally in days. In such applications where the formulated nucleic acid will be delivered from a reservoir over a period of several days or longer, the stability of the nucleic acid at room or body temperature for that period of time, as well as its continued sterility, take on increased importance. The addition of bacteriostatic agents (e.g., benzyl or ethyl alcohol) and chelating agents (e.g. EDTA) is useful toward these ends. Formulations containing about 0.5-2 % ethyl alcohol, 0.25-0.5mM EDTA generally perform well. Such formulations are also appropriate for bolus injections.

[0142] Generally the amount of the antigen in the antigen composition will vary from patient to patient and from antigen to antigen, depending on such factors as the activity of the antigen in inducing a response and the flow rate of the lymph through the patient's system. In general the antigen composition may be delivered at a rate of from about 1 to about 500 microliters/hour or about 24 to about 12000 microliters/day. The concentration of the antigen is such that about 0.1 micrograms to about 10,000 micrograms of the antigen will be delivered during 24 hours. The flow rate is based on the knowledge that each minute approximately about 100 to about 1000 microliters of lymph fluid flows through an adult inguinal lymph node. The objective is to maximize local concentration of vaccine formulation in the lymph system. A certain amount of empirical investigation on patients will be necessary to determine the most efficacious level of infusion for a given vaccine preparation in humans.

[0143] To introduce the antigen composition into the lymphatic system of the patient the composition is preferably directed to a lymph vessel, lymph node, the spleen, or other appropriate portion of the lymphatic system. Preferably, the composition is directed to a lymph node such as an inguinal or axillary node by inserting a catheter or needle to the node and maintaining the catheter or needle throughout the delivery. Suitable needles or catheters are available made of metal or plastic (e.g., polyurethane, polyvinyl chloride [PVC], TEFLON, polyethylene, and the like). In inserting the catheter or needle into the inguinal node for example, the inguinal node is punctured under ultrasonographic control using a Vialon™ Insyte-W™ cannula and catheter of 24G3/4 (Becton Dickinson, USA) which is

fixed using Tegaderm™ transparent dressing (Tegaderm™ 1624, 3M, St. Paul, MN 55144, USA). This procedure is generally done by an experienced radiologist. The location of the catheter tip inside the inguinal lymph node is confirmed by injection of a minimal volume of saline, which immediately and visibly increases the size of the lymph node. The latter procedure allows confirmation that the tip is inside the node. This procedure can be performed to ensure that the tip does not slip out of the lymph node and can be repeated on various days after implantation of the catheter. In the event that the tip does slip out of location inside the lymph node, a new catheter can be implanted.

Formulation and Treatment protocol

[0144] There are several approaches to utilizing the combination of TuAAs with DNA vaccines. A first approach is to include all the antigens or epitopes from all the antigens in a given combination into a single DNA expression vector. This approach has the advantages of simplicity for manufacturing and administration to patients. However, in some instances, epitope competition can limit the usefulness of this approach. That is, it is possible that only the most immunogenic epitope will elicit an immune response when a vaccine with several epitopes representing all TuAAs in the combination is given to patients. It is also more difficult to design and construct a DNA vaccine in which all epitopes are expressed at high efficiencies. Nevertheless, because the procedure for treating patients is simple and uniform within each type of cancer, the cost is likely to be lower than for the other approaches described below.

[0145] An alternate approach is to include only one antigen or epitopes of one antigen in a DNA expression vector. This approach has the advantages of simplicity in designing and constructing the DNA vector, flexibility, and customized administration to patients. If a large number of individual TuAA vaccines are available, then one can customize treatment for each individual patient based on the TuAA expression profile of his or her tumor. For example, if the standard combination for treating a given type of cancer is TuAAs A, B, and C (where A, B, and C designate different tumor associated antigens), but a patient's tumor expresses TuAAs A, C, and Z (but not B), then the patient can be treated with separate vaccines for each of A, C, and Z. This flexibility and customizability improves the success rate of immunotherapy because antigen redundancy can be achieved for each patient.

However, the procedure of treating the patient can be more complex. For example, delivery using this approach can include a sequential administration scheme (one antigen at a time), or injection into multiple, anatomically separate sites of the patient at about the same time.

[0146] Still another approach is to combine epitopes from multiple TuAAs that have similar immunogenicity into a DNA expression vector (more than one vector may be used for some combinations).

[0147] A profile of the antigen expression of a particular tumor can be used to determine which antigen or combination of antigens to use. Exemplary methodology and specific antigenic combinations of particular benefit in directing an immune response against particular cancers are disclosed in U.S. Provisional Application No. 60/479,554, filed on June 17, 2003, U.S. Patent Application No. 10/871,708 (Publication No. 20050079152 A1), filed on June 17, 2004, and PCT Patent Application No. PCT/US2004/019571, filed June 17, 2004, U.S. Provisional Patent Application No. 60/640,598, filed December 29, 2004, all entitled "COMBINATIONS OF TUMOR-ASSOCIATED ANTIGENS IN VACCINES FOR VARIOUS TYPES OF CANCER", each of which is also hereby incorporated by reference in its entirety.

[0148] Patients that can benefit from such methods of immunization can be recruited using methods to define their MHC protein expression profile and general level of immune responsiveness. In addition, their level of immunity can be monitored using standard techniques in conjunction with access to peripheral blood. Finally, treatment protocols can be adjusted based on the responsiveness to induction or amplification phases and variation in antigen expression. For example, rather than amplifying after some set number of entrainment doses, repeated entrainment doses can be administered until a detectable response is obtained, and then amplifying peptide dose(s) can be administered. Similarly, scheduled amplifying or maintenance doses of peptide can be discontinued if their effectiveness wanes, antigen-specific regulatory T cell numbers rise, or some other evidence of tolerization is observed, and further entrainment can be administered before resuming amplification with the peptide. The integration of diagnostic techniques to assess and monitor immune responsiveness with methods of immunization is discussed more fully in Provisional U.S. Patent Application No. 60/580,964, filed on June 17, 2004, and U.S. Patent Application

No. ____/____ (Attorney Docket No. MANNK.040A), filed on same date as the instant application, both entitled "IMPROVED EFFICACY OF ACTIVE IMMUNOTHERAPY BY INTEGRATING DIAGNOSTIC WITH THERAPEUTIC METHODS," which is hereby incorporated by reference in its entirety.

[0149] Combination of active immunotherapies, as disclosed herein, with other treatment modalities can increase the susceptibility of tumoral processes to the elicited immune response and thereby result in increased therapeutic benefit. Tumor debulking prior to or during active immunotherapy increases the potential for any particular level of immune response to slow or halt disease progression or to bring about tumor regression or elimination. Additionally, tissue damage, necrosis, or apoptosis initiated with antibody therapy, radiotherapy, biotherapy, chemotherapy, passive immunotherapy or surgery, can facilitate the active immunotherapeutic approach via general inflammation resulting in recruitment of immune effector cells including antigen-specific effectors. In general, any method to induce a transient or more permanent general inflammation within one or multiple tumors / metastatic lesions can facilitate the active immunotherapy. Alternatively or in addition to enabling recruitment of effectors, general inflammation can also increase the susceptibility of target cells to immune mediated attack (e.g., as interferons increase expression of target molecules on cancer cells and underlying stroma). Still other strategies to increase susceptibility of tumor cells to immune mediated attack – by providing factors that interfere with the "stress response" or increase target molecules on cancer cells or stromal cells – can synergize with active immunotherapy.

[0150] Many variations and alternative elements of the invention have been disclosed. Still further variations and alternate elements will be apparent to one of skill in the art. Among these variations, without limitation, are the specific number of antigens in a screening panel or targeted by a therapeutic product, the type of antigen, the type of cancer, and the particular antigen(s) specified. Various embodiments of the invention can specifically include or exclude any of these variations or elements.

[0151] Each of the references cited herein is hereby incorporated herein by reference in its entirety.

[0152] The following examples are for illustrative purposes only and are not intended to limit the scope of the embodiments in any way.

Examples

Example 1

TuAA analysis and selection of combinations

[0153] The presence of TuAAs was measured by Real-Time PCR (RT-PCR). Briefly, total RNA was isolated from tumor specimens by standard methods and cDNA was made with standard reverse transcription procedures. Complementary DNA (cDNA) was amplified with specially designed, gene specific, primers that anneal only to cDNA but not genomic DNA. TuAA expression patterns of 12 ovarian and 7 colorectal tumor specimens were analyzed by RT-PCR. The results are summarized in the Table 4 below.

Table 4

	Total #	PRAME	NY-ESO-1	SSX-2	PSMA	MAGE1	MAGE3
Ovarian	12	12	5	6	6	4	3
Colorectal	7	5	1	2	5	0	1

Example 2

Ovarian Cancer

[0154] In the case of ovarian cancer, all samples analyzed were positive for PRAME. Thus the inclusion of PRAME in the combination improves coverage of the cases with ovarian cancer.

[0155] In order to achieve antigen redundancy and improve coverage in a large population, combinations of other antigens in addition to PRAME were considered. SSX-2 as well as PSMA were present in 6 of the 12 cases individually, but the combination of SSX-2 and PSMA provided coverage in 9 of 12 cases. Although NY-ESO-1 and SSX-2 were only present in 5 and 6 of the 12 cases, respectively, either NYESO-1 or SSX-2 was detected in 7 of the 12 cases.

[0156] Thus, for assembling panels, the combination of PRAME, SSX-2, and PSMA or PRAME, NY-ESO-1, and SSX-2 provided preferable coverage and redundancy compared to the combination of PRAME and PSMA or the combination of PRAME and SSX-2. The combination of PRAME, SSX-2, and PSMA provided excellent coverage of cases and good antigen redundancy because the majority of ovarian tumor samples analyzed had at least two of the four TuAA in the combination present. The combination of PRAME, SSX-2, PSMA, and NY-ESO-1 provided more preferred antigen redundancy, and thus, lower possibility of tumor escape.

Example 3

Colorectal cancer

[0157] In the case of colorectal cancer, PRAME and PSMA were each detected in 5 of the 7 samples analyzed. In 6 of the 7 cases, either PRAME or PSMA was detected. Although SSX-2 was only detected in 2 of 7 cases, both SSX-2-PRAME and SSX2-PSMA combinations increased coverage to 6 of 7. Similarly, although NYESO-1 was detected in only 1 of 7 cases, the combination of NY-ESO-1-PRAME as well as the NYESO-1-PSMA combination increased coverage to 6 of 7. The addition of SSX-2 or NYESO-1 to the PRAME and PSMA combination improved coverage to 7 of 7. Thus, for assembling panels, the combination of PRAME, PSMA, and NYESO-1, or the combination of PRAME, PSMA, and SSX-2 provided good coverage of cases and redundancy of antigens for a majority of patients. The combination of PRAME, PSMA, NY-ESO-1, and SSX-2 provided further redundancy.

