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(54) Title: ANTIBODIES THAT BIND HUMAN DENDRITIC AND EPITHELIAL CELL 205 (DEC-205)

(57) Abstract: Isolated monoclonal antibodies which bind to human DEC-205 and related antibody-based compositions and molecules are disclosed. Also disclosed are pharmaceutical compositions comprising the antibodies, as well as therapeutic and diagnostic methods for using the antibodies.

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ANTIBODIES THAT BIND HUMAN DENDRITIC AND EPITHELIAL CELL 205 (DEC-205)

Related Applications

This application claims priority to U.S. Provisional Application No.: 61/002253, filed on November 7, 2007 and U.S. Provisional Application No.: 61/191551, filed on September 10, 2008, the contents of which are incorporated herein by reference.

Background of the Invention

Any discussion of the prior art throughout the specification should in no way be considered as an admission that such prior art is widely known or forms part of common general knowledge in the field.

Dendritic cells (DCs) are specialized cells of the immune system. DCs have the unique capacity for initiating primary and secondary T and B lymphocyte responses by presenting antigens in the form of peptides bound to cell-surface major histocompatibility complex (MHC) molecules. The antigen-presentation function of dendritic cells has been correlated with the high-level expression of human dendritic and epithelial cell 205 receptor (DEC-205) (Jiang *et al.* (1995) Nature 375(11)151).

DEC-205 is an endocytic receptor found primarily on dendritic cells, but is also found on B cells, brain capillaries, bone marrow stroma, epithelia of intestinal villi and pulmonary airways, as well as the cortical epithelium of the thymus and the dendritic cells in the T cell areas of peripheral lymphoid organs. DEC-205 is expressed at high levels on DCs in the T cell areas of lymphoid organs (Kraal *et al.* (1986) *J. Exp. Med.* 163:981; Witmer-Pack *et al.* (1995) *Cell. Immunol.* 163:157). DEC-205 has ten membrane-external, contiguous C-type lectin domains (*Id.*; Mahnke *et al.* (2000) *J. Cell Biol.* 151:673) which mediate the efficient processing and presentation of antigens on MHC class II products *in vivo* (Hawiger *et al.* (2001) *J. Exp. Med.* 194:769). It has been shown that small amounts of injected antigen, targeted to DCs by the DEC-205 adsorptive pathway, are able to induce solid peripheral $CD8^{+}$ T cell tolerance (Bonifaz *et al.* (2002) *J. Exp. Med.* 196(12):1627).

Despite recent advances in the characterization of dendritic cells, very little is known regarding dendritic cell-specific receptors, such as DEC-205, and few reagents are available which are specific to dendritic cells. Reagents, in particular antibodies, which react specifically or preferentially with dendritic cells, such as through DEC-205, have great potential as targeting agents to induce potent immune responses to tumor or infectious disease antigens. These cell-specific targeting agents could also be engineered to deliver toxins to eliminate potent antigen presenting cells (*e.g.*, dendritic cells) in bone marrow and organ transplantations or other autoimmune disorders. Accordingly, such dendritic cell-specific binding agents possess great therapeutic and diagnostic value.

Summary of the Invention

According to a first aspect, the present invention provides an isolated human monoclonal antibody, which binds to human Dendritic and Epithelial Cell 205 receptor (DEC-205) and comprises heavy and light chain variable region CDR1, CDR2 and CDR3 sequences, wherein:

(i) the heavy chain variable region CDR1 comprises an amino acid sequence selected from the consensus sequence: (I,N,T,S) Y (G,N,A) M (H,Y) (SEQ ID NO: 97);

(ii) the heavy chain variable region CDR2 comprises an amino acid sequence selected from the consensus sequence: (V,I,F,T,A) I (W,G) (Y,T) (D,G) G (S,G,Y) (N,T) (K,P) Y (Y,A,V) (A,G,-) D S V K G (SEQ ID NO: 98);

(iii) the heavy chain variable region CDR3 comprises an amino acid sequence selected from the consensus sequence: (A,G,Y,S,P,-) (P,W,S,R) (Y,A,H) F D (Y,L,V) (SEQ ID NO: 99);

(iv) the light chain variable region CDR1 comprises an amino acid sequence selected from the consensus sequence: R A S Q (S,G) (I,V) S S (Y,W,A) L A (SEQ ID NO: 100);

(v) the light chain variable region CDR2 comprises an amino acid sequence selected from the consensus sequence: (D,A) A S (N,S) (R,L) (A,Q,E) (T,S) (SEQ ID NO: 101); and

(vi) the light chain variable region CDR3 comprises an amino acid sequence selected from the consensus sequence: Q Q (R,Y,F) (R,N) (T,S,N) (Y,W,-) (P,-) (Y,L,H,-) (T,-) (SEQ ID NO: 102); and

wherein "-" denotes the option of no amino acid residue being present at that consensus position.

According to a second aspect, the present invention provides an isolated antibody that competes for binding with the isolated monoclonal antibody of the first aspect.

According to a third aspect, the present invention provides an isolated antibody which binds to an epitope bound by the isolated monoclonal antibody of the first aspect.

According to a fourth aspect, the present invention provides an expression vector comprising a nucleotide sequence encoding the antibody according to any one of the first to third aspects.

According to a fifth aspect, the present invention provides a cell transformed with an expression vector as claimed in the fourth aspect.

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According to a sixth aspect, the present invention provides a molecular conjugate comprising the antibody according to any one of the first to third aspects, linked to an antigen.

According to a seventh aspect, the present invention provides a bispecific molecule comprising the antibody according to any one of the first to third aspects linked to a molecule having a binding specificity which is different from the antibody.

According to an eighth aspect, the present invention provides a composition comprising the antibody according to any one of the first to third aspects and a pharmaceutically effective carrier.

According to a ninth aspect, the present invention provides use of the antibody according to any one of the first to third aspects in the preparation of a medicament for targeting an antigen to DEC-205 in a subject.

According to a tenth aspect, the present invention provides use of the antibody according to any one of the first to third aspects in the preparation of a medicament for inducing or enhancing an immune response against an antigen in a subject.

According to an eleventh aspect, the present invention provides use of the antibody according to any one of the first to third aspects in the preparation of a medicament for inducing or enhancing a T cell-mediated immune response in a subject against an antigen.

According to a twelfth aspect, the present invention provides use of the antibody according to any one of the first to third aspects in the preparation of a medicament for immunizing a subject.

According to a thirteenth aspect, the present invention provides use of the antibody according to any one of the first to third aspects in the preparation of a medicament for treating a disorder in a subject.

According to a fourteenth aspect, the present invention provides a method for detecting the presence or absence of DEC-205 in a biological sample, comprising:

(a) contacting a biological sample with the antibody of any one of the first to third aspects, wherein the antibody is labeled with a detectable substance; and

(b) detecting the antibody bound to DEC-205 to thereby detect the presence or absence of DEC-205 in the biological sample.

According to a fifteenth aspect, the present invention provides use of a molecular conjugate comprising the antibody according to any one of the first to third aspects linked to an antigen in the preparation of a medicament for targeting the antigen to a B cell in a subject.

According to a sixteenth aspect, the present invention provides use of a molecular conjugate comprising the antibody according to any one of the first to third aspects linked to an antigen in the preparation of a medicament for inducing or enhancing an immune response against the antigen in a subject.

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According to a seventeenth aspect, the present invention provides use of a molecular conjugate comprising the antibody of according to any one of the first to third aspects linked to an antigen in the preparation of a medicament for immunizing a subject against the antigen.

According to an eighteenth aspect, the present invention provides a method for targeting an antigen to DEC-205 in a subject, said method comprising the step of administering to the subject the antibody according to any one of the first to third aspects or the composition according to the eighth aspect.

According to a nineteenth aspect, the present invention provides a method for inducing or enhancing an immune response against an antigen in a subject, said method comprising the step of administering to the subject the antibody according to any one of the first to third aspects or the composition according to the eighth aspect.

According to a twentieth aspect, the present invention provides a method for inducing or enhancing a T cell-mediated immune response in a subject, said method comprising the step of administering to the subject the antibody according to any one of the first to third aspects or the composition according to the eighth aspect.

According to a twenty-first aspect, the present invention provides a method for immunizing a subject, said method comprising the step of administering to the subject antibody according to any one of the first to third aspects or the composition according to the eighth aspect.

According to a twenty-second aspect, the present invention provides a method for treating a disorder in a subject, said method comprising the step of administering to the subject antibody according to any one of the first to third aspects or the composition according to the eighth aspect.

According to a twenty-third aspect, the present invention provides a method for targeting an antigen to a B cell in a subject, said method comprising the step of administering to the subject a molecular conjugate comprising the antibody according to any one of the first to third aspects linked to the antigen.

According to a twenty-fourth aspect, the present invention provides a method for inducing or enhancing an immune response against an antigen in a subject, said method comprising the step of administering to the subject the antibody according to any one of the first to third aspects linked to the antigen.

According to a twenty-fifth aspect, the present invention provides a method for immunizing a subject against an antigen, said method comprising the step of administering to the subject the antibody according to any one of the first to third aspects linked to the antigen.

Unless the context clearly requires otherwise, throughout the description and the claims, the words “comprise”, “comprising”, and the like are to be construed in an inclusive sense as opposed to an exclusive or exhaustive sense; that is to say, in the sense of "including, but not limited to".

The present invention provides isolated antibodies, *e.g.*, human antibodies, which bind to human DEC-205 and exhibit particular properties. The present invention also provides vaccine conjugates, bispecific molecules, and therapeutic compositions containing such antibodies. Accordingly, the antibodies and compositions of the invention can be used in a variety of dendritic cell-targeted therapies, for example, to enhance antigen presentation and/or induce T cell responses, such as cytotoxic T cell (CTL) responses, against a variety of target cells or pathogens, or to treat antigen presenting cell (APC)-mediated diseases.

In one embodiment, the antibodies of the present invention exhibit one or more of the following properties: (1) binding to human DEC-205 with an affinity constant of at least $10^8 M^{-1}$ as measured by surface plasmon resonance; (2) internalization after binding to human dendritic cells expressing DEC-205; (3) generation or enhancement of human T-cell responses, *e.g.*, CD4+ and CD8+ (CTL) T-cell responses to an antigen (which may be linked to the antibody), suitably mediated by either MHC Class I and/or Class II pathways; and (4) inducement of peripheral $CD8^+$ T cell tolerance. Furthermore, the antibodies may cross-react with DEC-205 on non-human primate dendritic cells or those of other species. Still further, the antibodies may suitably exhibit one or more of additional properties including for example: (1) selectively bind to an epitope located on the extracellular domain of human DEC-205, for example, on one or a combination of the cysteine rich domain, the FnII domain, or one or more of the ten C-type lectin-like domains; and (2) localization to antigen processing compartments in the cell.

Particular examples of antibodies of the invention comprise heavy and light chain variable regions that utilize particular human germlines, *i.e.*, are encoded by the germline genes, but include genetic rearrangements and mutations, *e.g.*, somatic mutations, which occur during antibody maturation. In one embodiment, the heavy chain variable region of the antibodies of the present invention utilizes a human germline V_H 3-33 gene and comprises at least one of the amino acid substitutions in any one of SEQ ID NOS: 4, 16, 28, 40, 52, 76 and 88 as compared to SEQ ID NO: 95. Alternatively, the heavy chain variable region utilizes a human germline Orph-C16 gene and comprises at least one of the amino acid substitutions in either of SEQ ID NOS: 64 and 70 as compared to SEQ ID NO: 96.

In another embodiment, the light chain variable region of the antibody is selected from the group consisting of a region that (a) utilizes a human germline VK1-L15 gene and comprises at least one of the amino acid substitutions in SEQ ID NO: 10 as compared to SEQ ID NO: 94; (b) utilizes a human germline VK1- L4 gene and comprises at least one of the amino acid substitutions in any one of SEQ ID NOs: 22 or 82 as compared to SEQ ID NO: 93; or (c) utilizes a human germline VK3-L6 gene and comprises at least one of the amino acid substitutions in any one of SEQ ID NOs: 34, 46, 58, as compared to SEQ ID NO: 92.