Example 4

Pancreatic Cancer

[0158] Real-Time PCR (RT-PCR) was utilized to determine the presence of PRAME, SSX2, NY-ESO-1, and PSMA. Briefly, total RNA was isolated from 5 pancreatic tumor specimens by standard methods and cDNA was made with standard reverse transcription procedures. Complementary DNA (cDNA) was amplified with specially designed, gene specific, primers that anneal only to cDNA but not genomic DNA.

[0159] In the pancreatic cancer specimens, the presence of PRAME, NYESO-1, SSX-2, and PSMA was detected in 100%, 40%, 20%, and 100% of the specimens,

respectively (see Table 5). Elsewhere, PSMA and over-expression of HER2/neu were reported to be present in 100% and 21% of pancreatic tumors, respectively (Chang SS et al, Cancer Res 1999, 59:3192; Safran H et al, Am J Clin Oncol. 2001, 24:496, each of which is hereby incorporated by reference in its entirety). Although over-expression of HER2/neu may render the cancer tissue a preferred target, thus providing some specificity for immunotherapy, low level expression of HER2/neu in normal tissues remains a concern. Thus, for assembling panels of antigens, the combination of NYESO-1, SSX-2, plus PRAME or PSMA provides excellent coverage and some redundancy for pancreatic cancer. Inclusion of both PRAME and PSMA significantly improves redundancy.

Table 5

TAA	PRAME	SSX2	NY-ESO-1	PSMA
Detection Freq.	5/5	1/5	2/5	5/5
% positive	100	20	40	100

Example 5

Renal cell carcinoma

[0160] For renal cell carcinoma, SSX-2, PSMA and PRAME were detected with frequencies of 5, 100 and 40%, respectively (Sahin, U et al, Clin Cancer Res. 2000, 6:3916; Chang SS et al, Urology 2001, 57:801; Neumann E et al, Cancer Res. 1998, 58:4090, each of which is hereby incorporated by reference in its entirety). Thus, the combination of PSMA and PRAME provides excellent coverage and redundancy for renal cell carcinoma. Adding SSX-2 to the combination of PSMA and PRAME improves redundancy.

Example 6

Non-small cell lung cancer

[0161] For non-small cell lung cancer, the reported presence of NYESO-1, SSX-2, MAGE-3, BAGE, over-expression of Her2/neu, and PSMA was 21, 15, 60, 6, 16, and 100%, respectively (Scanlan MJ et al, Cancer lett 2000, 150:155; Chang SS et al, Cancer Res 1999, 59:3192; Selvaggi G et al, Cancer 2002, 94:2669, each of which is hereby incorporated by reference in its entirety). Thus, the combination of NYESO-1, SSX-2, MAGE-3, and PSMA provides coverage and antigen redundancy for the immunotherapy of non-small cell lung cancer.

Example 7Melanoma

[0162] For melanoma, Melan A, Tyrosinase, NYESO-1, and SSX-2 were reported to be present in 92, 92, 41, and 35% of tumor specimens, respectively (Fetsch PA, et al, Cancer 1999, 87:37; Fetsch PA, et al, Cancer 2000, 90:252; Schultz-Thater E et al, Br J Cancer 2000, 83:204; Sahin, U et al, Clin Cancer Res. 2000, 6:3916). Therefore, the combination of Melan A, Tyrosinase, NYESO-1, and SSX-2 provides excellent coverage and antigen redundancy for the immunotherapy of melanoma. Significant redundancy is achieved using tyrosinase and melan-A together, or by combining NY-ESO-1 and SSX-2 with either of tyrosinase or melan-A.

Example 8

[0163] Further studies involving the foregoing tumor types established more robust support for the observed expression patterns and preferred panels of TuAA. A total of 34 ovarian, 44 colon, 18 renal, and 13 pancreatic tissue samples obtained from various vendors were analyzed for tumor-associated antigen expression using qRT-PCR. The results of these assays showed that PRAME and PSMA were expressed frequently (ranging from 68% to 100%) in all four types of tumors studied. NY-ESO-1 and SSX2 were expressed in 20% to 40% of ovarian and pancreatic tumors, although the expression of NY-ESO-1 and SSX-2 in colorectal and renal tumors was substantially lower (6% to 12%).

Table 6:Overall Expression Profiles for Tumor Associated AntigensFrom RTPCR analysis of Primary Tumors and Metastases

Tumor-Associated Antigen	% Samples Expressing a Given Antigen			
	Ovarian ^a	Renal ^b	Pancreatic ^c	Colorectal ^d
SSX2	36	6	20	8
NY-ESO-1	30	6	40	12
PRAME	97	83	80	76
PSMA	91	100	100	68
MAGE-1	27	6	33	8
MAGE-3	30	22	42	20
SCP-1	30	11	0	0
CEA	30	0	58	92

^a 33 samples (27 primary tumors and 6 metastases)

^b 18 samples (18 primary tumors)

^c 15 samples (14 primary tumors and 1 metastasis; PSMA on 10 samples)

^d 25 samples (13 primary tumors and 12 metastases)

Example 9

Schedule of immunization with plasmids expressing epitopes from two antigens

[0164] Two groups of HHD mice (n=4) were immunized via intra lymph node injection with either pSEM expressing Melan-A₂₆₋₃₅A27L (ELA) and pCBP expressing SSX-2₄₁₋₄₉ as a mixture; or with pSEM in the left inguinal lymph node and pCBP in the right inguinal lymph node, twice, at day 0 and 4 as shown in Figure 1. The amount of the plasmid was 25µg/plasmid/dose. Two weeks later, the animals were sacrificed, and cytotoxicity was measured against T2 cells pulsed or not with peptide.

Example 10

Co-administration of different vectors carrying distinct antigens

[0165] The animals immunized as described in Example 9, were sacrificed and splenocytes from each group pooled and stimulated with the two peptides (ELA or SSX-2₄₁₋₄₉) in parallel. The cytotoxicity was measured by incubation with Cr⁵¹-tagged, peptide loaded T2 target cells. Data in Figure 2 show mean of specific cytotoxicity (n=4/group) against various target cells.

[0166] The results show that use of plasmid mixture interferes with the response elicited by pCBP plasmid; however, segregating the two plasmids relative to site of administration rescues the activity of pCBP. Thus, the co-administration of different vectors carrying distinct antigens can result in establishment of a hierarchy with regard to immunogenicity. Vector segregation can rescue the immunogenicity of the less dominant component, resulting in a multivalent response.

Example 11

Rescue of Multivalent Response by Addition of Peptide Boost Steps

[0167] Four groups of HHD mice (n=6) were immunized via intra lymph node injection with either pSEM and pCBP as a mixture; or with pSEM in the left inguinal lymph node and pCBP in the right inguinal lymph node, twice, at day 0 and 4 as shown in Figure 3.

As a control, mice were immunized with either pSEM or pCBP plasmid. The amount of the plasmid was 25µg/plasmid/dose. Two weeks later, the animals were boosted with melan A and/or SSX-2 peptides, mirroring the plasmid immunization dose and combination. Two weeks later, the animals were challenged with splenocytes stained with CFSE and loaded or not with Melan A or SSX-2 peptide, for evaluation of *in vivo* cytotoxicity.

Example 12

Peptide amplification rescues the immunogenicity of the less dominant epitope

[0168] Mice were immunized as described in Example 11 and challenged with HHD littermate splenocytes coated with ELA or SSX-2 peptide, employing a triple peak CFSE *in vivo* cytotoxicity assay that allows the assessment of the specific lysis of two antigen targets simultaneously. Equal numbers of control-CFSE^{lo}, SSX-2₄₁₋₄₉-CFSE^{med}, and ELA-CFSE^{hi} cells were intravenously infused into immunized mice and 18 hours later the mice were sacrificed and target cell elimination was measured in the spleen (Figure 4) by CFSE fluorescence using a flow cytometry. Figure 4 shows the percent specific lysis of the SSX-2 and Melan-A antigen targets from individual mice, as well as the mean and SEM for each group.

[0169] The results show that immunizing the animals with a mixture of the two vaccines comprising plasmids followed by peptides generated immunity to both antigens and resulted in the highest immune response, representing an average SSX-2 percent specific lysis in the spleen of 30+/-11, and an average Melan-A percent specific lysis of 97+/-1.

Example 13

Clinical practice for entrain-and-amplify immunization

[0170] The data in figures 2 and 4 suggest two scenarios for achieving a strong multivalent response in the clinic, shown in Figure 5. In the first scenario (A), use of peptides for boosting restores multivalent immune responses even if plasmids and peptides are used as mixtures. In the second scenario (B), segregation of plasmid and peptide components respectively, allows induction of multivalent immune responses.

Example 14

MKC1207: an Entrain-and-Amplify Therapeutic for Melanoma

[0171] MKC1207 comprises the plasmid pSEM (described in U.S. Patent Application No. 10/292,413, filed November 7, 2002, which is hereby incorporated by reference in its entirety, in which it is referred to as pMA2M) and peptides corresponding to Melan-A 26-35 and tyrosinase 369-377. The plasmid encodes the A27L analogue of the Melan-A epitope and the native tyrosinase epitope sequence. The plasmids encode both of these epitopes in such a manner that they can be expressed and presented by pAPC. In alternate embodiments of the therapeutic the peptides can comprise the native sequence or be analogues such as those disclosed in U.S. Patent Application No. ____/____ (Attorney Docket No. MANNK.051A) entitled EPITOPE ANALOGUES, filed on date even with this disclosure, and incorporated herein by reference in its entirety.

[0172] Briefly, the plasmid is administered intranodally to the inguinal lymph nodes as an entraining immunogen. Subsequently the peptides are administered intranodally, one to the left node, the other to the right as amplifying immunogens. The entrain-and-amplify protocol is described in greater detail in U.S. Patent Application Nos. 10/871,707, filed on June 17, 2004 and 60/640,402, filed on June 17, 2003, each of which was previously incorporated by reference.

[0173] Melanoma patients can be screened according to the methods disclosed herein and MKC1207 administered to patients whose tumor antigen profile includes Melan-A and/or tyrosinase. In a preferred embodiment the patient's tumor tissue also expresses HLA-A2, particularly HLA-A*0201.

Example 15

MKC1106: a Tetravalent Entrain-and-Amplify Therapeutic for Carcinoma

[0174] MKC1106 comprises the plasmids pCBP (described in U.S. Patent Application No. 10/292,413, filed November 7, 2002, which is hereby incorporated by reference in its entirety) and pRP12 (described in U.S. Provisional Application No. ____/____ (Atty Docket No. MANNK.053PR), entitled METHODS AND COMPOSITIONS TO ELICIT MULTIVALENT IMMUNE RESPONSES AGAINST DOMINANT AND SUBDOMINANT EPITOPES, EXPRESSED ON CANCER CELLS AND TUMOR

STROMA, filed on date even with this disclosure, and incorporated herein by reference in its entirety; and peptides corresponding to NY-ESO-1 157-165, SSX-2 41-49, PRAME 425-433 and PSMA 288-297. The plasmids encode both of these epitopes in such a manner that they can be expressed and presented by pAPC. In alternate embodiments of the therapeutic the peptides can comprise the native sequence or be analogues such as those disclosed in U.S. Patent Application Nos. __/____ (Attorney Docket No. MANNK.038A), entitled SSX-2 PEPTIDE ANALOGS, and __/____ (Attorney Docket No. MANNK.039A), entitled NY-ESO-1 PEPTIDE ANALOGS, and __/____ (Attorney Docket No. MANNK.051A), entitled EPITOPE ANALOGS, and U.S. Provisional Patent Application No. __/____ (Attorney Docket No. MANNK.052PR), entitled EPITOPE ANALOGS, each of which is filed on date even with the instant application, and each of which is expressly incorporated by reference in its entirety.

[0175] Briefly, the plasmids are administered intranodally to the inguinal lymph nodes, one to the left side and one to the right, as an entraining immunogen. Subsequently the peptides are sequentially administered intranodally, two on separate days to the left node, the other two on separate days to the right as amplifying immunogens. It is preferred, but not absolutely required that the peptides be administered to the same lymph node that received the plasmid encoding the corresponding epitopes. The entrain-and-amplify protocol is described in greater detail in U.S. Patent Application Nos. 10/871,707, filed on June 17, 2004 and 60/640,402, filed on June 17, 2003, each of which is expressly incorporated by reference in its entirety.

[0176] Carcinoma patients, especially those with ovarian, colorectal, pancreatic, or renal cell carcinoma, can be screened according to the methods disclosed herein and MKC1106 administered to patients whose tumor profile includes PRAME, PSMA, NY-ESO-1, and/or SSX-2. The NY-ESO-1 epitope targeted by MKC1106 is also found in LAGE 1a/s, so the presence of this antigen in a profile would also be considered a match. As tumor antigen expression tends to be heterogeneous, any particular tissue sample is likely not to give a complete indication of all the antigens expressed. Thus, it is not necessary that a patient's profile contain all four of the antigens for that patient to be a candidate for treatment with MKC1106. However, preferably the profile contains 2, 3, or 4 of the antigens.

WHAT IS CLAIMED IS:

1. A method of matching a cancer condition in a patient with an immunotherapeutic agent, comprising the steps of:

assaying tumor tissue of the patient for two or more expressed tumor-associated antigens (TuAAs) in a preselected panel, to develop an antigen profile for the tumor; and

selecting an immunotherapeutic agent for the patient based on the profile, wherein the immunotherapeutic agent targets one or more of the expressed antigens in the profile.

2. The method of Claim 1, wherein at least one of the TuAAs is selected from the group consisting of a cancer testis antigen, a tissue-specific antigen, an oncofetal antigen, a differentiation antigen, a growth factor, a growth factor receptor, an adhesion factor, a signal transduction protein, a transcription factor, an oncogene product, a tumor suppressor gene product, and a microbial antigen.

3. The method of Claim 1, wherein the preselected panel comprises two or more antigens selected from the group consisting of an SSX protein, SSX-2, SSX-4, a MAGE protein, MAGE-1, MAGE-3, PRAME, NY-ESO-1, LAGE, PSMA, PSCA, SCP-1, melan-A/MART-1 and tyrosinase; and wherein the cancer condition is carcinoma.

4. The method of Claim 3, wherein the carcinoma is selected from the group consisting of breast, colorectal, prostate, pancreatic, lung, ovarian, renal cell, and melanocyte.

5. The method of Claim 1, wherein the immunotherapeutic agent is an active immunotherapeutic.

6. The method of Claim 1, wherein the immunotherapeutic agent comprises or encodes at least a segment of at least one of the expressed TuAAs.

7. The method of Claim 1, wherein the immunotherapeutic agent is a passive immunotherapeutic.

8. The method of Claim 7, wherein the immunotherapeutic agent is a monoclonal antibody.

9. The method of Claim 1, comprising at least two assaying steps carried out at different time points during the course of disease, wherein comparative information is obtained from the assaying steps.

10. The method of Claim 9, where the obtained information is used to implement, modify or withdraw a therapy.

11. The method of Claim 1, wherein the tumor is melanoma and the panel of TuAAs comprises at least two TuAAs selected from the group consisting of tyrosinase, melan-A/MART-1, NY-ESO-1, PRAME, an SSX protein, and a MAGE protein.

12. The method of Claim 11, wherein the SSX protein is SSX-2 or SSX-4.

13. The method of Claim 11, wherein the MAGE protein is MAGE-1 or MAGE-3.

14. The method of Claim 1, wherein the tumor is breast cancer and the panel of TuAAs comprises at least two TuAAs selected from the group consisting of NY-ESO-1, Her2/neu, an SSX protein, and a MAGE protein.

15. The method of Claim 1, wherein the tumor is colorectal cancer and the panel of TuAAs comprises at least two TuAAs selected from the group consisting of CEA, an SSX protein, PRAME, NY-ESO, LAGE, PSCA, SCP-1, PSMA and a MAGE protein.

16. The method of Claim 1, wherein the tumor is lung cancer and the panel of TuAAs comprises at least two TuAAs selected from the group consisting of PSMA, NY-ESO-1, SSX-2, and a MAGE protein.

17. The method of Claim 1, wherein the tumor is prostate cancer and the panel of TuAAs comprises at least two TuAAs selected from the group consisting of NY-ESO-1, PSA, PSCA, PSMA, an SSX protein, and a MAGE protein.

18. The method of Claim 1, wherein the tumor is ovarian cancer and the panel of TuAAs comprises at least two TuAAs selected from the group consisting of PRAME, PSMA, PSCA, a MAGE protein, SCP-1, an SSX protein, CEA, Her-2/Neu, NY-ESO-1, and LAGE.

19. The method of Claim 18, wherein the ovarian cancer is selected from the group consisting of serous carcinoma, non-serous carcinoma, mucinous (cell) carcinoma, and clear cell carcinoma.

20. The method of Claim 1, wherein the tumor is renal cancer and the panel of TuAAs comprises at least two TuAAs selected from the group consisting of an SSX protein, PRAME, NY-ESO, LAGE, PSCA, SCP-1, PSMA and a MAGE protein.

21. The method of Claim 1, wherein the tumor is pancreatic cancer and the panel of TuAAs comprises at least two TuAAs selected from the group consisting of an SSX protein, PRAME, NY-ESO, LAGE, PSCA, PSMA and a MAGE protein.

22. The method of Claim 1, wherein antigen expression is detected by a technique comprising at least one of RT-PCR, transcript determination, protein determination, epitope determination or any combination thereof.

23. The method of Claim 1, wherein antigen expression is detected on neoplastic cells, or tumor-associated stromal cells, or both.

24. The method of Claim 23, wherein the tumor-associated stromal cells are neovasculature.

25. The method of Claim 24, wherein the neovasculature-associated antigen is PSMA and the neoplastic cell antigen is selected from the group consisting of NY-ESO-1, SSX2, LAGE, and PRAME.

26. The method of Claim 1, wherein the tumor tissue comprises primary tumor tissue.

27. The method of Claim 1, wherein the tumor tissue comprises metastatic tumor tissue.

28. A method of matching a cancer condition in a patient with an immunotherapeutic regimen, comprising the steps of:

assaying the patient's tumor tissue for two or more expressed tumor-associated antigens (TuAAs) in a preselected panel, to develop an antigen profile for the tumor; and

selecting an immunotherapeutic regimen based on the profile, the regimen comprising administration of one or more immunotherapeutic agents targeting two or more antigens in the profile.

29. The method of Claim 28, wherein the regimen comprises administering both an active immunotherapeutic agent and a passive immunotherapeutic agent.

30. A method of matching a cancer condition in a patient with an immunotherapeutic agent, comprising the steps of:

- determining the patient's class I MHC type;
- assaying the patient's tumor tissue for two or more expressed tumor-associated antigens (TuAAs) in a preselected panel;
- assaying the patient's tumor tissue for the expression of MHC class I or β 2-microglobulin;
- selecting an immunotherapeutic agent for administration to the patient based on the assays, wherein the immunotherapeutic agent comprises or encodes an epitope restricted by the patient's class I MHC type, for each of two or more antigens expressed by the tumor.

31. The method of Claim 30, wherein antigen expression is detected on neoplastic cells, or tumor-associated stromal cells, or both.

32. The method of Claim 31, wherein the two or more antigens expressed by the tumor include an antigen expressed by a neoplastic cell and an antigen expressed by a tumor-associated stromal cell.

33. A method of confirming a cancer diagnosis comprising the steps of:
- assaying a patient's tumor tissue to detect one or more expressed polypeptides in a preselected panel, wherein the panel comprises two or more TuAAs and at least one lineage marker, to develop an expression profile for the tumor; and
 - confirming a cancer diagnosis based upon the expression profile.

34. The method of Claim 33, wherein the panel comprises at least three TuAAs selected from the group consisting of NY-ESO-1, CEA, PSA, PSMA, tyrosinase, melan-A/MART-1, an SSX protein, and a MAGE protein.

35. The method of Claim 33, wherein the diagnosis is melanoma and the lineage marker is selected from the group consisting of melan-A/MART-1, tyrosinase, and gp100.

36. The method of Claim 33, wherein the diagnosis is breast cancer and the lineage marker is selected from the group consisting of mammaglobin and prolactin-inducible protein (Brst2).

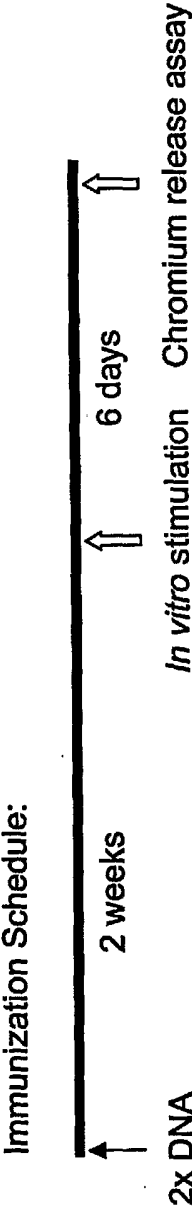
37. The method of Claim 33, wherein the diagnosis is colon cancer and the lineage marker is CEA.