In another embodiment, the heavy chain variable region CDR3 sequence is selected from the group consisting of SEQ ID NOs: 7, 19, 31, 43, 55, 67, 73, 79, 91 and conservative sequence modifications thereof (*e.g.*, conservative amino acid substitutions). The antibodies may further include a light chain variable region CDR3 sequence selected from the group consisting of SEQ ID NOs: 13, 25, 37, 49, 61, 85, and conservative sequence modifications thereof. In another embodiment, the heavy chain CDR2 and CDR1 sequences are selected from SEQ ID NOs: 6, 18, 30, 42, 54, 66, 72, 78, 90 and SEQ ID NOs: 5, 17, 29, 41, 53, 65, 71, 77, 89, respectively, and conservative sequence modifications thereof. The light chain CDR2 and CDR1 sequences are selected from SEQ ID NOs: 12, 24, 36, 48, 60, 84, and SEQ ID NOs: 11, 23, 35, 47, 59, 83, respectively, and conservative sequence modifications thereof.

In still another embodiment, the invention provides an isolated antibody that binds DEC-205 and includes heavy and light chain variable region CDR1, CDR2 and CDR3 sequences selected from the group consisting of:

(i) a heavy chain variable region CDR1 comprising SEQ ID NO: 5;
a heavy chain variable region CDR2 comprising SEQ ID NO: 6;
a heavy chain variable region CDR3 comprising SEQ ID NO: 7;
a light chain variable region CDR1 comprising SEQ ID NO: 11;

a light chain variable region CDR2 comprising SEQ ID NO: 12;
a light chain variable region CDR3 comprising SEQ ID NO: 13;

or

conservative sequence modifications thereof;

(ii) a heavy chain variable region CDR1 comprising SEQ ID NO: 17;
a heavy chain variable region CDR2 comprising SEQ ID NO: 18;
a heavy chain variable region CDR3 comprising SEQ ID NO: 19;
a light chain variable region CDR1 comprising SEQ ID NO: 23;
a light chain variable region CDR2 comprising SEQ ID NO: 24;
a light chain variable region CDR3 comprising SEQ ID NO: 25;

or

conservative sequence modifications thereof;

(iii) a heavy chain variable region CDR1 comprising SEQ ID NO: 29;
a heavy chain variable region CDR2 comprising SEQ ID NO: 30;
a heavy chain variable region CDR3 comprising SEQ ID NO: 31;
a light chain variable region CDR1 comprising SEQ ID NO: 35;
a light chain variable region CDR2 comprising SEQ ID NO: 36;
a light chain variable region CDR3 comprising SEQ ID NO: 37;

or

conservative sequence modifications thereof;

(iv) a heavy chain variable region CDR1 comprising SEQ ID NO: 41;
a heavy chain variable region CDR2 comprising SEQ ID NO: 42;
a heavy chain variable region CDR3 comprising SEQ ID NO: 43;
a light chain variable region CDR1 comprising SEQ ID NO: 47;
a light chain variable region CDR2 comprising SEQ ID NO: 48;
a light chain variable region CDR3 comprising SEQ ID NO: 49;

or

conservative sequence modifications thereof;

(v) a heavy chain variable region CDR1 comprising SEQ ID NO: 53;
a heavy chain variable region CDR2 comprising SEQ ID NO: 54;
a heavy chain variable region CDR3 comprising SEQ ID NO: 55;
a light chain variable region CDR1 comprising SEQ ID NO: 59;
a light chain variable region CDR2 comprising SEQ ID NO: 60;
a light chain variable region CDR3 comprising SEQ ID NO: 61;

or

conservative sequence modifications thereof;

(vi) a heavy chain variable region CDR1 comprising SEQ ID NO: 77;
a heavy chain variable region CDR2 comprising SEQ ID NO: 78;
a heavy chain variable region CDR3 comprising SEQ ID NO: 79;
a light chain variable region CDR1 comprising SEQ ID NO: 83;
a light chain variable region CDR2 comprising SEQ ID NO: 84;
a light chain variable region CDR3 comprising SEQ ID NO: 85;

or

conservative sequence modifications thereof.

For example, the isolated antibody binds to human DEC-205 and comprises:

a heavy chain variable region CDR1 comprising SEQ ID NO: 29
a heavy chain variable region CDR2 comprising SEQ ID NO: 30
a heavy chain variable region CDR3 comprising SEQ ID NO: 31
a light chain variable region CDR1 comprising SEQ ID NO: 35;
a light chain variable region CDR2 comprising SEQ ID NO: 36;

and

a light chain variable region CDR3 comprising SEQ ID NO: 37.

In another embodiment, the heavy chain variable region CDR3 sequence comprises an amino acid sequence selected from the consensus sequence: (A,G,Y,S,P,-) (P,W,S,R) (Y,A,H) F D (Y,L,V) (SEQ ID NO: 99), wherein "-" denotes the option of no amino acid residue being present at that consensus position. The antibodies may further include a light chain variable region CDR3 sequence comprising an amino acid sequence selected from the consensus sequence: Q Q (R,Y,F) (R,N) (T,S,N) (Y,W,-)

(P,-) (Y,L,H,-) (T,-) (SEQ ID NO: 102), wherein "-" denotes the option of no amino acid residue being present at that consensus position. In another embodiment, the heavy chain variable region CDR2 sequence comprises an amino acid sequence selected from the consensus sequence: (V,I,F,T,A) I (W,G) (Y,T) (D,G) G (S,G,Y) (N,T) (K,P) Y (Y,A,V) (A,G,-) D S V K G (SEQ ID NO: 98), wherein "-" denotes the option of no amino acid residue being present at that consensus position, and the light chain variable region CDR2 sequence comprises an amino acid sequence selected from the consensus sequence: (D,A) A S (N,S) (R,L) (A,Q,E) (T,S) (SEQ ID NO: 101). In another embodiment, the heavy chain variable region CDR1 sequence comprises an amino acid sequence selected from the consensus sequence: (I,N,T,S) Y (G,N,A) M (H,Y) (SEQ ID NO: 97); and the light chain variable region CDR1 sequence comprises an amino acid sequence selected from the consensus sequence: R A S Q (S,G) (I,V) S S (Y,W,A) L A (SEQ ID NO: 100).

In still another embodiment, the invention provides an isolated antibody that binds DEC-205 and includes heavy and light chain variable region CDR1, CDR2 and CDR3 sequences comprising:

(i) a heavy chain variable region CDR1 comprising an amino acid sequence selected from the consensus sequence: (I,N,T,S) Y (G,N,A) M (H,Y) (SEQ ID NO: 97);

(ii) a heavy chain variable region CDR2 comprising an amino acid sequence selected from the consensus sequence: (V,I,F,T,A) I (W,G) (Y,T) (D,G) G (S,G,Y) (N,T) (K,P) Y (Y,A,V) (A,G,-) D S V K G (SEQ ID NO: 98);

(iii) a heavy chain variable region CDR3 comprising an amino acid sequence selected from the consensus sequence: (A,G,Y,S,P,-) (P,W,S,R) (Y,A,H) F D (Y,L,V) (SEQ ID NO: 99);

(iv) a light chain variable region CDR1 comprising an amino acid sequence selected from the consensus sequence: R A S Q (S,G) (I,V) S S (Y,W,A) L A (SEQ ID NO: 100);

(v) a light chain variable region CDR2 comprising an amino acid sequence selected from the consensus sequence: (D,A) A S (N,S) (R,L) (A,Q,E) (T,S) (SEQ ID NO: 101); and

(vi) a light chain variable region CDR3 comprising an amino acid sequence selected from the consensus sequence: Q Q (R,Y,F) (R,N) (T,S,N) (Y,W,-) (P,-)

(Y,L,H,-) (T,-) (SEQ ID NO: 102), wherein "-" denotes the option of no amino acid residue being present at that consensus position.

In another embodiment, isolated antibodies of the invention bind to human DEC-205 and include a heavy chain variable region including an amino acid sequence selected from the group consisting of SEQ ID NOs: 4, 16, 28, 40, 52, 64, 70, 76, 88 and conservative sequence modifications thereof. The antibody may further include a light chain variable region including an amino acid sequence selected from the group consisting of SEQ ID NOs: 10, 22, 34, 46, 58, 82, and conservative sequence modifications thereof.

In a still further embodiment, isolated antibodies of the invention bind to human DEC-205 and include a heavy chain variable region and a light chain variable region including the amino acid sequences selected from the group consisting of:

(a) SEQ ID NOs:4 and 10, respectively, and conservative sequence modifications thereof;

(b) SEQ ID NOs: 16 and 22, respectively, and conservative sequence modifications thereof;

(c) SEQ ID NOs: 28 and 34, respectively, and conservative sequence modifications thereof;

(d) SEQ ID NOs: 40 and 46, respectively, and conservative sequence modifications thereof;

(e) SEQ ID NOs: 52 and 58, respectively, and conservative sequence modifications thereof; and

(f) SEQ ID NOs: 76 and 82, respectively, and conservative sequence modifications thereof.

Isolated antibodies which include heavy and light chain variable regions having at least 80%, or at least 85%, or at least 90%, or at least 95%, or at least 96%, or at least 97%, or at least 98%, or at least 99%, or more sequence identity to any of the above sequences are also included in the present invention. Ranges intermediate to the above-recited values, *e.g.*, heavy and light chain variable regions having at least 80-85%, 85-90%, 90-95% or 95-100% sequence identity to any of the above sequences are also intended to be encompassed by the present invention.

In another embodiment, the isolated antibody binds to human DEC-205 and includes a heavy chain variable region comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 4, 16, 28, 40, 52, 64, 70, 76, 88 or sequences where at least one amino acid residue in the framework region of the heavy chain variable region is substituted with the corresponding germline residue. The antibody may further include a light chain variable region comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 10, 22, 34, 46, 58, 82, or sequences where at least one amino acid residue in framework region of the light chain variable region is substituted with the corresponding germline residue. The substituted amino acid residue can include: a residue that non-covalently binds antigen directly; a residue adjacent to a CDR; a CDR-interacting residue; a residue participating in the VL-VH interface, a canonical residue, a vernier zone residue, or an interchain packing residue.

Also encompassed by the present invention are isolated antibodies which compete for binding to DEC-205 with the antibodies of the invention.

The antibodies of the invention can either be full-length, for example, any of the following isotypes: IgG1, IgG2, IgG3, IgG4, IgM, IgA1, IgA2, IgAsec, IgD, and IgE. Alternatively, the antibodies can be fragments such as an antigen-binding portion or a single chain antibody (*e.g.*, a Fab, $F(ab')_2$, Fv, a single chain Fv fragment, an isolated complementarity determining region (CDR) or a combination of two or more isolated CDRs).

The invention also provides a molecular conjugate comprising an antibody of the invention linked to an antigen (including fragments, epitopes and antigenic determinants), such as component of a pathogen, a tumor antigen or an autoantigen. For example, the antigen may include a tumor antigen, such as βhCG, gp100 or Pmel17, CEA, gp100, TRP-2, NY-BR-1, NY-CO-58, MN (gp250), idiotype, Tyrosinase, Telomerase, SSX2, MUC-1, MAGE-A3, and high molecular weight-melanoma associated antigen (HMW-MAA) MART1, melan-A, NY-ESO-1, MAGE-1, MAGE-3, WT1, Her2, mesothelin or high molecular weight-melanoma associated antigen (HMW-MAA).

The term "tumor antigen" as used herein preferably means any antigen or antigenic determinant which is present on (or associated with) a tumor cell and not typically on normal cells, or an antigen or antigenic determinant which is present on or associated with tumor cells in greater amounts than on normal (non-tumor) cells, or an antigen or antigenic determinant which is present on tumor cells in a different form than that found on normal (non-tumor) cells. The term thus includes tumor-specific antigens including tumor-specific membrane antigens, tumor-associated antigens, including tumor-associated membrane antigens, embryonic antigens on tumors, growth factor receptors, growth factor ligands, and any other type of antigen that is associated with cancer. A tumor antigen may be, for example, an epithelial cancer antigen, (e.g., breast, gastrointestinal, lung), a prostate specific cancer antigen (PSA) or prostate specific membrane antigen (PSMA), a bladder cancer antigen, a lung (e.g., small cell lung) cancer antigen, a colon cancer antigen, an ovarian cancer antigen, a brain cancer antigen, a gastric cancer antigen, a renal cell carcinoma antigen, a pancreatic cancer antigen, a liver cancer antigen, an esophageal cancer antigen, a head and neck cancer antigen, or a colorectal cancer antigen.