38. The method of Claim 33, wherein the diagnosis is lung cancer and the lineage marker is thyroid transcription factor 1 (TTF1).

39. The method of Claim 33, wherein the diagnosis is prostate cancer and the lineage marker is selected from the group consisting of PSA and PSMA.

Schedule of immunization with plasmids (pCBP expressing SSX2 41-49; and pSEM expressing Melan A)

Schedule of immunization



Experimental Setup:

- Group 1: Plasmids separately (pCBP, pSEM)
- Group 2: Plasmids admixed (pCBP+pSEM)

FIG. 1

Co-administration of different vectors carrying distinct antigens results in establishment of a hierarchy in regard to immunogenicity.
 Vector segregation rescues the immunogenicity of the less dominant component, resulting in a multivalent response.

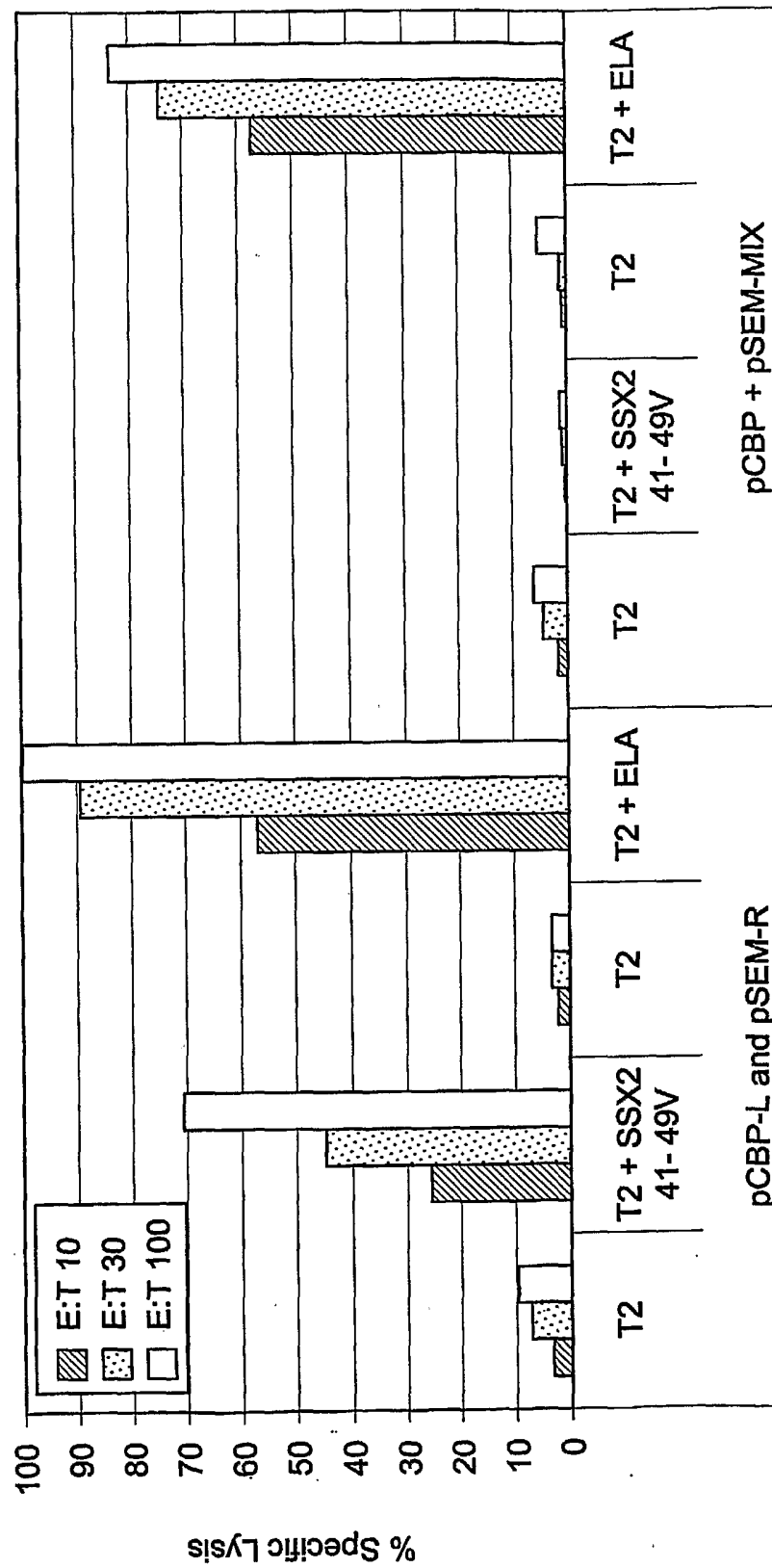
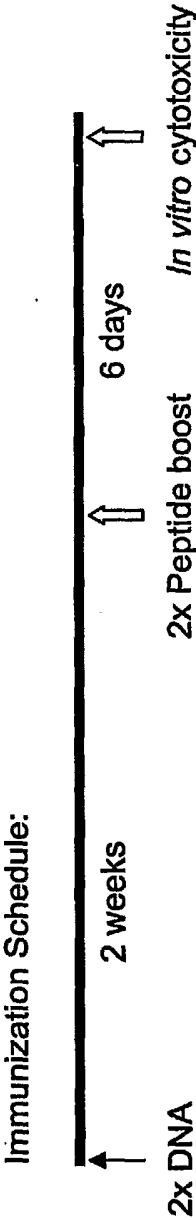


FIG. 2

Addition of peptide boost steps to the immunization protocol described in Fig. 1.

Schedule of immunization



Experimental Setup:

- Group 1: Naive controls
- Group 2: Mixture of plasmids followed by mixture of peptides
- Group 3: Plasmids and peptides into different lymph nodes
- Group 4: pSEM plasmid and melan A peptide only
- Group 5: pCBP plasmid and SSX2 peptide only

FIG. 3

Peptide boost rescues the immunogenicity of a less dominant epitope even when the vectors and peptides respectively, are used as a mixture.

<u>Animal #</u>	<u>Spleen Treatment</u>	<u>Specific Lysis (%)</u>	
		<u>SSX2</u>	<u>Melan A</u>
#3505	Control	Control	Control
#3473	Control	6	4
#3481	Control	8	6
#3951	Control	Control	Control
#3474	Control	-4	-8
#3513	Control	-3	-4
	Mean	2	-1
	SEM	4	4
#3125	pSEM + pCBP	71	95
#3075	pSEM + pCBP	26	93
#3088	pSEM + pCBP	10	94
#3081	pSEM + pCBP	22	100
#3078	pSEM + pCBP	44	100
#3102	pSEM + pCBP	9	100
	Mean	30	97
	SEM	11	1
#3076	L=pSEM, R=pCBP	16	37
#3112	L=pSEM, R=pCBP	15	88
#3068	L=pSEM, R=pCBP	7	93
#3051	L=pSEM, R=pCBP	46	100
#3146	L=pSEM, R=pCBP	4	100
#3103	L=pSEM, R=pCBP	13	100
	Mean	17	86
	SEM	7	11
#3111	pSEM	3	57
#3036	pSEM	6	94
#3052	pSEM	-1	95
#3067	pSEM		5
#3049	pSEM	1	100
#3039	pSEM		38
	Mean	2	65
	SEM	1	17
#3069	pCBP	26	-3
#3037	pCBP	15	3
#3042	pCBP	6	7
#3070	pCBP	11	11
#3046	pCBP	18	17
#3053	pCBP	33	15
	Mean	18	8
	SEM	4	3

FIG. 4

Methodology to induce strong, multivalent responses: reduction to practice in clinic

Schedule of immunization

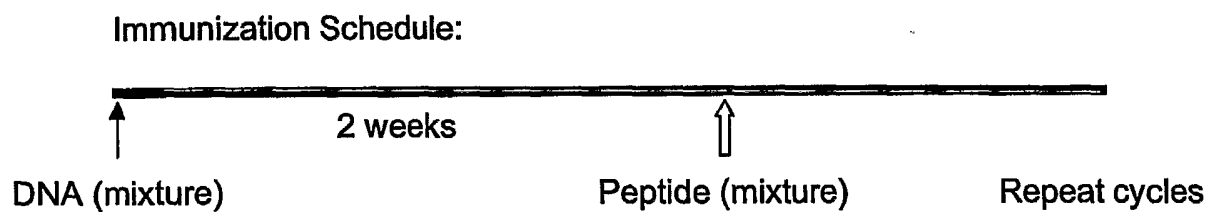


FIG. 5A

Schedule of immunization

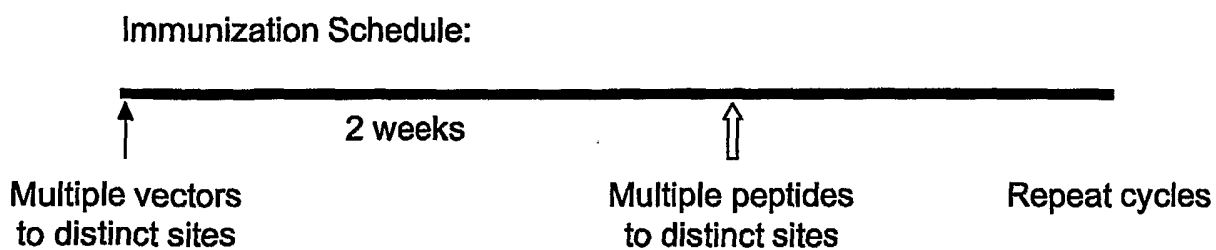


FIG. 5B

SEQUENCE LISTING

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Simard, John J.L.

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Pro His Leu Ala Gly Thr Glu Gln Asn Phe Gln Leu Ala Lys Gln Ile
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Gln Ser Gln Trp Lys Glu Phe Gly Leu Asp Ser Val Glu Leu Ala His
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Tyr Asp Val Leu Leu Ser Tyr Pro Asn Lys Thr His Pro Asn Tyr Ile
          115          120          125
Ser Ile Ile Asn Glu Asp Gly Asn Glu Ile Phe Asn Thr Ser Leu Phe
          130          135          140
Glu Pro Pro Pro Pro Gly Tyr Glu Asn Val Ser Asp Ile Val Pro Pro
145          150          155          160
Phe Ser Ala Phe Ser Pro Gln Gly Met Pro Glu Gly Asp Leu Val Tyr
          165          170          175
Val Asn Tyr Ala Arg Thr Glu Asp Phe Phe Lys Leu Glu Arg Asp Met

```

[illegible]

```

        675                680                685
His Val Ile Tyr Ala Pro Ser Ser His Asn Lys Tyr Ala Gly Glu Ser
    690                695                700
Phe Pro Gly Ile Tyr Asp Ala Leu Phe Asp Ile Glu Ser Lys Val Asp
705                710                715                720
Pro Ser Lys Ala Trp Gly Glu Val Lys Arg Gln Ile Tyr Val Ala Ala
    725                730                735
Phe Thr Val Gln Ala Ala Ala Glu Thr Leu Ser Glu Val Ala
    740                745                750

```

<210> 5
 <211> 309
 <212> PRT
 <213> Homo sapiens

```

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

```

<210> 6
 <211> 314
 <212> PRT

<213> Homo sapiens

<400> 6

```

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

```

<210> 7

<211> 180

<212> PRT

<213> Homo sapiens

<400> 7

```

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

```

				85				90				95			
Ala	Thr	Pro	Met	Glu	Ala	Glu	Leu	Ala	Arg	Arg	Ser	Leu	Ala	Gln	Asp
100				105				110							
Ala	Pro	Pro	Leu	Pro	Val	Pro	Gly	Val	Leu	Leu	Lys	Glu	Phe	Thr	Val
115				120				125							
Ser	Gly	Asn	Ile	Leu	Thr	Ile	Arg	Leu	Thr	Ala	Ala	Asp	His	Arg	Gln
130				135				140							
Leu	Gln	Leu	Ser	Ile	Ser	Ser	Cys	Leu	Gln	Gln	Leu	Ser	Leu	Leu	Met
145				150				155				160			
Trp	Ile	Thr	Gln	Cys	Phe	Leu	Pro	Val	Phe	Leu	Ala	Gln	Pro	Pro	Ser
165				170				175							
Gly	Gln	Arg	Arg												
180															

```
<210> 8
<211> 509
<212> PRT
<213> Homo sapiens
```

<400>	8															
Met	Glu	Arg	Arg	Arg	Leu	Trp	Gly	Ser	Ile	Gln	Ser	Arg	Tyr	Ile	Ser	
1				5					10					15		
Met	Ser	Val	Trp	Thr	Ser	Pro	Arg	Arg	Leu	Val	Glu	Leu	Ala	Gly	Gln	
			20					25					30			
Ser	Leu	Leu	Lys	Asp	Glu	Ala	Leu	Ala	Ile	Ala	Ala	Leu	Glu	Leu	Leu	
		35					40					45				
Pro	Arg	Glu	Leu	Phe	Pro	Pro	Leu	Phe	Met	Ala	Ala	Phe	Asp	Gly	Arg	
	50					55					60					
His	Ser	Gln	Thr	Leu	Lys	Ala	Met	Val	Gln	Ala	Trp	Pro	Phe	Thr	Cys	
65					70					75					80	
Leu	Pro	Leu	Gly	Val	Leu	Met	Lys	Gly	Gln	His	Leu	His	Leu	Glu	Thr	
				85					90					95		
Phe	Lys	Ala	Val	Leu	Asp	Gly	Leu	Asp	Val	Leu	Leu	Ala	Gln	Glu	Val	
			100					105					110			
Arg	Pro	Arg	Arg	Trp	Lys	Leu	Gln	Val	Leu	Asp	Leu	Arg	Lys	Asn	Ser	
		115					120					125				
His	Gln	Asp	Phe	Trp	Thr	Val	Trp	Ser	Gly	Asn	Arg	Ala	Ser	Leu	Tyr	
	130					135					140					
Ser	Phe	Pro	Glu	Pro	Glu	Ala	Ala	Gln	Pro	Met	Thr	Lys	Lys	Arg	Lys	
145					150					155					160	
Val	Asp	Gly	Leu	Ser	Thr	Glu	Ala	Glu	Gln	Pro	Phe	Ile	Pro	Val	Glu	
				165					170					175		
Val	Leu	Val	Asp	Leu	Phe	Leu	Lys	Glu	Gly	Ala	Cys	Asp	Glu	Leu	Phe	
			180					185					190			
Ser	Tyr	Leu	Ile	Glu	Lys	Val	Lys	Arg	Lys	Lys	Asn	Val	Leu	Arg	Leu	
		195				200						205				
Cys	Cys	Lys	Lys	Leu	Lys	Ile	Phe	Ala	Met	Pro	Met	Gln	Asp	Ile	Lys	
	210					215					220					
Met	Ile	Leu	Lys	Met	Val	Gln	Leu	Asp	Ser	Ile	Glu	Asp	Leu	Glu	Val	
225					230					235					240	
Thr	Cys	Thr	Trp	Lys	Leu	Pro	Thr	Leu	Ala	Lys	Phe	Ser	Pro	Tyr	Leu	
				245					250					255		
Gly	Gln	Met	Ile	Asn	Leu	Arg	Arg	Leu	Leu	Leu	Ser	His	Ile	His	Ala	
			260					265					270			
Ser	Ser	Tyr	Ile	Ser	Pro	Glu	Lys	Glu	Glu	Gln	Tyr	Ile	Ala	Gln	Phe	
		275				280						285				
Thr	Ser	Gln	Phe	Leu	Ser	Leu	Gln	Cys	Leu	Gln	Ala	Leu	Tyr	Val	Asp	
	290					295					300					
Ser	Leu	Phe	Phe	Leu	Arg	Gly	Arg	Leu	Asp	Gln	Leu	Leu	Arg	His	Val	
305					310					315					320	
Met	Asn	Pro	Leu	Glu	Thr	Leu	Ser	Ile	Thr	Asn	Cys	Arg	Leu	Ser	Glu	

```

          325          330          335
Gly Asp Val Met His Leu Ser Gln Ser Pro Ser Val Ser Gln Leu Ser
          340          345          350
Val Leu Ser Leu Ser Gly Val Met Leu Thr Asp Val Ser Pro Glu Pro
          355          360          365
Leu Gln Ala Leu Leu Glu Arg Ala Ser Ala Thr Leu Gln Asp Leu Val
          370          375          380
Phe Asp Glu Cys Gly Ile Thr Asp Asp Gln Leu Leu Ala Leu Leu Pro
385          390          395          400
Ser Leu Ser His Cys Ser Gln Leu Thr Thr Leu Ser Phe Tyr Gly Asn
          405          410          415
Ser Ile Ser Ile Ser Ala Leu Gln Ser Leu Leu Gln His Leu Ile Gly
          420          425          430
Leu Ser Asn Leu Thr His Val Leu Tyr Pro Val Pro Leu Glu Ser Tyr
          435          440          445
Glu Asp Ile His Gly Thr Leu His Leu Glu Arg Leu Ala Tyr Leu His
          450          455          460
Ala Arg Leu Arg Glu Leu Leu Cys Glu Leu Gly Arg Pro Ser Met Val
465          470          475          480
Trp Leu Ser Ala Asn Pro Cys Pro His Cys Gly Asp Arg Thr Phe Tyr
          485          490          495
Asp Pro Glu Pro Ile Leu Cys Pro Cys Phe Met Pro Asn
          500          505

```

<210> 9

<211> 1255

<212> PRT

<213> Homo sapiens

<400> 9

```

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

```

9/34

10/34

1235 1240 1245
 Leu Gly Leu Asp Val Pro Val
 1250 1255

<210> 10
 <211> 261
 <212> PRT
 <213> Homo sapiens

<400> 10
 Met Trp Val Pro Val Val Phe Leu Thr Leu Ser Val Thr Trp Ile Gly
 1 5 10 15
 Ala Ala Pro Leu Ile Leu Ser Arg Ile Val Gly Gly Trp Glu Cys Glu
 20 25 30
 Lys His Ser Gln Pro Trp Gln Val Leu Val Ala Ser Arg Gly Arg Ala
 35 40 45
 Val Cys Gly Gly Val Leu Val His Pro Gln Trp Val Leu Thr Ala Ala
 50 55 60
 His Cys Ile Arg Asn Lys Ser Val Ile Leu Leu Gly Arg His Ser Leu
 65 70 75 80
 Phe His Pro Glu Asp Thr Gly Gln Val Phe Gln Val Ser His Ser Phe
 85 90 95
 Pro His Pro Leu Tyr Asp Met Ser Leu Leu Lys Asn Arg Phe Leu Arg
 100 105 110
 Pro Gly Asp Asp Ser Ser His Asp Leu Met Leu Leu Arg Leu Ser Glu
 115 120 125
 Pro Ala Glu Leu Thr Asp Ala Val Lys Val Met Asp Leu Pro Thr Gln
 130 135 140
 Glu Pro Ala Leu Gly Thr Thr Cys Tyr Ala Ser Gly Trp Gly Ser Ile
 145 150 155 160
 Glu Pro Glu Glu Phe Leu Thr Pro Lys Lys Leu Gln Cys Val Asp Leu
 165 170 175
 His Val Ile Ser Asn Asp Val Cys Ala Gln Val His Pro Gln Lys Val
 180 185 190
 Thr Lys Phe Met Leu Cys Ala Gly Arg Trp Thr Gly Gly Lys Ser Thr
 195 200 205
 Cys Ser Gly Asp Ser Gly Gly Pro Leu Val Cys Asn Gly Val Leu Gln
 210 215 220
 Gly Ile Thr Ser Trp Gly Ser Glu Pro Cys Ala Leu Pro Glu Arg Pro
 225 230 235 240
 Ser Leu Tyr Thr Lys Val Val His Tyr Arg Lys Trp Ile Lys Asp Thr
 245 250 255
 Ile Val Ala Asn Pro
 260

<210> 11
 <211> 115
 <212> PRT
 <213> Homo sapiens

<400> 11
 Met Ser Gly Glu Pro Gly Gln Thr Ser Val Ala Pro Pro Pro Glu Glu
 1 5 10 15
 Val Glu Pro Gly Ser Gly Val Arg Ile Val Val Glu Tyr Cys Glu Pro
 20 25 30
 Cys Gly Phe Glu Ala Thr Tyr Leu Glu Leu Ala Ser Ala Val Lys Glu
 35 40 45
 Gln Tyr Pro Gly Ile Glu Ile Glu Ser Arg Leu Gly Gly Thr Gly Ala
 50 55 60
 Phe Glu Ile Glu Ile Asn Gly Gln Leu Val Phe Ser Lys Leu Glu Asn

```

65          70          75          80
Gly Gly Phe Pro Tyr Glu Lys Asp Leu Ile Glu Ala Ile Arg Arg Ala
      85          90          95
Ser Asn Gly Glu Thr Leu Glu Lys Ile Thr Asn Ser Arg Pro Pro Cys
      100          105          110
Val Ile Leu
      115

```