The term "fragment" refers to an amino acid sequence that is a portion of a full-length protein or polypeptide, for example between about 8 and about 1500 amino acids in length, suitably between about 8 and about 745 amino acids in length, suitably about 8 to about 300, for example about 8 to about 200 amino acids, or about 10 to about 50 or 100 amino acids in length.

In another embodiment, the molecular complex further includes a therapeutic agent, such as a cytotoxic agent, an immunosuppressive agent, or a chemotherapeutic agent.

The invention also provides a bispecific molecule comprising an antibody of the invention linked to a second functional moiety having a different binding specificity than said antibody.

Compositions including an antibody, a molecular conjugate or a bispecific molecule described herein, and a pharmaceutically effective carrier, are also provided. The compositions may further include a therapeutic agent (*e.g.*, an immunosuppressive agent or an antibody different from an antibody of the invention).

Nucleic acid molecules encoding the antibodies of the invention are also encompassed by the invention, as well as expression vectors comprising such nucleic acids and host cells comprising such expression vectors. Moreover, the invention provides a transgenic mouse comprising human immunoglobulin heavy and light chain transgenes, wherein the mouse expresses an antibody of the invention, as well as hybridomas prepared from such a mouse, wherein the hybridoma produces the antibody of the invention.

In another embodiment, the present invention provides methods for targeting an antigen to a cell, e.g., a cell capable of antigen presentation (such as peripheral blood mononuclear cells (PBMC), monocytes (such as THP-1), B lymphoblastoid cells (such as C1R.A2, 1518 B-LCL) and monocyte-derived DCs in a subject by administering a molecule which binds a receptor on the cell (e.g., the previously described DEC-205 antibodies) linked to an antigen. In one embodiment the targeted cell (which may be a B-cell) stimulates MHC Class I restricted T-cells.

The antibodies and other compositions of the present invention can also be used to induce or enhance an immune response (*e.g.*, a T cell-mediated immune response) against an antigen in a subject. Accordingly, in one embodiment, the present invention provides a method for inducing or enhancing a CTL response against an antigen by forming a conjugate of the antigen and a antibody which binds to a receptor on an antigen presenting cell, e.g., human DEC-205. The conjugate is then contacted, either *in vivo* or *ex vivo*, with cells expressing human DEC-205 such that the antigen is internalized, processed and presented to T cells in a manner which induces or enhances a CTL response (*e.g.*, a response mediated by $CD8^+$ cytotoxic T cells) against the antigen. In another embodiment, this serves also to induce a helper T cell response (*e.g.*, a response mediated by $CD4^+$ helper T cells) against the antigen. Thus, the immune response may be induced through both MHC class I and MHC class II pathways. The cells expressing DEC-205 can also be contacted with an adjuvant, a cytokine which stimulates proliferation of dendritic cells, and/or an immunostimulatory agent to further enhance the immune response.

In another embodiment, methods of detecting the presence of DEC-205, or a cell expressing DEC-205, in a sample are provided by: (a) contacting the sample with the antibody of the invention under conditions that allow for formation of a complex between the antibody and DEC-205; and (b) detecting the formation of a complex between the antibody and DEC-205 in the sample.

Also within the scope of the invention are kits comprising the compositions (*e.g.*, antibodies, molecular conjugates, multispecific and bispecific molecules) of the invention and, optionally, instructions for use. The kit can further contain a least one additional reagent, such as a cytokine or complement, or one or more additional human antibodies of the invention (*e.g.*, a human antibody having a complementary activity which binds to an epitope on dendritic cells distinct from the first human antibody).

Other features and advantages of the instant invention will be apparent from the following detailed description and claims.

Brief Description of the Drawings

Figures 1A-1I include graphs showing the binding of human anti-DEC-205 antibodies (3D6-2F4, 3D6-4C8, 3G9-2D2, 5A8-1F1, 2D3-1F5-2A9, 3C7-3A3, 5D12-5G1, 1G6-1G6 and 3A4-1C10) to CHO-S cells expressing human DEC-205 by fluorescence analysis using a LSR™ instrument (BD Biosciences, NJ, USA).

Figures 2A-2I include graphs showing the binding of human anti-DEC-205 antibodies (3D6-2F4, 3D6-4C8, 3G9-2D2, 5A8-1F1, 2D3-1F5-2A9, 3C7-3A3, 5D12-5G1, 1G6-1G6 and 3A4-1C10) to DEC-205 on human dendritic cells by flow cytometry.

Figure 3 is a graph showing the binding of human anti-DEC-205 antibodies (3D6-2F4, 3D6-4C8, 3G9-2D2, 5A8-1F1, 2D3-1F5-2A9, 3C7-3A3, 5D12-5G1, 1G6-1G6 and 3A4-1C10) to DEC-205 using ELISA.

Figures 4A-4C show internalization into the dendritic cells of FITC-labelled HuMab (FITC-3G9-2D2) compared to the control (FITC-human IgG1) using confocal microscopy.

Figure 5 is an alignment of human VH and VK Germline Sequences with VH and VK sequences of anti-DEC-205 antibodies (3D6-2F4, 3D6-4C8, 3G9-2D2, 5A8-1F1, 2D3-1F5-2A9, 3C7-3A3, 5C3-2-3F6, 1E6-3D10). Figure discloses SEQ ID NOS 92, 34, 46, 58, 93, 82, 22, 94, 10, 95, 4, 16, 103-105, 76, 88, 96, 106 and 70, respectively, in order of appearance.

Figure 6 shows alignments of VH CDR1, CDR2 and CDR3 sequences of human anti-DEC-205 antibodies (3D6-2F4, 3D6-4C8, 3G9-2D2, 5A8-1F1, 3C7-3A3, 2D3-1F5-2A9, 1E6-3D10, 5C3-2-3F6, 5D12-5G1).

Figure 7 shows alignments of human anti-DEC-205 HuMab VK CDR1, CDR2 and CDR3 sequences of human anti-DEC-205 antibodies (3D6-2F4, 3D6-4C8, 3G9-2D2, 5A8-1F1, 3C7-3A3, 5C3-2-3F6).

Figure 8 shows a schematic representation of an example of an anti-DEC-205/antigen fusion APC targeted vaccine construct.

Figures 9A and B include graphs showing antigen-specific activity using 3G9-βhCG APC-targeted vaccine conjugate in peripheral blood mononuclear cells (PBMC), monocytes (THP-1), B lymphoblastoid cells (C1R.A2, 1518 B-LCL) and monocyte-derived DCs.

Detailed Description of the Invention

The present invention provides antibodies (*e.g.*, human antibodies) which bind to human DEC-205. In certain embodiments, the antibodies exhibit a variety of functional properties, *e.g.*, binding to human DEC-205 with an affinity constant of at least 10^8 M^{-1} as measured by surface plasmon resonance, internalization after binding to human dendritic cells expressing DEC-205, generating or enhancing human T-cell responses, for example CD4+ or CD8+ (CTL) or NKT cell responses, to an antigen which may be linked to the antibody, e.g., CTL responses mediated by both MHC Class I and Class II pathways; localization to antigen processing compartments in dendritic cells; inducement of peripheral $CD8^+$ T cell tolerance; or cross-reaction with DEC-205 on non-human primate dendritic cells or those of other species. In other embodiments, the antibodies include heavy and light chain variable regions which utilize particular human germline genes and include particular structural features such as, particular CDR sequences. The invention further provides methods of making such antibodies, molecular conjugates and bispecific molecules including such antibodies, as well as compositions containing the antibodies. The invention also provides methods of targeting antigens to antigen presenting cells (e.g., peripheral blood mononuclear cells

(PBMC), monocytes (such as THP-1), B lymphoblastoid cells (such as C1R.A2, 1518 B-LCL) and monocyte-derived DCs either *in vitro* or *in vivo*, for example, by using the anti-DEC-205 antibodies of the present invention. Methods of the present invention also include methods of inducing and enhancing an immune response (*e.g.*, a T cell-mediated immune response) against an antigen in a subject. Such methods include the presentation of the antigen *via* a receptor on an antigen presenting cell (e.g., DEC-205) as a component of an MHC-I and/or MHC-II conjugate (*e.g.*, the T cell response is mediated by both CD4+ and CD8+ T cells or by cytotoxic T cells or helper T cells). In one embodiment the targeted cell (which may be a B-cell) stimulates MHC Class I restricted T-cells.

In order that the present invention may be more readily understood, certain terms are first defined. Additional definitions are set forth throughout the detailed description.

The term "human Dendritic and Epithelial Cell 205 receptor" (DEC-205) includes any variants or isoforms of DEC-205 which are naturally expressed by cells (*e.g.*, human DEC-205 deposited with GENBANK® having accession no. AAC17636, and mouse DEC-205 deposited with GENBANK® having accession no. AAL81722). Accordingly, human antibodies of the invention may cross-react with DEC-205 from species other than human. Alternatively, the antibodies may be specific for human DEC-205 and may not exhibit any cross-reactivity with other species. DEC-205 or any variants and isoforms thereof, may either be isolated from cells or tissues which naturally express them (*e.g.* human, mouse and cynomologous monkey cells) or be recombinantly produced using well-known techniques in the art and/or those described herein.

Genbank® (Accession No. AAC17636A) reports the amino acid sequence of human DEC-205 as follows (SEQ ID NO:1):

1 mrtgwatprr pagllmllfw ffdlaepsgr aandpftivh gntgkcikpv ygwivaddcd
61 etedklwkwv sqhrlfhlhs qkclglditk svnelrmfsc dssamlwwkc ehhslygaar
121 yrlalkdghg taisnasdvw kkggseeslc dqpyheiytr dgnsygrpce fpflidgtwh
181 hdcildedhs gpwcattlny eydrkwgicl kpengcednw ekneqfgscy qfntqtalsw
241 keayvscqnq gadllsinsa aeltylkeke giakifwigl nqlysargwe wsdhkplnfl

301 nwdpdrpsap tiggsscarm daesglwqsf sceaqlpyvc rkplnntvel tdvwtysdtr
361 cdagwlpnng fcyllvnesn swdkahakck afssdlisih sladvevvvt klhnedikee
421 vwiglknini ptlfqwsdgt evtltywden epnvpynktp ncvsylgelg qwkvqsceek
481 lkyvckrkge klndassdkm cppdegwkrh getcykiyed evpfgtncnl titsrfeqey
541 lndlmkkydk slrkyfwtgl rdvdscgeyn watvggrrra vtfsnwnfle paspggcvam
601 stgksvgkwe vkdcrsfkal sickkmsgpl gpeeaspkpd dpcpegwqsf paslscykvf
661 haerivrkrn weeaerfcqa lgahlssfsh vdeikeflhf ltdqfsgqhw lwiglnkrsp
721 dlqgswqwsd rtpvstiimp nefqqdydir dcaavkvfhr pwrrgwhfyd drefiylrpf
781 acdtklewvc qipkgrtpkt pdwynpdrag ihgppliieg seywfvadlh lnyeeavlyc
841 asnhsflati tsfvglkaik nkianisgdg qkwwirisew piddhftysr ypwhrfpvtf
901 geeclymsak twlidlgkpt dcstklpfic ekynvsslek yspdsaakvq cseqwipfqn
961 kcflkikpvs ltfsqasdtc hsyggtlpsv lsqieqdfit sllpdmeatl wiglrwtaye
1021 kinkwtdnre ltysnfhpll vsgrlripen ffeeesryhc alilnlqksp ftgtwnftsc
1081 serhfvslcq kysevksrqt lqnasetvky lnnlykiipk tltwhsakre clksnmqlvs
1141 itdpyqqafl svqallhnss lwiglfsqdd elnfgwsdgk rlhfsrwaet ngqledcvvl
1201 dtdgfwktvd cndnqpgaic yysgneteke vkpvdsvkcp spvlntpwip fqnccynfii
1261 tknrhmattq devhtkcqkl npkshilsir dekennfvle qllyfnymas wvmlgityrn
1321 nslmwfdktp lsythwragr ptiknekfla glstdgfwdi qtfkvieeav yfhqhsilac
1381 kiemvdykee hnttlpqfmp yedgiysviq kkvtwyealn mcsqsgghla svhnqngqlf
1441 ledivkrdgf plwvglsshd gsessfewsd gstfdyipwk gqtspgncvl ldpkgtwkhe
1501 kcnsvkdgai cykptkskkl srltyssrcp aakengsrwi qykghcyksd qalhsfseak
1561 klcskhdhsa tivsikdede nkfvsrlmre nnnitmrvwl glsqhsvdqs wswldgsevt
1621 fvkwenksks gvgrcsmlia snetwkkvec ehgfgrvvck vplgpdytai aiivatlsil
1681 vlmggliwfl fqrhrlhlag fssvryaqgv nedeimlpsf hd

The major domains of human DEC-205 can be represented as follows:

N-CR-FNII-CTLD1-CTLD2-CTLD3-CTLD4-CTLD5-CTLD6-CTLD7-CTLD8-CTLD9-CTLD10-TMC

Where N is the N-terminus, CR represents the “Cys Rich” domain, FNII represents the "Fibronectin Type II" domain, CTLD1 to CTLD10 represent the ten “C-Type Lectin-Like” domains and TMC represents the transmembrane and cytoplasmic domains.