```

<210> 12
<211> 153
<212> PRT
<213> Homo sapiens

```

```

<400> 12
Met Asn Gly Asp Asp Ala Phe Ala Arg Arg Pro Arg Asp Asp Ala Gln
 1          5          10          15
Ile Ser Glu Lys Leu Arg Lys Ala Phe Asp Asp Ile Ala Lys Tyr Phe
      20          25          30
Ser Lys Lys Glu Trp Glu Lys Met Lys Ser Ser Glu Lys Ile Val Tyr
      35          40          45
Val Tyr Met Lys Leu Asn Tyr Glu Val Met Thr Lys Leu Gly Phe Lys
      50          55          60
Val Thr Leu Pro Pro Phe Met Arg Ser Lys Arg Ala Ala Asp Phe His
65          70          75          80
Gly Asn Asp Phe Gly Asn Asp Arg Asn His Arg Asn Gln Val Glu Arg
      85          90          95
Pro Gln Met Thr Phe Gly Ser Leu Gln Arg Ile Phe Pro Lys Asp Pro
      100          105          110
Lys Gly Gly Asn Met Pro Gly Pro Thr Asp Cys Val Arg Glu Ser Ser
      115          120          125
Trp Trp Phe Met Lys Arg Ser Ala Thr Leu Arg Lys Met Thr Ser Asn
      130          135          140
Ser Pro Arg Gly Tyr Asp Thr Cys Pro
145          150

```

```

<210> 13
<211> 661
<212> PRT
<213> Homo sapiens

```

```

<400> 13
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
				165					170				175
Ala	Met	Leu	Gly	Thr	His	Thr	Met	Glu	Val	Thr	Val	Tyr	His
			180					185				190	
Gly	Ser	Arg	Ser	Tyr	Val	Pro	Leu	Ala	His	Ser	Ser	Ser	Ala
		195					200					205	
Ile	Thr	Asp	Gln	Val	Pro	Phe	Ser	Val	Ser	Val	Ser	Gln	Leu
	210					215					220		
Leu	Asp	Gly	Gly	Asn	Lys	His	Phe	Leu	Arg	Asn	Gln	Pro	Leu
225				230						235			Phe
Ala	Leu	Gln	Leu	His	Asp	Pro	Ser	Gly	Tyr	Leu	Ala	Glu	Ala
				245					250				255
Ser	Tyr	Thr	Trp	Asp	Phe	Gly	Asp	Ser	Ser	Gly	Thr	Leu	Ile
			260				265					270	Ser
Ala	Leu	Val	Val	Thr	His	Thr	Tyr	Leu	Glu	Pro	Gly	Pro	Val
	275						280					285	Thr
Gln	Val	Val	Leu	Gln	Ala	Ala	Ile	Pro	Leu	Thr	Ser	Cys	Gly
	290					295					300		Ser
Pro	Val	Pro	Gly	Thr	Thr	Asp	Gly	His	Arg	Pro	Thr	Ala	Glu
305					310					315			Ala
Asn	Thr	Thr	Ala	Gly	Gln	Val	Pro	Thr	Thr	Glu	Val	Val	Gly
				325					330				Thr
Pro	Gly	Gln	Ala	Pro	Thr	Ala	Glu	Pro	Ser	Gly	Thr	Thr	Ser
		340					345						Val
Val	Pro	Thr	Thr	Glu	Val	Ile	Ser	Thr	Ala	Pro	Val	Gln	Met
	355						360					365	Pro
Ala	Glu	Ser	Thr	Gly	Met	Thr	Pro	Glu	Lys	Val	Pro	Val	Ser
	370					375					380		Glu
Met	Gly	Thr	Thr	Leu	Ala	Glu	Met	Ser	Thr	Pro	Glu	Ala	Thr
385					390					395			Gly
Thr	Pro	Ala	Glu	Val	Ser	Ile	Val	Val	Leu	Ser	Gly	Thr	Thr
				405					410				Ala
Gln	Val	Thr	Thr	Thr	Glu	Trp	Val	Glu	Thr	Thr	Ala	Arg	Glu
				420				425					Leu
Ile	Pro	Glu	Pro	Glu	Gly	Pro	Asp	Ala	Ser	Ser	Ile	Met	Ser
	435						440					445	Thr
Ser	Ile	Thr	Gly	Ser	Leu	Gly	Pro	Leu	Leu	Asp	Gly	Thr	Ala
	450					455					460		Thr
Arg	Leu	Val	Lys	Arg	Gln	Val	Pro	Leu	Asp	Cys	Val	Leu	Tyr
465					470					475			Arg
Gly	Ser	Phe	Ser	Val	Thr	Leu	Asp	Ile	Val	Gln	Gly	Ile	Glu
				485					490				Ser
Glu	Ile	Leu	Gln	Ala	Val	Pro	Ser	Gly	Glu	Gly	Asp	Ala	Phe
			500					505				510	Glu
Thr	Val	Ser	Cys	Gln	Gly	Gly	Leu	Pro	Lys	Glu	Ala	Cys	Met
	515						520					525	Glu
Ser	Ser	Pro	Gly	Cys	Gln	Pro	Pro	Ala	Gln	Arg	Leu	Cys	Gln
	530					535					540		Pro
Leu	Pro	Ser	Pro	Ala	Cys	Gln	Leu	Val	Leu	His	Gln	Ile	Leu
545					550					555			Lys
Gly	Ser	Gly	Thr	Tyr	Cys	Leu	Asn	Val	Ser	Leu	Ala	Asp	Thr
				565				570					Asn
Leu	Ala	Val	Val	Ser	Thr	Gln	Leu	Ile	Met	Pro	Gly	Gln	Glu
			580					585				590	Ala
Leu	Gly	Gln	Val	Pro	Leu	Ile	Val	Gly	Ile	Leu	Leu	Val	Leu
	595						600					605	Met
Val	Val	Leu	Ala	Ser	Leu	Ile	Tyr	Arg	Arg	Arg	Leu	Met	Lys
	610					615				620			Gln
Phe	Ser	Val	Pro	Gln	Leu	Pro	His	Ser	Ser	Ser	His	Trp	Leu
625					630					635			Arg
Pro	Arg	Ile	Phe	Cys	Ser	Cys	Pro	Ile	Gly	Glu	Asn	Ser	Pro
													Leu

645
 Ser Gly Gln Gln Val
 660

650

655

<210> 14
 <211> 371
 <212> PRT
 <213> Homo sapiens

<400> 14
 Met Ser Met Ser Pro Lys His Thr Thr Pro Phe Ser Val Ser Asp Ile
 1 5 10 15
 Leu Ser Pro Leu Glu Glu Ser Tyr Lys Lys Val Gly Met Glu Gly Gly
 20 25 30
 Gly Leu Gly Ala Pro Leu Ala Ala Tyr Arg Gln Gly Gln Ala Ala Pro
 35 40 45
 Pro Thr Ala Ala Met Gln Gln His Ala Val Gly His His Gly Ala Val
 50 55 60
 Thr Ala Ala Tyr His Met Thr Ala Ala Gly Val Pro Gln Leu Ser His
 65 70 75 80
 Ser Ala Val Gly Gly Tyr Cys Asn Gly Asn Leu Gly Asn Met Ser Glu
 85 90 95
 Leu Pro Pro Tyr Gln Asp Thr Met Arg Asn Ser Ala Ser Gly Pro Gly
 100 105 110
 Trp Tyr Gly Ala Asn Pro Asp Pro Arg Phe Pro Ala Ile Ser Arg Phe
 115 120 125
 Met Gly Pro Ala Ser Gly Met Asn Met Ser Gly Met Gly Gly Leu Gly
 130 135 140
 Ser Leu Gly Asp Val Ser Lys Asn Met Ala Pro Leu Pro Ser Ala Pro
 145 150 155 160
 Arg Arg Lys Arg Arg Val Leu Phe Ser Gln Ala Gln Val Tyr Glu Leu
 165 170 175
 Glu Arg Arg Phe Lys Gln Gln Lys Tyr Leu Ser Ala Pro Glu Arg Glu
 180 185 190
 His Leu Ala Ser Met Ile His Leu Thr Pro Thr Gln Val Lys Ile Trp
 195 200 205
 Phe Gln Asn His Arg Tyr Lys Met Lys Arg Gln Ala Lys Asp Lys Ala
 210 215 220
 Ala Gln Gln Gln Leu Gln Gln Asp Ser Gly Gly Gly Gly Gly Gly
 225 230 235 240
 Gly Thr Gly Cys Pro Gln Gln Gln Ala Gln Gln Gln Ser Pro Arg
 245 250 255
 Arg Val Ala Val Pro Val Leu Val Lys Asp Gly Lys Pro Cys Gln Ala
 260 265 270
 Gly Ala Pro Ala Pro Gly Ala Ala Ser Leu Gln Gly His Ala Gln Gln
 275 280 285
 Gln Ala Gln His Gln Ala Gln Ala Ala Gln Ala Ala Ala Ala Ile
 290 295 300
 Ser Val Gly Ser Gly Gly Ala Gly Leu Gly Ala His Pro Gly His Gln
 305 310 315 320
 Pro Gly Ser Ala Gly Gln Ser Pro Asp Leu Ala His His Ala Ala Ser
 325 330 335
 Pro Ala Ala Leu Gln Gly Gln Val Ser Ser Leu Ser His Leu Asn Ser
 340 345 350
 Ser Gly Ser Asp Tyr Gly Thr Met Ser Cys Ser Thr Leu Leu Tyr Gly
 355 360 365
 Arg Thr Trp
 370

<210> 15

<211> 93
 <212> PRT
 <213> Homo sapiens

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

<210> 16
 <211> 146
 <212> PRT
 <213> Homo sapiens

<400> 16
 Met Arg Leu Leu Gln Leu Leu Phe Arg Ala Ser Pro Ala Thr Leu Leu
 1 5 10 15
 Leu Val Leu Cys Leu Gln Leu Gly Ala Asn Lys Ala Gln Asp Asn Thr
 20 25 30
 Arg Lys Ile Ile Ile Lys Asn Phe Asp Ile Pro Lys Ser Val Arg Pro
 35 40 45
 Asn Asp Glu Val Thr Ala Val Leu Ala Val Gln Thr Glu Leu Lys Glu
 50 55 60
 Cys Met Val Val Lys Thr Tyr Leu Ile Ser Ser Ile Pro Leu Gln Gly
 65 70 75 80
 Ala Phe Asn Tyr Lys Tyr Thr Ala Cys Leu Cys Asp Asp Asn Pro Lys
 85 90 95
 Thr Phe Tyr Trp Asp Phe Tyr Thr Asn Arg Thr Val Gln Ile Ala Ala
 100 105 110
 Val Val Asp Val Ile Arg Glu Leu Gly Ile Cys Pro Asp Asp Ala Ala
 115 120 125
 Val Ile Pro Ile Lys Asn Asn Arg Phe Tyr Thr Ile Glu Ile Leu Lys
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 Val Glu
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<210> 17
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 <212> PRT
 <213> Homo sapiens

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 Pro Ser Arg Thr Leu Ala Gly Glu Thr Gly Gln Glu Ala Ala Pro Leu
 35 40 45
 Asp Gly Val Leu Ala Asn Pro Pro Asn Ile Ser Ser Leu Ser Pro Arg
 50 55 60
 Gln Leu Leu Gly Phe Pro Cys Ala Glu Val Ser Gly Leu Ser Thr Glu

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Arg	Val	Arg	Glu	Leu	Ala	Val	Ala	Leu	Ala	Gln	Lys	Asn	Val	Lys
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Ser	Thr	Glu	Gln	Leu	Arg	Cys	Leu	Ala	His	Arg	Leu	Ser	Glu	Pro
			100					105					110	
Glu	Asp	Leu	Asp	Ala	Leu	Pro	Leu	Asp	Leu	Leu	Leu	Phe	Leu	Asn
			115					120					125	
Asp	Ala	Phe	Ser	Gly	Pro	Gln	Ala	Cys	Thr	Arg	Phe	Phe	Ser	Arg
			130					135						Ile
Thr	Lys	Ala	Asn	Val	Asp	Leu	Leu	Pro	Arg	Gly	Ala	Pro	Glu	Arg
					150					155				Gln
Arg	Leu	Leu	Pro	Ala	Ala	Leu	Ala	Cys	Trp	Gly	Val	Arg	Gly	Ser
				165					170					Leu
Leu	Ser	Glu	Ala	Asp	Val	Arg	Ala	Leu	Gly	Gly	Leu	Ala	Cys	Asp
			180					185					190	
Pro	Gly	Arg	Phe	Val	Ala	Glu	Ser	Ala	Glu	Val	Leu	Leu	Pro	Arg
			195				200					205		Leu
Val	Ser	Cys	Pro	Gly	Pro	Leu	Asp	Gln	Asp	Gln	Gln	Glu	Ala	Ala
			210			215					220			Arg
Ala	Ala	Leu	Gln	Gly	Gly	Gly	Pro	Pro	Tyr	Gly	Pro	Pro	Ser	Thr
					230					235				Trp
Ser	Val	Ser	Thr	Met	Asp	Ala	Leu	Arg	Gly	Leu	Leu	Pro	Val	Leu
				245					250					Gly
Gln	Pro	Ile	Ile	Arg	Ser	Ile	Pro	Gln	Gly	Ile	Val	Ala	Ala	Trp
			260					265						Arg
Gln	Arg	Ser	Ser	Arg	Asp	Pro	Ser	Trp	Arg	Gln	Pro	Glu	Arg	Thr
			275				280					285		Ile
Leu	Arg	Pro	Arg	Phe	Arg	Arg	Glu	Val	Glu	Lys	Thr	Ala	Cys	Pro
			290			295					300			Ser
Gly	Lys	Lys	Ala	Arg	Glu	Ile	Asp	Glu	Ser	Leu	Ile	Phe	Tyr	Lys
					310					315				Lys
Trp	Glu	Leu	Glu	Ala	Cys	Val	Asp	Ala	Ala	Leu	Leu	Ala	Thr	Gln
				325				330						Met
Asp	Arg	Val	Asn	Ala	Ile	Pro	Phe	Thr	Tyr	Glu	Gln	Leu	Asp	Val
			340					345					350	Leu
Lys	His	Lys	Leu	Asp	Glu	Leu	Tyr	Pro	Gln	Gly	Tyr	Pro	Glu	Ser
			355				360					365		Val
Ile	Gln	His	Leu	Gly	Tyr	Leu	Phe	Leu	Lys	Met	Ser	Pro	Glu	Asp
			370			375					380			Ile
Arg	Lys	Trp	Asn	Val	Thr	Ser	Leu	Glu	Thr	Leu	Lys	Ala	Leu	Leu
					390					395				Glu
Val	Asn	Lys	Gly	His	Glu	Met	Ser	Pro	Gln	Val	Ala	Thr	Leu	Ile
				405					410					Asp
Arg	Phe	Val	Lys	Gly	Arg	Gly	Gln	Leu	Asp	Lys	Asp	Thr	Leu	Asp
				420				425					430	Thr
Leu	Thr	Ala	Phe	Tyr	Pro	Gly	Tyr	Leu	Cys	Ser	Leu	Ser	Pro	Glu
			435				440					445		Glu
Leu	Ser	Ser	Val	Pro	Pro	Ser	Ser	Ile	Trp	Ala	Val	Arg	Pro	Gln
						455					460			Asp
Leu	Asp	Thr	Cys	Asp	Pro	Arg	Gln	Leu	Asp	Val	Leu	Tyr	Pro	Lys
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Arg	Leu	Ala	Phe	Gln	Asn	Met	Asn	Gly	Ser	Glu	Tyr	Phe	Val	Lys
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Gln	Ser	Phe	Leu	Gly	Gly	Ala	Pro	Thr	Glu	Asp	Leu	Lys	Ala	Leu
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Gln	Gln	Asn	Val	Ser	Met	Asp	Leu	Ala	Thr	Phe	Met	Lys	Leu	Arg
			515				520					525		Thr
Asp	Ala	Val	Leu	Pro	Leu	Thr	Val	Ala	Glu	Val	Gln	Lys	Leu	Leu
						535					540			Gly
Pro	His	Val	Glu	Gly	Leu	Lys	Ala	Glu	Glu	Arg	His	Arg	Pro	Val
					550				555					Arg
Asp	Trp	Ile	Leu	Arg	Gln	Arg	Gln	Asp	Asp	Leu	Asp	Thr	Leu	Gly
														Leu

				565					570					575			
Gly	Leu	Gln	Gly	Gly	Ile	Pro	Asn	Gly	Tyr	Leu	Val	Leu	Asp	Leu	Ser		
			580					585					590				
Met	Gln	Glu	Ala	Leu	Ser	Gly	Thr	Pro	Cys	Leu	Leu	Gly	Pro	Gly	Pro		
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Val	Leu	Thr	Val	Leu	Ala	Leu	Leu	Leu	Ala	Ser	Thr	Leu	Ala				
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<210> 18

<211> 630

<212> PRT

<213> Homo sapiens

<400> 18

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Pro	Ser	Arg	Thr	Leu	Ala	Gly	Glu	Thr	Gly	Gln	Glu	Ala	Ala	Pro	Leu		
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Asp	Gly	Val	Leu	Ala	Asn	Pro	Asn	Ile	Ser	Ser	Leu	Ser	Pro	Arg			
	50				55					60							
Gln	Leu	Leu	Gly	Phe	Pro	Cys	Ala	Glu	Val	Ser	Gly	Leu	Ser	Thr	Glu		
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Arg	Val	Arg	Glu	Leu	Ala	Val	Ala	Leu	Ala	Gln	Lys	Asn	Val	Lys	Leu		
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Ser	Thr	Glu	Gln	Leu	Arg	Cys	Leu	Ala	His	Arg	Leu	Ser	Glu	Pro	Pro		
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Glu	Asp	Leu	Asp	Ala	Leu	Pro	Leu	Asp	Leu	Leu	Leu	Phe	Leu	Asn	Pro		
	115						120					125					
Asp	Ala	Phe	Ser	Gly	Pro	Gln	Ala	Cys	Thr	Arg	Phe	Phe	Ser	Arg	Ile		
	130					135					140						
Thr	Lys	Ala	Asn	Val	Asp	Leu	Leu	Pro	Arg	Gly	Ala	Pro	Glu	Arg	Gln		
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			165					170						175			
Leu	Ser	Glu	Ala	Asp	Val	Arg	Ala	Leu	Gly	Gly	Leu	Ala	Cys	Asp	Leu		
			180					185					190				
Pro	Gly	Arg	Phe	Val	Ala	Glu	Ser	Ala	Glu	Val	Leu	Leu	Pro	Arg	Leu		
	195						200					205					
Val	Ser	Cys	Pro	Gly	Pro	Leu	Asp	Gln	Asp	Gln	Gln	Glu	Ala	Ala	Arg		
	210					215				220							
Ala	Ala	Leu	Gln	Gly	Gly	Gly	Pro	Pro	Tyr	Gly	Pro	Pro	Ser	Thr	Trp		
225				230						235					240		
Ser	Val	Ser	Thr	Met	Asp	Ala	Leu	Arg	Gly	Leu	Leu	Pro	Val	Leu	Gly		
				245				250					255				
Gln	Pro	Ile	Ile	Arg	Ser	Ile	Pro	Gln	Gly	Ile	Val	Ala	Ala	Trp	Arg		
			260					265					270				
Gln	Arg	Ser	Ser	Arg	Asp	Pro	Ser	Trp	Arg	Gln	Pro	Glu	Arg	Thr	Ile		
	275					280						285					
Leu	Arg	Pro	Arg	Phe	Arg	Arg	Glu	Val	Glu	Lys	Thr	Ala	Cys	Pro	Ser		
	290				295					300							
Gly	Lys	Lys	Ala	Arg	Glu	Ile	Asp	Glu	Ser	Leu	Ile	Phe	Tyr	Lys	Lys		
305				310						315					320		
Trp	Glu	Leu	Glu	Ala	Cys	Val	Asp	Ala	Ala	Leu	Leu	Ala	Thr	Gln	Met		
			325					330						335			
Asp	Arg	Val	Asn	Ala	Ile	Pro	Phe	Thr	Tyr	Glu	Gln	Leu	Asp	Val	Leu		
			340					345					350				
Lys	His	Lys	Leu	Asp	Glu	Leu	Tyr	Pro	Gln	Gly	Tyr	Pro	Glu	Ser	Val		
	355					360						365					
Ile	Gln	His	Leu	Gly	Tyr	Leu	Phe	Leu	Lys	Met	Ser	Pro	Glu	Asp	Ile		

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

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 <212> PRT
 <213> Homo sapiens

<400> 19
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 35 40 45
 Trp Thr Ala Arg Ile Arg Ala Val Gly Leu Leu Thr Val Ile Ser Lys
 50 55 60
 Gly Cys Ser Leu Asn Cys Val Asp Asp Ser Gln Asp Tyr Tyr Val Gly
 65 70 75 80
 Lys Lys Asn Ile Thr Cys Cys Asp Thr Asp Leu Cys Asn Ala Ser Gly
 85 90 95
 Ala His Ala Leu Gln Pro Ala Ala Ala Ile Leu Ala Leu Leu Pro Ala
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 Leu Gly Leu Leu Trp Gly Pro Gly Gln Leu
 115 120