The term “dendritic cell” as used herein, includes immature and mature dendritic cells and related myeloid progenitor cells that are capable of differentiating into dendritic cells, or related antigen presenting cells (*e.g.*, monocytes and macrophages) in that they express antigens in common with dendritic cells. As used herein, the term "related" includes a cell that is derived from a common progenitor cell or cell lineage. In one embodiment, binding of an antibody of the invention to dendritic cells mediates an effect on dendritic cell growth and/or function by targeting molecules or cells with defined functions (*e.g.*, tumor cells, effector cells, microbial pathogens) to dendritic cells. In a further embodiment, binding of an antibody of the invention to a dendritic cell results in internalization of the antibody by the dendritic cell.

"MHC molecules" include two types of molecules, MHC class I and MHC class II. MHC class I molecules present antigen to specific $CD8^+$ T cells and MHC class II molecules present antigen to specific $CD4^+$ T cells. Antigens delivered exogenously to APCs are processed primarily for association with MHC class II. In contrast, antigens delivered endogenously to APCs are processed primarily for association with MHC class I. However, under specific conditions, DCs have the unique capacity to allow exogenous antigens access to internal compartments for binding to MHC class I molecules, in addition to MHC class II molecules. This process is called "cross-priming" or "cross-presentation."

As used herein, the term "immunostimulatory agent" refers to compounds capable of stimulating APCs, such as DCs and macrophages. For example, suitable immunostimulatory agents for use in the present invention are capable of stimulating APCs so that the maturation process of the APCs is accelerated, the proliferation of APCs is increased, and/or the recruitment or release of co-stimulatory molecules (*e.g.*, CD80, CD86, ICAM-1, MHC molecules and CCR7) and pro-inflammatory cytokines (*e.g.*, IL-1β, IL-6, IL-12, IL-15, and IFN-γ) is upregulated. Suitable immunostimulatory agents are also capable of increasing T cell proliferation. Such immunostimulatory agents include, but are not be limited to, CD40 ligand; cytokines, such as IFN-α, IFN-β, IFN-γ and IL-2; colony-stimulating factors, such as G-CSF (granulocyte colony-stimulating factor) and GM-CSF (granulocyte-macrophage colony-stimulating factor); an anti-CTLA-4 antibody; LPS (endotoxin); ssRNA; dsRNA; Bacille Calmette-Guerin (BCG); Levamisole hydrochloride; and intravenous immune globulins. In one embodiment an immunostimulatory agant may be a Toll-like Receptor (TLR) agonist. For example the immunostimulatory agent may be a TLR3 agonist such as double-stranded inosine:cytosine polynucleotide (Poly I:C, for example available as AmpligenTM from Hemispherx Bipharma, PA, US) or Poly A:U; a TLR4 agonist such as monophosphoryl lipid A (MPL) or RC-529 (for example as available from GSK, UK); a TLR5 agonist such as flagellin; a TLR7 or TLR8 agonist such as an imidazoquinoline TLR7 or TLR 8 agonist, for example imiquimod (eg AldaraTM) or resiquimod and related imidazoquinoline agents (for example as available from 3M Corporation); or a TLR 9 agonist such as a deoxynucleotide with unmethylated CpG motifs (so-called "CpGs", for example as available from Coley Pharmaceutical). Such immunostimulatory agents may be administered simultaneously, separately or sequentially with the antibodies and constructs of the present invention and may also be physically linked to the antibodies and constructs.

As used herein, the term "linked" refers to the association of two or more molecules. The linkage can be covalent or non-covalent. The linkage also can be genetic (*i.e.*, recombinantly fused). Such linkages can be achieved using a wide variety of art recognized techniques, such as chemical conjugation and recombinant protein production.

As used herein, the term antigen "cross-presentation" refers to presentation of exogenous protein antigens to T cells via MHC class I and class II molecules on APCs.

As used herein, the term "T cell-mediated response" refers to any response mediated by T cells, including effector T cells (*e.g.*, $CD8^+$ cells) and helper T cells (*e.g.*, $CD4^+$ cells). T cell mediated responses include, for example, T cell cytotoxicity and proliferation.

As used herein, the term "cytotoxic T lymphocyte (CTL) response" refers to an immune response induced by cytotoxic T cells. CTL responses are mediated primarily by $CD8^+$ T cells.

The term "antibody" as referred to herein includes whole antibodies and any antigen binding fragment (*i.e.*, "antigen-binding portion") or single chain thereof. An "antibody" refers, in one preferred embodiment, to a glycoprotein comprising at least two heavy (H) chains and two light (L) chains inter-connected by disulfide bonds, or an antigen binding portion thereof. Each heavy chain is comprised of a heavy chain variable region (abbreviated herein as V_H) and a heavy chain constant region. The heavy chain constant region is comprised of three domains, CH1, CH2 and CH3. Each light chain is comprised of a light chain variable region (abbreviated herein as V_L) and a light chain constant region. The light chain constant region is comprised of one domain, CL. The V_H and V_L regions can be further subdivided into regions of hypervariability, termed complementarity determining regions (CDR), interspersed with regions that are more conserved, termed framework regions (FR). Each V_H and V_L is composed of three CDRs and four FRs, arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4. The variable regions of the heavy and light chains contain a binding domain that interacts with an antigen. The constant regions of the antibodies may mediate the binding of the immunoglobulin to host tissues or factors, including various cells of the immune system (*e.g.*, effector cells) and the first component (Clq) of the classical complement system.

The term "antigen-binding portion" of an antibody (or simply "antibody portion"), as used herein, refers to one or more fragments of an antibody that retain the ability to specifically bind to an antigen (*e.g.*, human DEC-205). It has been shown that the antigen-binding function of an antibody can be performed by fragments of a full-length antibody. Examples of binding fragments encompassed within the term "antigen-binding portion" of an antibody include (i) a Fab fragment, a monovalent fragment consisting of the V_L, V_H, CL and CH1 domains; (ii) a $F(ab')_2$ fragment, a bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region; (iii) a Fd fragment consisting of the V_H and CH1 domains; (iv) a Fv fragment consisting of the V_L and V_H domains of a single arm of an antibody, (v) a dAb fragment (Ward *et al.*, (1989) *Nature* 341:544-546), which consists of a V_H domain; and (vi) an isolated complementarity determining region (CDR) or (vii) a combination of two or more isolated CDRs which may optionally be joined by a synthetic linker. Furthermore, although the two domains of the Fv fragment, V_L and V_H, are coded for by separate genes, they can be joined, using recombinant methods, by a synthetic linker that enables them to be made as a single protein chain in which the V_L and V_H regions pair to form monovalent molecules (known as single chain Fv (scFv); see *e.g.*, Bird *et al.* (1988) *Science* 242:423-426; and Huston *et al.* (1988) *Proc. Natl. Acad. Sci. USA* 85:5879-5883). Such single chain antibodies are also intended to be encompassed within the term "antigen-binding portion" of an antibody. These antibody fragments are obtained using conventional techniques known to those with skill in the art, and the fragments are screened for utility in the same manner as are intact antibodies. Antigen-binding portions can be produced by recombinant DNA techniques, or by enzymatic or chemical cleavage of intact immunoglobulins.

A "bispecific" or "bifunctional antibody" is an artificial hybrid antibody having two different heavy/light chain pairs and two different binding sites. Bispecific antibodies can be produced by a variety of methods including fusion of hybridomas or linking of Fab' fragments. See, *e.g.*, Songsivilai & Lachmann, *Clin. Exp. Immunol.* 79:315-321 (1990); Kostelny *et al.*, *J. Immunol.* 148, 1547-1553 (1992).

The term "monoclonal antibody," as used herein, refers to an antibody which displays a single binding specificity and affinity for a particular epitope. Accordingly, the term "human monoclonal antibody" refers to an antibody which displays a single binding specificity and which has variable and optional constant regions derived from human germline immunoglobulin sequences. In one embodiment, human monoclonal antibodies are produced by a hybridoma which includes a B cell obtained from a transgenic non-human animal, *e.g.*, a transgenic mouse, having a genome comprising a human heavy chain transgene and a light chain transgene fused to an immortalized cell.

The term "recombinant human antibody," as used herein, includes all human antibodies that are prepared, expressed, created or isolated by recombinant means, such as (a) antibodies isolated from an animal (*e.g.*, a mouse) that is transgenic or transchromosomal for human immunoglobulin genes or a hybridoma prepared therefrom, (b) antibodies isolated from a host cell transformed to express the antibody, *e.g.*, from a transfectoma, (c) antibodies isolated from a recombinant, combinatorial human antibody library, and (d) antibodies prepared, expressed, created or isolated by any other means that involve splicing of human immunoglobulin gene sequences to other DNA sequences. Such recombinant human antibodies comprise variable and constant regions that utilize particular human germline immunoglobulin sequences are encoded by the germline genes, but include subsequent rearrangements and mutations which occur, for example, during antibody maturation. As known in the art (see, *e.g.*, Lonberg (2005) Nature Biotech. 23(9):1117-1125), the variable region contains the antigen binding domain, which is encoded by various genes that rearrange to form an antibody specific for a foreign antigen. In addition to rearrangement, the variable region can be further modified by multiple single amino acid changes (referred to as somatic mutation or hypermutation) to increase the affinity of the antibody to the foreign antigen. The constant region will change in further response to an antigen (*i.e.*, isotype switch). Therefore, the rearranged and somatically mutated nucleic acid molecules that encode the light chain and heavy chain immunoglobulin polypeptides in response to an antigen may not have sequence identity with the original nucleic acid molecules, but instead will be substantially identical or similar (*i.e.*, have at least 80% identity).

The term "human antibody" includes antibodies having variable and constant regions (if present) of human germline immunoglobulin sequences. Human antibodies of the invention can include amino acid residues not encoded by human germline immunoglobulin sequences (*e.g.*, mutations introduced by random or site-specific mutagenesis *in vitro* or by somatic mutation *in vivo*) (*see*, Lonberg, N. *et al.* (1994) *Nature* 368(6474): 856-859); Lonberg, N. (1994) *Handbook of Experimental Pharmacology* 113:49-101; Lonberg, N. and Huszar, D. (1995) *Intern. Rev. Immunol.* Vol. 13: 65-93, and Harding, F. and Lonberg, N. (1995) *Ann. N.Y. Acad. Sci* 764:536-546). However, the term "human antibody" does not include antibodies in which CDR sequences derived from the germline of another mammalian species, such as a mouse, have been grafted onto human framework sequences (*i.e.*, humanized antibodies).

As used herein, a "heterologous antibody" is defined in relation to the transgenic non-human organism producing such an antibody. This term refers to an antibody having an amino acid sequence or an encoding nucleic acid sequence corresponding to that found in an organism not consisting of the transgenic non-human animal, and generally from a species other than that of the transgenic non-human animal.

An "isolated antibody," as used herein, is intended to refer to an antibody which is substantially free of other antibodies having different antigenic specificities (*e.g.*, an isolated antibody that specifically binds to human DEC-205 is substantially free of antibodies that specifically bind antigens other than human DEC-205). An isolated antibody that specifically binds to an epitope of may, however, have cross-reactivity to other DEC-205 proteins from different species. However, the antibody preferably always binds to human DEC-205. In addition, an isolated antibody is typically substantially free of other cellular material and/or chemicals. In one embodiment of the invention, a combination of "isolated" antibodies having different DEC-205 specificities is combined in a well defined composition.

The term "epitope" or "antigenic determinant" refers to a site on an antigen to which an immunoglobulin or antibody specifically binds. Epitopes can be formed both from contiguous amino acids or noncontiguous amino acids juxtaposed by tertiary folding of a protein. Epitopes formed from contiguous amino acids are typically retained on exposure to denaturing solvents, whereas epitopes formed by tertiary folding are typically lost on treatment with denaturing solvents. An epitope typically includes at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15 amino acids in a unique spatial conformation. Methods of determining spatial conformation of epitopes include techniques in the art and those described herein, for example, x-ray crystallography and 2-dimensional nuclear magnetic resonance (see, *e.g.*, *Epitope Mapping Protocols in Methods in Molecular Biology,* Vol. 66, G. E. Morris, Ed. (1996)). In the present case an epitope is preferably located in the extracellular domain of human DEC-205, for example in one or a combination of the cysteine rich domain, the FnII domain or one or more of the ten C-type lectin-like domains of human DEC-205.

As used herein, the terms "specific binding," "selective binding," "selectively binds," and "specifically binds," refer to antibody binding to an epitope on a predetermined antigen. Typically, the antibody binds with an equilibrium dissociation constant (K_D) of approximately less than 10^{-7} M, such as approximately less than 10^{-8} M, 10^{-9} M or 10^{-10} M or even lower when determined by surface plasmon resonance (SPR) technology in a BIACORE 2000 instrument using recombinant human DEC-205 as the analyte and the antibody as the ligand and binds to the predetermined antigen with an affinity that is at least two-fold greater than its affinity for binding to a non-specific antigen (*e.g.*, BSA, casein) other than the predetermined antigen or a closely-related antigen. The phrases "an antibody recognizing an antigen" and "an antibody specific for an antigen" are used interchangeably herein with the term "an antibody which binds specifically to an antigen."

Also encompassed by the present invention are antibodies that bind the same epitope and/or antibodies that compete for binding to human DEC-205 with the antibodies described herein. Antibodies that recognize the same epitope or compete for binding can be identified using routine techniques. Such techniques include, for example, an immunoassay, which shows the ability of one antibody to block the binding of another antibody to a target antigen, *i.e.*, a competitive binding assay. Competitive binding is determined in an assay in which the immunoglobulin under test inhibits specific binding of a reference antibody to a common antigen, such as DEC-205. Numerous types of competitive binding assays are known, for example: solid phase direct or indirect radioimmunoassay (RIA), solid phase direct or indirect enzyme immunoassay (EIA), sandwich competition assay (see Stahli *et al.*, *Methods in*

Enzymology 9:242 (1983)); solid phase direct biotin-avidin EIA (see Kirkland *et al.*, *J. Immunol.* 137:3614 (1986)); solid phase direct labeled assay, solid phase direct labeled sandwich assay (see Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Press (1988)); solid phase direct label RIA using I-125 label (see Morel *et al.*, *Mol. Immunol.* 25(1):7 (1988)); solid phase direct biotin-avidin EIA (Cheung *et al.*, *Virology* 176:546 (1990)); and direct labeled RIA. (Moldenhauer *et al.*, *Scand. J. Immunol.* 32:77 (1990)). Typically, such an assay involves the use of purified antigen bound to a solid surface or cells bearing either of these, an unlabeled test immunoglobulin and a labeled reference immunoglobulin. Competitive inhibition is measured by determining the amount of label bound to the solid surface or cells in the presence of the test immunoglobulin. Usually the test immunoglobulin is present in excess. Usually, when a competing antibody is present in excess, it will inhibit specific binding of a reference antibody to a common antigen by at least 50-55%, 55-60%, 60-65%, 65-70% 70-75% or more.

Other techniques include, for example, epitope mapping methods, such as, x-ray analyses of crystals of antigen:antibody complexes which provides atomic resolution of the epitope. Other methods monitor the binding of the antibody to antigen fragments or mutated variations of the antigen where loss of binding due to a modification of an amino acid residue within the antigen sequence is often considered an indication of an epitope component. In addition, computational combinatorial methods for epitope mapping can also be used. These methods rely on the ability of the antibody of interest to affinity isolate specific short peptides from combinatorial phage display peptide libraries. The peptides are then regarded as leads for the definition of the epitope corresponding to the antibody used to screen the peptide library. For epitope mapping, computational algorithms have also been developed which have been shown to map conformational discontinuous epitopes.

The term "K_D" as used herein, is intended to refer to the dissociation equilibrium constant of a particular antibody-antigen interaction. Typically, the human antibodies of the invention bind to DEC-205 with a dissociation equilibrium constant (K_D) of approximately 10^{-8} M or less, such as less than 10^{-9} M or 10^{-10} M or even lower when determined by surface plasmon resonance (SPR) technology in a BIACORE 2000 instrument using recombinant human DEC-205 as the analyte and the antibody as the ligand.

The term "kd" as used herein, is intended to refer to the off rate constant for the dissociation of an antibody from the antibody/antigen complex.

The term "ka" as used herein, is intended to refer to the on rate constant for the association of an antibody with the antigen.

The term "EC50," as used herein, refers to the concentration of an antibody or an antigen-binding portion thereof, which induces a response, either in an *in vitro* or an *in vivo* assay, which is 50% of the maximal response, *i.e.*, halfway between the maximal response and the baseline.

As used herein, "isotype" refers to the antibody class (*e.g.*, IgM or IgGl) that is encoded by heavy chain constant region genes. In one embodiment, a human monoclonal antibody of the invention is of the IgG1 isotype. In another embodiment, a human monoclonal antibody of the invention is of the IgG2 isotype.

The term "binds to immobilized DEC-205," refers to the ability of a human antibody of the invention to bind to DEC-205, for example, expressed on the surface of a cell or which is attached to a solid support.

The term "cross-reacts," as used herein, refers to the ability of an antibody of the invention to bind to DEC-205 from a different species. For example, an antibody of the present invention which binds human DEC-205 may also bind cynomologous DEC-205. As used herein, cross-reactivity is measured by detecting a specific reactivity with purified antigen in binding assays (*e.g.*, SPR, ELISA) or binding to, or otherwise functionally interacting with, cells physiologically expressing DEC-205. Methods for determining cross-reactivity include standard binding assays as described herein, for example, by Biacore™ surface plasmon resonance (SPR) analysis using a Biacore™ 2000 SPR instrument (Biacore AB, Uppsala, Sweden), or binding to DEC-205 expressing cells from the species concerned (*e.g.*, dendritic cells) by, for example, flow cytometric techniques.

As used herein, "isotype switching" refers to the phenomenon by which the class, or isotype, of an antibody changes from one Ig class to one of the other Ig classes.

As used herein, "nonswitched isotype" refers to the isotypic class of heavy chain that is produced when no isotype switching has taken place; the CH gene encoding the nonswitched isotype is typically the first CH gene immediately downstream from the functionally rearranged VDJ gene. Isotype switching has been classified as classical or non-classical isotype switching. Classical isotype switching occurs by recombination events which involve at least one switch sequence region in the transgene. Non-classical isotype switching may occur by, for example, homologous recombination between human σ_μ and human $\sum_\mu$ (δ-associated deletion). Alternative non-classical switching mechanisms, such as intertransgene and/or interchromosomal recombination, among others, may occur and effectuate isotype switching.

As used herein, the term "switch sequence" refers to those DNA sequences responsible for switch recombination. A "switch donor" sequence, typically a μ switch region, will be 5' (*i.e.*, upstream) of the construct region to be deleted during the switch recombination. The "switch acceptor" region will be between the construct region to be deleted and the replacement constant region (*e.g.*, γ, ε, etc.). As there is no specific site where recombination always occurs, the final gene sequence will typically not be predictable from the construct.

As used herein, "glycosylation pattern" is defined as the pattern of carbohydrate units that are covalently attached to a protein, more specifically to an immunoglobulin protein. A glycosylation pattern of a heterologous antibody can be characterized as being substantially similar to glycosylation patterns which occur naturally on antibodies produced by the species of the nonhuman transgenic animal, when one of ordinary skill in the art would recognize the glycosylation pattern of the heterologous antibody as being more similar to said pattern of glycosylation in the species of the nonhuman transgenic animal than to the species from which the CH genes of the transgene were derived.

The term "naturally-occurring" as used herein as applied to an object refers to the fact that an object can be found in nature. For example, a polypeptide or polynucleotide sequence that is present in an organism (including viruses) that can be isolated from a source in nature and which has not been intentionally modified by man in the laboratory is naturally-occurring.

The term "rearranged" as used herein refers to a configuration of a heavy chain or light chain immunoglobulin locus wherein a V segment is positioned immediately adjacent to a D-J or J segment in a conformation encoding essentially a complete V_H or V_L domain, respectively. A rearranged immunoglobulin gene locus can be identified by comparison to germline DNA; a rearranged locus will have at least one recombined heptamer/nonamer homology element.

The term "unrearranged" or "germline configuration" as used herein in reference to a V segment refers to the configuration wherein the V segment is not recombined so as to be immediately adjacent to a D or J segment.

The term "nucleic acid molecule," as used herein, is intended to include DNA molecules and RNA molecules. A nucleic acid molecule may be single-stranded or double-stranded, but preferably is double-stranded DNA.

The term "isolated nucleic acid molecule," as used herein in reference to nucleic acids encoding antibodies or antibody portions (*e.g.*, V_H, V_L, CDR3) that bind to DEC-205, is intended to refer to a nucleic acid molecule in which the nucleotide sequences encoding the antibody or antibody portion are free of other nucleotide sequences encoding antibodies or antibody portions that bind antigens other than DEC-205, which other sequences may naturally flank the nucleic acid in human genomic DNA. For example, SEQ ID NOs: 2, 3 (with signal peptide) / 4 (without signal peptide), and SEQ ID NOs: 8, 9(with signal peptide) / 10 (without signal peptide) correspond, respectively, to the nucleotide and amino acid sequences comprising the heavy chain (V_H) and light chain (V_L) variable regions of the human anti-DEC-205 antibody 3D6-2F4 of the invention. In particular, SEQ ID NO: 2 and 3/4 correspond to the nucleotide and amino acid sequence, respectively, of V_H of the 3D6-2F4 antibody, SEQ ID NO: 8 and 9/10 correspond to the nucleotide and amino acid sequence, respectively, of V_L of the 3D6-2F4 antibody.

The present invention also encompasses "conservative sequence modifications" of the sequences set forth in SEQ ID NOs: 2-91, *i.e.*, nucleotide and amino acid sequence modifications which do not abrogate the binding of the antibody encoded by the nucleotide sequence or containing the amino acid sequence, to the antigen. Such conservative sequence modifications include conservative nucleotide and amino acid substitutions, as well as, nucleotide and amino acid additions and deletions. For example, modifications can be introduced into SEQ ID NOs: 2-91 by standard techniques known in the art, such as site-directed mutagenesis and PCR-mediated mutagenesis. Conservative amino acid substitutions include ones in which the amino acid residue is replaced with an amino acid residue having a similar side chain. Families of amino acid residues having similar side chains have been defined in the art. These families include amino acids with basic side chains (*e.g.*, lysine, arginine, histidine), acidic side chains (*e.g.*, aspartic acid, glutamic acid), uncharged polar side chains (*e.g.*, glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine, tryptophan), nonpolar side chains (*e.g.*, alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine), beta-branched side chains (*e.g.*, threonine, valine, isoleucine) and aromatic side chains (*e.g.*, tyrosine, phenylalanine, tryptophan, histidine). Thus, a predicted nonessential amino acid residue in a human anti-DEC-205 antibody is preferably replaced with another amino acid residue from the same side chain family. Methods of identifying nucleotide and amino acid conservative substitutions which do not eliminate antigen binding are well-known in the art (see, *e.g.*, Brummell *et al.*, *Biochem.* 32:1180-1187 (1993); Kobayashi *et al. Protein Eng.* 12(10):879-884 (1999); and Burks *et al. Proc. Natl. Acad. Sci. USA* 94:412-417 (1997))

Alternatively, in another embodiment, mutations can be introduced randomly along all or part of an anti-DEC-205 antibody coding sequence, such as by saturation mutagenesis, and the resulting modified anti-DEC-205 antibodies can be screened for binding activity.