<210> 20
 <211> 976
 <212> PRT

<213> Homo sapiens

<400> 20

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Thr Phe Phe Lys Ser Phe Asn Lys Cys Thr Glu Asp Asp Leu Glu Phe
      35          40          45
Pro Phe Ala Lys Thr Asn Leu Ser Lys Asn Gly Glu Asn Ile Asp Ser
      50          55          60
Asp Pro Ala Leu Gln Lys Val Asn Phe Leu Pro Val Leu Glu Gln Val
      65          70          75          80
Gly Asn Ser Asp Cys His Tyr Gln Glu Gly Leu Lys Asp Ser Asp Leu
      85          90          95
Glu Asn Ser Glu Gly Leu Ser Arg Val Phe Ser Lys Leu Tyr Lys Glu
      100          105          110
Ala Glu Lys Ile Lys Lys Trp Lys Val Ser Thr Glu Ala Glu Leu Arg
      115          120          125
Gln Lys Glu Ser Lys Leu Gln Glu Asn Arg Lys Ile Ile Glu Ala Gln
      130          135          140
Arg Lys Ala Ile Gln Glu Leu Gln Phe Gly Asn Glu Lys Val Ser Leu
      145          150          155          160
Lys Leu Glu Glu Gly Ile Gln Glu Asn Lys Asp Leu Ile Lys Glu Asn
      165          170          175
Asn Ala Thr Arg His Leu Cys Asn Leu Lys Glu Thr Cys Ala Arg
      180          185          190
Ser Ala Glu Lys Thr Lys Lys Tyr Glu Tyr Glu Arg Glu Glu Thr Arg
      195          200          205
Gln Val Tyr Met Asp Leu Asn Asn Asn Ile Glu Lys Met Ile Thr Ala
      210          215          220
His Gly Glu Leu Arg Val Gln Ala Glu Asn Ser Arg Leu Glu Met His
      225          230          235          240
Phe Lys Leu Lys Glu Asp Tyr Glu Lys Ile Gln His Leu Glu Gln Glu
      245          250          255
Tyr Lys Lys Glu Ile Asn Asp Lys Glu Lys Gln Val Ser Leu Leu Leu
      260          265          270
Ile Gln Ile Thr Glu Lys Glu Asn Lys Met Lys Asp Leu Thr Phe Leu
      275          280          285
Leu Glu Glu Ser Arg Asp Lys Val Asn Gln Leu Glu Glu Lys Thr Lys
      290          295          300
Leu Gln Ser Glu Asn Leu Lys Gln Ser Ile Glu Lys Gln His His Leu
      305          310          315          320
Thr Lys Glu Leu Glu Asp Ile Lys Val Ser Leu Gln Arg Ser Val Ser
      325          330          335
Thr Gln Lys Ala Leu Glu Glu Asp Leu Gln Ile Ala Thr Lys Thr Ile
      340          345          350
Cys Gln Leu Thr Glu Glu Lys Glu Thr Gln Met Glu Glu Ser Asn Lys
      355          360          365
Ala Arg Ala Ala His Ser Phe Val Val Thr Glu Phe Glu Thr Thr Val
      370          375          380
Cys Ser Leu Glu Glu Leu Leu Arg Thr Glu Gln Gln Arg Leu Glu Lys
      385          390          395          400
Asn Glu Asp Gln Leu Lys Ile Leu Thr Met Glu Leu Gln Lys Lys Ser
      405          410          415
Ser Glu Leu Glu Glu Met Thr Lys Leu Thr Asn Asn Lys Glu Val Glu
      420          425          430
Leu Glu Glu Leu Lys Lys Val Leu Gly Glu Lys Glu Thr Leu Leu Tyr
      435          440          445
Glu Asn Lys Gln Phe Glu Lys Ile Ala Glu Glu Leu Lys Gly Thr Glu
      450          455          460
Gln Glu Leu Ile Gly Leu Leu Gln Ala Arg Glu Lys Glu Val His Asp

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465					470					475					480
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Lys	Glu	Val	Lys	Asp	Leu	Lys	Thr	Glu	Leu	Glu	Asn	Glu	Lys	Leu	Lys
			500					505					510		
Asn	Thr	Glu	Leu	Thr	Ser	His	Cys	Asn	Lys	Leu	Ser	Leu	Glu	Asn	Lys
		515					520					525			
Glu	Leu	Thr	Gln	Glu	Thr	Ser	Asp	Met	Thr	Leu	Glu	Leu	Lys	Asn	Gln
	530					535					540				
Gln	Glu	Asp	Ile	Asn	Asn	Asn	Lys	Lys	Gln	Glu	Glu	Arg	Met	Leu	Lys
545				550					555						560
Gln	Ile	Glu	Asn	Leu	Gln	Glu	Thr	Glu	Thr	Gln	Leu	Arg	Asn	Glu	Leu
			565						570					575	
Glu	Tyr	Val	Arg	Glu	Glu	Leu	Lys	Gln	Lys	Arg	Asp	Glu	Val	Lys	Cys
			580					585					590		
Lys	Leu	Asp	Lys	Ser	Glu	Glu	Asn	Cys	Asn	Asn	Leu	Arg	Lys	Gln	Val
		595					600					605			
Glu	Asn	Lys	Asn	Lys	Tyr	Ile	Glu	Glu	Leu	Gln	Gln	Glu	Asn	Lys	Ala
	610					615					620				
Leu	Lys	Lys	Lys	Gly	Thr	Ala	Glu	Ser	Lys	Gln	Leu	Asn	Val	Tyr	Glu
625					630					635					640
Ile	Lys	Val	Asn	Lys	Leu	Glu	Leu	Glu	Leu	Glu	Ser	Ala	Lys	Gln	Lys
			645						650					655	
Phe	Gly	Glu	Ile	Thr	Asp	Thr	Tyr	Gln	Lys	Glu	Ile	Glu	Asp	Lys	Lys
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Ile	Ser	Glu	Glu	Asn	Leu	Leu	Glu	Glu	Val	Glu	Lys	Ala	Lys	Val	Ile
		675					680					685			
Ala	Asp	Glu	Ala	Val	Lys	Leu	Gln	Lys	Glu	Ile	Asp	Lys	Arg	Cys	Gln
	690					695					700				
His	Lys	Ile	Ala	Glu	Met	Val	Ala	Leu	Met	Glu	Lys	His	Lys	His	Gln
705					710					715					720
Tyr	Asp	Lys	Ile	Ile	Glu	Glu	Arg	Asp	Ser	Glu	Leu	Gly	Leu	Tyr	Lys
			725					730						735	
Ser	Lys	Glu	Gln	Glu	Gln	Ser	Ser	Leu	Arg	Ala	Ser	Leu	Glu	Ile	Glu
			740					745					750		
Leu	Ser	Asn	Leu	Lys	Ala	Glu	Leu	Leu	Ser	Val	Lys	Lys	Gln	Leu	Glu
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Ile	Glu	Arg	Glu	Glu	Lys	Glu	Lys	Leu	Lys	Arg	Glu	Ala	Lys	Glu	Asn
	770					775					780				
Thr	Ala	Thr	Leu	Lys	Glu	Lys	Lys	Asp	Lys	Lys	Thr	Gln	Thr	Phe	Leu
785					790					795					800
Leu	Glu	Thr	Pro	Glu	Ile	Tyr	Trp	Lys	Leu	Asp	Ser	Lys	Ala	Val	Pro
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Ser	Gln	Thr	Val	Ser	Arg	Asn	Phe	Thr	Ser	Val	Asp	His	Gly	Ile	Ser
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Lys	Asp	Lys	Arg	Asp	Tyr	Leu	Trp	Thr	Ser	Ala	Lys	Asn	Thr	Leu	Ser
		835					840					845			
Thr	Pro	Leu	Pro	Lys	Ala	Tyr	Thr	Val	Lys	Thr	Pro	Thr	Lys	Pro	Lys
	850					855					860				
Leu	Gln	Gln	Arg	Glu	Asn	Leu	Asn	Ile	Pro	Ile	Glu	Glu	Ser	Lys	Lys
865					870					875					880
Lys	Arg	Lys	Met	Ala	Phe	Glu	Phe	Asp	Ile	Asn	Ser	Asp	Ser	Ser	Glu
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Thr	Thr	Asp	Leu	Leu	Ser	Met	Val	Ser	Glu	Glu	Glu	Thr	Leu	Lys	Thr
		900						905					910		
Leu	Tyr	Arg	Asn	Asn	Asn	Pro	Pro	Ala	Ser	His	Leu	Cys	Val	Lys	Thr
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Pro	Lys	Lys	Ala	Pro	Ser	Ser	Leu	Thr	Thr	Pro	Gly	Pro	Thr	Leu	Lys
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Phe	Gly	Ala	Ile	Arg	Lys	Met	Arg	Glu	Asp	Arg	Trp	Ala	Val	Ile	Ala
945					950					955					960
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965

970

975

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 <212> DNA
 <213> Homo sapiens

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 ctctcatttg caaggtcaaa tcatcattag ttttgtagtc tattaactgg gtttgcttag 180
 gtcaggcatt attattacta accttattgt taatattcta accataagaa ttaactatt 240
 aatgggtgaat agagtttttc actttaacat aggcctatcc cactgggtggg atacgagcca 300
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 tcagcccttt taacattttc ccctaagccc atatgtctaa ggaaaggatg ctatttggtg 2340
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 <212> DNA
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<211> 1466

<212> DNA

<213> Homo sapiens

<400> 23

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<211> 2653

<212> DNA

<213> Homo sapiens

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<211> 2420

<212> DNA

<213> Homo sapiens

<400> 25

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<210> 26

<211> 4204

<212> DNA

<213> Homo sapiens

<400> 26

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<211> 752

<212> DNA

<213> Homo sapiens

<400> 27

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 <212> DNA
 <213> Homo sapiens

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 <212> DNA
 <213> Homo sapiens

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<212> DNA

<213> Homo sapiens

<400> 30

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<210> 31

<211> 781

<212> DNA

<213> Homo sapiens

<400> 31

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<210> 32

<211> 1114

<212> DNA

<213> Homo sapiens

<400> 32

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<211> 2143

<212> DNA

<213> Homo sapiens

<400> 33

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<210> 34
<211> 2352
<212> DNA
<213> Homo sapiens

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<212> DNA
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<210> 36

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<212> DNA

<213> Homo sapiens

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<212> DNA

<213> Homo sapiens

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<211> 2412

<212> DNA

<213> Homo sapiens

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<211> 946

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<212> DNA

<213> Homo sapiens

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