For nucleic acids, the term "substantial homology" indicates that two nucleic acids, or designated sequences thereof, when optimally aligned and compared, are identical, with appropriate nucleotide insertions or deletions, in at least about 80% of the nucleotides, usually at least about 90% to 95%, and more preferably at least about 98% to 99.5% of the nucleotides. Alternatively, substantial homology exists when the segments will hybridize under selective hybridization conditions, to the complement of the strand.

The percent identity between two sequences is a function of the number of identical positions shared by the sequences (*i.e.*, % homology = # of identical positions/total # of positions x 100), taking into account the number of gaps, and the length of each gap, which need to be introduced for optimal alignment of the two sequences. The comparison of sequences and determination of percent identity between two sequences can be accomplished using a mathematical algorithm, as described in the non-limiting examples below.

The percent identity between two nucleotide sequences can be determined using the GAP program in the GCG software package (available at http://www.gcg.com), using a NWSgapdna.CMP matrix and a gap weight of 40, 50, 60, 70, or 80 and a length weight of 1, 2, 3, 4, 5, or 6. The percent identity between two nucleotide or amino acid sequences can also be determined using the algorithm of E.

Meyers and W. Miller (CABIOS, 4:11-17 (1989)) which has been incorporated into the ALIGN program (version 2.0), using a PAM120 weight residue table, a gap length penalty of 12 and a gap penalty of 4. In addition, the percent identity between two amino acid sequences can be determined using the Needleman and Wunsch (*J. Mol. Biol.* (48):444-453 (1970)) algorithm which has been incorporated into the GAP program in the GCG software package (available at http://www.gcg.com), using either a Blossum 62 matrix or a PAM250 matrix, and a gap weight of 16, 14, 12, 10, 8, 6, or 4 and a length weight of 1, 2, 3, 4, 5, or 6.

The nucleic acid and protein sequences of the present invention can further be used as a "query sequence" to perform a search against public databases to, for example, identify related sequences. Such searches can be performed using the NBLAST and XBLAST programs (version 2.0) of Altschul, *et al.* (1990) *J. Mol. Biol.* 215:403-10. BLAST nucleotide searches can be performed with the NBLAST program, score = 100, wordlength = 12 to obtain nucleotide sequences homologous to the nucleic acid molecules of the invention. BLAST protein searches can be performed with the XBLAST program, score = 50, wordlength = 3 to obtain amino acid sequences homologous to the protein molecules of the invention. To obtain gapped alignments for comparison purposes, Gapped BLAST can be utilized as described in Altschul *et al.*, (1997) *Nucleic Acids Res.* 25(17):3389-3402. When utilizing BLAST and Gapped BLAST programs, the default parameters of the respective programs (*e.g.*, XBLAST and NBLAST) can be used. See http://www.ncbi.nlm.nih.gov.

The nucleic acids may be present in whole cells, in a cell lysate, or in a partially purified or substantially pure form. A nucleic acid is "isolated" or "rendered substantially pure" when purified away from other cellular components or other contaminants, *e.g.*, other cellular nucleic acids or proteins, by standard techniques, including alkaline/SDS treatment, CsCl banding, column chromatography, agarose gel electrophoresis and others well known in the art. *See*, F. Ausubel, *et al.*, ed. Current Protocols in Molecular Biology, Greene Publishing and Wiley Interscience, New York (1987).

The nucleic acid compositions of the present invention, while often in a native sequence (except for modified restriction sites and the like), from either cDNA, genomic or mixtures thereof may be mutated, in accordance with standard techniques to provide gene sequences. For coding sequences, these mutations, may affect amino acid sequence as desired. In particular, DNA sequences substantially homologous to or derived from native V, D, J, constant, switches and other such sequences described herein are contemplated (where "derived" indicates that a sequence is identical or modified from another sequence).

A nucleic acid is “operably linked” when it is placed into a functional relationship with another nucleic acid sequence. For instance, a promoter or enhancer is operably linked to a coding sequence if it affects the transcription of the sequence. With respect to transcription regulatory sequences, operably linked means that the DNA sequences being linked are contiguous and, where necessary to join two protein coding regions, contiguous and in reading frame. For switch sequences, operably linked indicates that the sequences are capable of effecting switch recombination.

The term “vector,” as used herein, is intended to refer to a nucleic acid molecule capable of transporting another nucleic acid to which it has been linked. One type of vector is a “plasmid,” which refers to a circular double stranded DNA loop into which additional DNA segments may be ligated. Another type of vector is a viral vector, wherein additional DNA segments may be ligated into the viral genome. Certain vectors are capable of autonomous replication in a host cell into which they are introduced (*e.g.*, bacterial vectors having a bacterial origin of replication and episomal mammalian vectors). Other vectors (*e.g.*, non-episomal mammalian vectors) can be integrated into the genome of a host cell upon introduction into the host cell, and thereby are replicated along with the host genome. Moreover, certain vectors are capable of directing the expression of genes to which they are operatively linked. Such vectors are referred to herein as “recombinant expression vectors”(or simply, “expression vectors”) In general, expression vectors of utility in recombinant DNA techniques are often in the form of plasmids. In the present specification, “plasmid” and “vector” may be used interchangeably as the plasmid is the most commonly used form of vector. However, the invention is intended to include such other forms of expression vectors, such as viral vectors (*e.g.*, replication defective retroviruses, adenoviruses and adeno-associated viruses), which serve equivalent functions.

The term “recombinant host cell” (or simply “host cell”), as used herein, is intended to refer to a cell into which a recombinant expression vector has been introduced. It should be understood that such terms are intended to refer not only to the particular subject cell but to the progeny of such a cell. Because certain modifications may occur in succeeding generations due to either mutation or environmental influences, such progeny may not, in fact, be identical to the parent cell, but are still included within the scope of the term "host cell" as used herein.

The term "antigen presenting cell" or "APC" is a cell that displays foreign antigen complexed with MHC on its surface. T-cells recognize this complex using T-cell receptor (TCR). Examples of APCs include, but are not limited to, dendritic cells (DCs), peripheral blood mononuclear cells (PBMC), monocytes (such as THP-1), B lymphoblastoid cells (such as C1R.A2, 1518 B-LCL) and monocyte-derived dendritic cells (DCs). Some APCs internalize antigens either by phagocytosis or by receptor-mediated endocytosis. Examples of APC receptors include, but are not limited to C-type lectins, such as, the human Dendritic and Epithelial Cell 205 receptor (DEC-205), and the human macrophage mannose receptor.

The term "antigen presentation" refers to the process by which APCs capture antigens and enables their recognition by T-cells, *e.g.*, as a component of an MHC-I and/or MHC-II conjugate.

The terms "inducing an immune response" and "enhancing an immune response" are used interchangeably and refer the stimulation of an immune response (*i.e.*, either passive or adaptive) to a particular antigen.

The terms "treat," "treating," and "treatment," as used herein, refer to therapeutic or preventative measures described herein. The methods of "treatment" employ administration to a subject, in need of such treatment, a human antibody of the present invention, for example, a subject in need of an enhanced immune response against a particular antigen or a subject who ultimately may acquire such a disorder, in order to prevent, cure, delay, reduce the severity of, or ameliorate one or more symptoms of the disorder or recurring disorder, or in order to prolong the survival of a subject beyond that expected in the absence of such treatment.

The term "effective dose" or "effective dosage" is defined as an amount sufficient to achieve or at least partially achieve the desired effect. The term "therapeutically effective dose" is defined as an amount sufficient to cure or at least partially arrest the disease and its complications in a patient already suffering from the disease. Amounts effective for this use will depend upon the severity of the disorder being treated and the general state of the patient's own immune system.

The term "patient" includes human and other mammalian subjects that receive either prophylactic or therapeutic treatment.

As used herein, the term "subject" includes any human or non-human animal. For example, the methods and compositions of the present invention can be used to treat a subject with an immune disorder. The term "non-human animal" includes all vertebrates, *e.g.*, mammals and non-mammals, such as non-human primates, sheep, dog, cow, chickens, amphibians, reptiles, *etc.*

Various aspects of the invention are described in further detail in the following subsections.

I. Production of Antibodies to DEC-205

The present invention encompasses antibodies, *e.g.*, fully human antibodies, that bind DEC-205, *e.g.*, human DEC-205. Exemplary monoclonal antibodies that bind DEC-205 include 3D6-2F4, 3D6-4C8, 3G9-2D2, 5A8-1F1, 2D3-1F5-2A9, 3C7-3A3, 5D12-5G1, 1G6-1G6, 5C3-2-3F6, 1E6-3D10 and 3A4-1C10.

Monoclonal antibodies of the invention can be produced using a variety of known techniques, such as the standard somatic cell hybridization technique described by Kohler and Milstein, Nature 256: 495 (1975). Although somatic cell hybridization procedures are preferred, in principle, other techniques for producing monoclonal antibodies also can be employed, *e.g.*, viral or oncogenic transformation of B lymphocytes, phage display technique using libraries of human antibody genes.

Accordingly, in one embodiment, a hybridoma method is used for producing an antibody that binds human DEC-205. In this method, a mouse or other appropriate host animal can be immunized with a suitable antigen in order to elicit lymphocytes that produce or are capable of producing antibodies that will specifically bind to the antigen used for immunization. Alternatively, lymphocytes may be immunized *in vitro*. Lymphocytes can then be fused with myeloma cells using a suitable fusing agent, such as polyethylene glycol, to form a hybridoma cell (Goding, Monoclonal Antibodies: Principles and Practice, pp.59-103 (Academic Press, 1986)). Culture medium in which hybridoma cells are growing is assayed for production of monoclonal antibodies directed against the antigen. After hybridoma cells are identified that produce antibodies of the desired specificity, affinity, and/or activity, the clones may be subcloned by limiting dilution procedures and grown by standard methods

(Goding, Monoclonal Antibodies:Principles and Practice, pp. 59-103 (Academic Press, 1986)). Suitable culture media for this purpose include, for example, D-MEM or RPMI-1640 medium. In addition, the hybridoma cells may be grown *in vivo* as ascites tumors in an animal. The monoclonal antibodies secreted by the subclones can be separated from the culture medium, ascites fluid, or serum by conventional immunoglobulin purification procedures such as, for example, protein A-Sepharose, hydroxylapatite chromatography, gel electrophoresis, dialysis, or affinity chromatography.

In another embodiment, antibodies and antibody portions that bind human DEC-205 can be isolated from antibody phage libraries generated using the techniques described in, for example, McCafferty *et al., Nature*, 348:552-554 (1990). Clackson *et al.*, Nature, 352:624-628 (1991), Marks *et al., J. Mol. Biol.*, 222:581-597 (1991) and Hoet *et al* (2005) *Nature Biotechnology* 23, 344-348 ; U.S. Patent Nos. 5,223,409; 5,403,484; and 5,571,698 to Ladner *et al.*; U.S. Patent Nos. 5,427,908 and 5,580,717 to Dower *et al.*; U.S. Patent Nos. 5,969,108 and 6,172,197 to McCafferty *et al.*; and U.S. Patent Nos. 5,885,793; 6,521,404; 6,544,731; 6,555,313; 6,582,915 and 6,593,081 to Griffiths *et al.*. Additionally, production of high affinity (nM range) human antibodies by chain shuffling (Marks *et al., Bio/Technology*, 10:779-783 (1992)), as well as combinatorial infection and *in vivo* recombination as a strategy for constructing very large phage libraries (Waterhouse *et al., Nuc. Acids. Res.*, 21:2265-2266 (1993)) may also be used.

In a particular embodiment, the antibody that binds human DEC-205 is produced using the phage display technique described by Hoet *et al., supra.* This technique involves the generation of a human Fab library having a unique combination of immunoglobulin sequences isolated from human donors and having synthetic diversity in the heavy-chain CDRs is generated. The library is then screened for Fabs that bind to human DEC-205.

The preferred animal system for generating hybridomas which produce antibodies of the invention is the murine system. Hybridoma production in the mouse is well known in the art, including immunization protocols and techniques for isolating and fusing immunized splenocytes.

In one embodiment, antibodies directed against DEC-205 are generated using transgenic or transchromosomal mice carrying parts of the human immune system rather than the mouse system. In one embodiment, the invention employs transgenic mice, referred to herein as "HuMAb mice" which contain a human immunoglobulin gene miniloci that encodes unrearranged human heavy (μ and γ) and κ light chain immunoglobulin sequences, together with targeted mutations that inactivate the endogenous μ and κ chain loci (Lonberg, N. *et al.* (1994) *Nature* 368(6474): 856-859). Accordingly, the mice exhibit reduced expression of mouse IgM or κ, and in response to immunization, the introduced human heavy and light chain transgenes undergo class switching and somatic mutation to generate high affinity human IgGκ monoclonal antibodies (Lonberg, N. *et al.* (1994), *supra*; reviewed in Lonberg, N. (1994) *Handbook of Experimental Pharmacology* 113:49-101; Lonberg, N. and Huszar, D. (1995) *Intern. Rev. Immunol.* Vol. 13: 65-93, and Harding, F. and Lonberg, N. (1995) *Ann. N.Y. Acad. Sci* 764:536-546). The preparation of HuMAb mice is described in detail in Section II below and in Taylor, L. *et al.* (1992) *Nucleic Acids Research* 20:6287-6295; Chen, J. *et al.* (1993) *International Immunology* 5: 647-656; Tuaillon *et al.* (1993) *Proc. Natl. Acad. Sci USA* 90:3720-3724; Choi *et al.* (1993) *Nature Genetics* 4:117-123; Chen, J. *et al.* (1993) *EMBO J.* 12: 821-830; Tuaillon *et al.* (1994) *J. Immunol.* 152:2912-2920; Lonberg *et al.*, (1994) *Nature* 368(6474): 856-859; Lonberg, N. (1994) *Handbook of Experimental Pharmacology* 113:49-101; Taylor, L. *et al.* (1994) *International Immunology* 6: 579-591; Lonberg, N. and Huszar, D. (1995) *Intern. Rev. Immunol.* Vol. 13: 65-93; Harding, F. and Lonberg, N. (1995) *Ann. N.Y. Acad. Sci* 764:536-546; Fishwild, D. *et al.* (1996) *Nature Biotechnology* 14: 845-851. See further, U.S. Patent Nos. 5,545,806; 5,569,825; 5,625,126; 5,633,425; 5,789,650; 5,877,397; 5,661,016; 5,814,318; 5,874,299; and 5,770,429; all to Lonberg and Kay, and GenPharm International; U.S. Patent No. 5,545,807 to Surani *et al.*; International Publication Nos. WO 98/24884, published on June 11, 1998; WO 94/25585, published November 10, 1994; WO 93/1227, published June 24, 1993; WO 92/22645, published December 23, 1992; WO 92/03918, published March 19, 1992.

Immunizations

To generate fully human antibodies to DEC-205, transgenic or transchromosomal mice containing human immunoglobulin genes (*e.g.*, HCo12, HCo7 or KM mice) can be immunized with a purified or enriched preparation of the DEC-205 antigen and/or cells expressing DEC-205, as described, for example, by Lonberg *et al.* (1994) *Nature* 368(6474): 856-859; Fishwild *et al.* (1996) *Nature Biotechnology* 14: 845-851 and WO 98/24884. As described herein, HuMAb mice are immunized either with recombinant DEC-205 proteins or cell lines expressing DEC-205 as immunogens. Alternatively, mice can be immunized with DNA encoding human DEC-205. Preferably, the mice will be 6-16 weeks of age upon the first infusion. For example, a purified or enriched preparation (5-50 μg) of the recombinant DEC-205 antigen can be used to immunize the HuMAb mice intraperitoneally. In the event that immunizations using a purified or enriched preparation of the DEC-205 antigen do not result in antibodies, mice can also be immunized with cells expressing DEC-205, *e.g.*, a cell line, to promote immune responses. Exemplary cell lines include DEC-205-overexpressing stable CHO and Raji cell lines.

Cumulative experience with various antigens has shown that the HuMAb transgenic mice respond best when initially immunized intraperitoneally (IP) or subcutaneously (SC) with antigen in complete Freund's adjuvant, followed by every other week IP/SC immunizations (up to a total of 10) with antigen in incomplete Freund's adjuvant. The immune response can be monitored over the course of the immunization protocol with plasma samples being obtained by retroorbital bleeds. The plasma can be screened by ELISA (as described below), and mice with sufficient titers of anti-DEC-205 human immunoglobulin can be used for fusions. Mice can be boosted intravenously with antigen 3 days before sacrifice and removal of the spleen.

Generation of Hybridomas Producing Monoclonal Antibodies to DEC-205

To generate hybridomas producing monoclonal antibodies to DEC-205, splenocytes and lymph node cells from immunized mice can be isolated and fused to an appropriate immortalized cell line, such as a mouse myeloma cell line. The resulting hybridomas can then be screened for the production of antigen-specific antibodies. For example, single cell suspensions of splenic lymphocytes from immunized mice can be fused to SP2/0-Ag8.653 nonsecreting mouse myeloma cells (ATCC, CRL 1580) with 50% PEG (w/v). Cells can be plated at approximately 1 x 10^5 in flat bottom microtiter plate, followed by a two week incubation in selective medium containing besides usual reagents 10% fetal Clone Serum, 5-10% origen hybridoma cloning factor (IGEN) and

1X HAT (Sigma). After approximately two weeks, cells can be cultured in medium in which the HAT is replaced with HT. Individual wells can then be screened by ELISA for human anti-DEC-205 monoclonal IgM and IgG antibodies, or for binding to the surface of cells expressing DEC-205, *e.g.*, a CHO cell line expressing DEC-205, by FLISA (fluorescence-linked immunosorbent assay). Once extensive hybridoma growth occurs, medium can be observed usually after 10-14 days. The antibody secreting hybridomas can be replated, screened again, and if still positive for IgG, anti-DEC-205 monoclonal antibodies can be subcloned at least twice by limiting dilution. The stable subclones can then be cultured *in vitro* to generate antibody in tissue culture medium for characterization.

Generation of Transfectomas Producing Monoclonal Antibodies to DEC-205

Aantibodies of the invention also can be produced in a host cell transfectoma using, for example, a combination of recombinant DNA techniques and gene transfection methods as is well known in the art (Morrison, S. (1985) Science 229:1202).

For example, in one embodiment, the gene(s) of interest, *e.g.*, human antibody genes, can be ligated into an expression vector such as a eukaryotic expression plasmid such as used by GS gene expression system disclosed in WO 87/04462, WO 89/01036 and EP 338 841 or other expression systems well known in the art. The purified plasmid with the cloned antibody genes can be introduced in eukaryotic host cells such as CHO-cells or NSO-cells or alternatively other eukaryotic cells like a plant derived cells, fungi or yeast cells. The method used to introduce these genes could be methods described in the art such as electroporation, lipofectine, lipofectamine or other. After introducing these antibody genes in the host cells, cells expressing the antibody can be identified and selected. These cells represent the transfectomas which can then be amplified for their expression level and upscaled to produce antibodies. Recombinant antibodies can be isolated and purified from these culture supernatants and/or cells.

Alternatively these cloned antibody genes can be expressed in other expression systems such as *E. coli* or in complete organisms or can be synthetically expressed.

Use of Partial Antibody Sequences to Express Intact Antibodies

Antibodies interact with target antigens predominantly through amino acid residues that are located in the six heavy and light chain complementarity determining regions (CDRs). For this reason, the amino acid sequences within CDRs are more diverse between individual antibodies than sequences outside of CDRs. Because CDR sequences are responsible for most antibody-antigen interactions, it is possible to express recombinant antibodies that mimic the properties of specific naturally occurring antibodies by constructing expression vectors that include CDR sequences from the specific naturally occurring antibody grafted onto framework sequences from a different antibody with different properties (see, *e.g.*, Riechmann, L. *et al.*, 1998, *Nature* 332:323-327; Jones, P. *et al.*, 1986, *Nature* 321:522-525; and Queen, C. *et al.*, 1989, *Proc. Natl. Acad. See.* U.S.A. 86:10029-10033). Such framework sequences can be obtained from public DNA databases that include germline antibody gene sequences. These germline sequences will differ from mature antibody gene sequences because they will not include completely assembled variable genes, which are formed by V(D)J joining during B cell maturation. Germline gene sequences will also differ from the sequences of a high affinity secondary repertoire antibody at individual evenly across the variable region. For example, somatic mutations are relatively infrequent in the amino-terminal portion of framework region. For example, somatic mutations are relatively infrequent in the amino terminal portion of framework region 1 and in the carboxy-terminal portion of framework region 4. Furthermore, many somatic mutations do not significantly alter the binding properties of the antibody. For this reason, it is not necessary to obtain the entire DNA sequence of a particular antibody in order to recreate an intact recombinant antibody having binding properties similar to those of the original antibody (see PCT/US99/05535 filed on March 12, 1999). Partial heavy and light chain sequence spanning the CDR regions is typically sufficient for this purpose. The partial sequence is used to determine which germline variable and joining gene segments contributed to the recombined antibody variable genes. The germline sequence is then used to fill in missing portions of the variable regions. Heavy and light chain leader sequences are cleaved during protein maturation and do not contribute to the properties of the final antibody. To add missing sequences, cloned cDNA sequences can be combined with synthetic oligonucleotides by ligation or PCR amplification. Alternatively, the entire variable region can be synthesized as a set of short, overlapping, oligonucleotides and combined by PCR amplification to create an entirely synthetic variable region clone. This process has certain advantages such as elimination or inclusion or particular restriction sites, or optimization of particular codons.

The nucleotide sequences of heavy and light chain transcripts from a hybridoma are used to design an overlapping set of synthetic oligonucleotides to create synthetic V sequences with identical amino acid coding capacities as the natural sequences. The synthetic heavy and kappa chain sequences can differ from the natural sequences in three ways: strings of repeated nucleotide bases are interrupted to facilitate oligonucleotide synthesis and PCR amplification; optimal translation initiation sites are incorporated according to Kozak's rules (Kozak, 1991, J. Biol. Chem. 266:19867-19870); and, HindIII sites are engineered upstream of the translation initiation sites.

For both the heavy and light chain variable regions, the optimized coding, and corresponding non-coding, strand sequences are broken down into 30 – 50 nucleotide approximately the midpoint of the corresponding non-coding oligonucleotide. Thus, for each chain, the oligonucleotides can be assembled into overlapping double stranded sets that span segments of 150 – 400 nucleotides. The pools are then used as templates to produce PCR amplification products of 150 – 400 nucleotides. Typically, a single variable region oligonucleotide set will be broken down into two pools which are separately amplified to generate two overlapping PCR products. These overlapping products are then combined by PCR amplification to form the complete variable region. It may also be desirable to include an overlapping fragment of the heavy or light chain constant region (including the BbsI site of the kappa light chain, or the AgeI site if the gamma heavy chain) in the PCR amplification to generate fragments that can easily be cloned into the expression vector constructs.

The reconstructed heavy and light chain variable regions are then combined with cloned promoter, leader sequence, translation initiation, leader sequence, constant region, 3' untranslated, polyadenylation, and transcription termination, sequences to form expression vector constructs. The heavy and light chain expression constructs can be combined into a single vector, co-transfected, serially transfected, or separately transfected into host cells which are then fused to form a host cell expressing both chains.

Plasmids for use in construction of expression vectors were constructed so that PCR amplified V heavy and V kappa light chain cDNA sequences could be used to reconstruct complete heavy and light chain minigenes. These plasmids can be used to express completely human $IgG_1\kappa$ or $IgG_4\kappa$ antibodies. Fully human and chimeric antibodies of the present invention also include IgG2, IgG3, IgE, IgA, IgM, and IgD antibodies. Similar plasmids can be constructed for expression of other heavy chain isotypes, or for expression of antibodies comprising lambda light chains.

Thus, in another aspect of the invention, structural features of anti-DEC-205 antibodies of the invention are used to create structurally related anti-DEC-205 antibodies that retain at least one functional property of the antibodies of the invention, such as, for example, binding to human DEC-205 with an affinity constant of at least 10^8 M^{-1} as measured by surface plasmon resonance;
internalizing after binding to human dendritic cells expressing DEC-205;
localizing to antigen processing compartments in human dendritic cells;
activating human dendritic cells expressing DEC-205; cross-reacting with DEC-205 on non-human primate dendritic cells or those of other species; and generating or enhancing human T cell, such as CTL, responses to an antigen, preferably CTL responses mediated by both MHC Class I and Class II pathways.

In one embodiment, one or more CDR regions of antibodies of the invention can be combined recombinantly with known framework regions and CDRs to create additional, recombinantly-engineered, anti-DEC-205 antibodies of the invention. The heavy and light chain variable framework regions can be derived from the same or different antibody sequences. The antibody sequences can be the sequences of naturally occurring antibodies or can be consensus sequences of several antibodies. See Kettleborough *et al.*, *Protein Engineering* 4:773 (1991); Kolbinger *et al.*, *Protein Engineering* 6:971 (1993) and Carter *et al.*, WO 92/22653.

Accordingly, in another embodiment, the invention provides a method for preparing an anti-DEC-205 antibody including:

preparing an antibody including (1) heavy chain framework regions and heavy chain CDRs, where at least one of the heavy chain CDRs includes an amino acid sequence selected from the amino acid sequences of CDRs shown in SEQ ID NOs: 5, 6, 7, 17, 18, 19, 29, 30, 31, 41, 42, 43, 53, 54, 55, 65, 66, 67, 71, 72, 73, 77, 78, 79, 89, 90 or 91; and (2) light chain framework regions and light chain CDRs, where at least one of the light chain CDRs includes an amino acid sequence selected from the amino acid sequences of CDRs shown in SEQ ID NOs: 11, 12, 13, 23, 24, 25, 35, 36, 37, 47, 48, 49, 59, 60, 61, 83, 84, or 85, where the antibody retains the ability to bind to DEC-205. The ability of the antibody to bind DEC-205 can be determined using standard binding assays, such as those set forth in the Examples (*e.g.*, an ELISA or a FLISA).

It is well known in the art that antibody heavy and light chain CDR3 domains play a particularly important role in the binding specificity/affinity of an antibody for an antigen (*see*, Hall *et al.*, *J. Imunol.*, 149:1605-1612 (1992); Polymenis *et al.*, *J. Immunol.*, 152:5318-5329 (1994); Jahn *et al.*, *Immunobiol.*, 193:400-419 (1995); Klimka *et al.*, *Brit. J. Cancer*, 83:252-260 (2000); Beiboer *et al.*, *J. Mol. Biol*, 296:833-849 (2000); Rader *et al.*, *Proc. Natl. Acad. Sci. USA*, 95:8910-8915 (1998); Barbas *et al.*, *J. Am. Chem. Soc.*, 116:2161-2162 (1994); Ditzel *et al.*, *J. Immunol.*, 157:739-749 (1996)). Accordingly, the recombinant antibodies of the invention prepared as set forth above preferably comprise the heavy and/or light chain CDR3s of antibodies 3D6-2F4, 3D6-4C8, 3G9-2D2, 5A8-1F1, 2D3-1F5-2A9, 3C7-3A3, 5D12-5G1, 1G6-1G6 and 3A4-1C10. The antibodies further can comprise the CDR2s of antibodies 3D6-2F4, 3D6-4C8, 3G9-2D2, 5A8-1F1, 2D3-1F5-2A9, 3C7-3A3, 5D12-5G1, 1G6-1G6 and 3A4-1C10. The antibodies further can comprise the CDR1s of antibodies 3D6-2F4, 3D6-4C8, 3G9-2D2, 5A8-1F1, 2D3-1F5-2A9, 3C7-3A3, 5D12-5G1, 1G6-1G6 and 3A4-1C10. The antibodies can further comprise any combinations of the CDRs.

Accordingly, in another embodiment, the invention further provides anti-DEC-205 antibodies comprising: (1) heavy chain framework regions, a heavy chain CDR1 region, a heavy chain CDR2 region, and a heavy chain CDR3 region, wherein the heavy chain CDR3 region is selected from the CDR3s of 3D6-2F4, 3D6-4C8, 3G9-2D2, 5A8-1F1, 2D3-1F5-2A9, 3C7-3A3, 5D12-5G1, 1G6-1G6 and 3A4-1C10, for example, a heavy chain CDR3 region of 3D6-2F4 as shown in SEQ ID NO: 7; and (2) light chain framework regions, a light chain CDR1 region, a light chain CDR2 region, and a light chain CDR3 region, wherein the light chain CDR3 region is selected from the CDR3s of 3D6-2F4, 3D6-4C8, 3G9-2D2, 5A8-1F1, 2D3-1F5-2A9, 3C7-3A3, 5D12-5G1, 1G6-1G6 and 3A4-1C10, for example, a light chain CDR3 region of 3D6-2F4 as shown in SEQ ID NO: 13 wherein the antibody binds DEC-205. The antibody may further include the heavy chain CDR2 and/or the light chain CDR2 of antibodies 3D6-2F4, 3D6-4C8, 3G9-2D2, 5A8-1F1, 2D3-1F5-2A9, 3C7-3A3, 5D12-5G1, 1G6-1G6 and 3A4-1C10. The antibody may further comprise the heavy chain CDR1 and/or the light chain

CDR1 of 3D6-2F4, 3D6-4C8, 3G9-2D2, 5A8-1F1, 2D3-1F5-2A9, 3C7-3A3, 5D12-5G1, 1G6-1G6 and 3A4-1C10.

Generation of Antibodies Having Modified Sequences

In another embodiment, the variable region sequences, or portions thereof, of the anti-DEC-205 antibodies of the invention are modified to create structurally related anti-DEC-205 antibodies that retain binding (*i.e.*, to the same epitope as the unmodified antibody) and, thus, are functionally equivalent. Methods for identifying residues that can be altered without removing antigen binding are well-known in the art (see, *e.g.*, Marks *et al.* (*Biotechnology* (1992) 10(7):779-83 (monoclonal antibodies diversification by shuffling light chain variable regions, then heavy chain variable regions with fixed CDR3 sequence changes), Jespers *et al.*(1994) Biotechnology 12(9):899-903 (selection of human antibodies from phage display repertoires to a single epitope of an antigen), Sharon *et al.* (1986) *PNAS USA* 83(8):2628-31 (site-directed mutagenesis of an invariant amino acid residue at the variable-diversity segments junction of an antibody); Casson *et al.* (1995) *J. Immunol.* 155(12):5647-54 (evolution of loss and change of specificity resulting from random mutagenesis of an antibody heavy chain variable region).

Accordingly, in one aspect of the invention, the CDR1, 2, and/or 3 regions of the engineered antibodies described above can comprise the exact amino acid sequence(s) as those of antibodies 3D6-2F4, 3D6-4C8, 3G9-2D2, 5A8-1F1, 2D3-1F5-2A9, 3C7-3A3, 5D12-5G1, 1G6-1G6 and 3A4-1C10 disclosed herein. However, in other aspects of the invention, the antibodies comprise derivatives from the exact CDR sequences of 3D6-2F4, 3D6-4C8, 3G9-2D2, 5A8-1F1, 2D3-1F5-2A9, 3C7-3A3, 5D12-5G1, 1G6-1G6 and 3A4-1C10 yet still retain the ability of to bind DEC-205 effectively. Such sequence modifications may include one or more amino acid additions, deletions, or substitutions, *e.g.*, conservative sequence modifications as described above. Sequence modifications may also be based on the consensus sequences described above for the particular CDR1, CDR2, and CDR3 sequences of antibodies 3D6-2F4, 3D6-4C8, 3G9-2D2, 5A8-1F1, 2D3-1F5-2A9, 3C7-3A3, 5D12-5G1, 1G6-1G6 and 3A4-1C10.

Accordingly, in another embodiment, the engineered antibody may be composed of one or more CDRs that are, for example, 90%, 95%, 98% or 99.5% identical to one or more CDRs of antibodies 3D6-2F4, 3D6-4C8, 3G9-2D2, 5A8-1F1, 2D3-1F5-2A9, 3C7-3A3, 5D12-5G1, 1G6-1G6 and 3A4-1C10. Ranges intermediate to the above-recited values, *e.g.*, CDRs that are 90-95%, 95-98%, or 98-100% identical identity to one or more of the above sequences are also intended to be encompassed by the present invention.

In another embodiment, one or more residues of a CDR may be altered to modify binding to achieve a more favored on-rate of binding, a more favored off-rate of binding, or both, such that an idealized binding constant is achieved. Using this strategy, an antibody having ultra high binding affinity of, for example, 10^{10} M^{-1} or more, can be achieved. Affinity maturation techniques, well known in the art and those described herein, can be used to alter the CDR region(s) followed by screening of the resultant binding molecules for the desired change in binding. Accordingly, as CDR(s) are altered, changes in binding affinity as well as immunogenicity can be monitored and scored such that an antibody optimized for the best combined binding and low immunogenicity are achieved.

In addition to or instead of modifications within the CDRs, modifications can also be made within one or more of the framework regions, FR1, FR2, FR3 and FR4, of the heavy and/or the light chain variable regions of a antibody, so long as these modifications do not eliminate the binding affinity of the antibody. For example, one or more non-germline amino acid residues in the framework regions of the heavy and/or the light chain variable region of a antibody of the invention, is substituted with a germline amino acid residue, *i.e.*, the corresponding amino acid residue in the human germline sequence for the heavy or the light chain variable region, which the antibody has significant sequence identity with. For example, a antibody chain can be aligned to a germline antibody chain which it shares significant sequence identity with, and the amino acid residues which do not match between antibody framework sequence and the germline chain framework can be substituted with corresponding residues from the germline sequence. When an amino acid differs between a antibody variable framework region and an equivalent human germline sequence variable framework region, the antibody framework amino acid should usually be substituted by the equivalent human germline sequence amino acid if it is reasonably expected that the amino acid falls within one of the following categories:

(1) an amino acid residue which noncovalently binds antigen directly,

(2) an amino acid residue which is adjacent to a CDR region,

(3) an amino acid residue which otherwise interacts with a CDR region (*e.g.*, is within about 3-6 Å of a CDR region as determined by computer modeling), or

(4) an amino acid reside which participates in the VL-VH interface.

Residues which "noncovalently bind antigen directly" include amino acids in positions in framework regions which have a good probability of directly interacting with amino acids on the antigen according to established chemical forces, for example, by hydrogen bonding, Van der Waals forces, hydrophobic interactions, and the like. Accordingly, in one embodiment, an amino acid residue in the framework region of a antibody of the invention is substituted with the corresponding germline amino acid residue which noncovalently binds antigen directly.

Residues which are "adjacent to a CDR region" include amino acid residues in positions immediately adjacent to one or more of the CDRs in the primary sequence of the antibody, for example, in positions immediately adjacent to a CDR as defined by Kabat, or a CDR as defined by Chothia (*see e.g.*, Chothia and Lesk *J. Mol. Biol.* 196:901 (1987)). Accordingly, in one embodiment, an amino acid residue within the framework region of an antibody of the invention is substituted with a corresponding germline amino acid residue which is adjacent to a CDR region.

Residues that "otherwise interact with a CDR region" include those that are determined by secondary structural analysis to be in a spatial orientation sufficient to affect a CDR region. Such amino acids will generally have a side chain atom within about 3 angstrom units (Å) of some atom in the CDRs and must contain an atom that could interact with the CDR atoms according to established chemical forces, such as those listed above. Accordingly, in one embodiment, an amino acid residue within the framework region of an antibody of the invention is substituted with the corresponding germline amino acid residue which otherwise interacts with a CDR region.

The amino acids at several positions in the framework are known to be important for determining CDR confirmation (*e.g.*, capable of interacting with the CDRs) in many antibodies (Chothia and Lesk, *supra*, Chothia *et al.*, *supra* and Tramontano *et al.*, J. Mol. Biol. 215:175 (1990), all of which are incorporated herein by reference). These authors identified conserved framework residues important for CDR conformation by analysis of the structures of several known antibodies. The antibodies analyzed fell into a limited number of structural or "canonical" classes based on the conformation of the CDRs. Conserved framework residues within members of a canonical class are referred to as "canonical" residues. Canonical residues include residues 2, 25, 29, 30, 33, 48, 64, 71, 90, 94 and 95 of the light chain and residues 24, 26, 29, 34, 54, 55, 71 and 94 of the heavy chain. Additional residues (*e.g.*, CDR structure-determining residues) can be identified according to the methodology of Martin and Thorton (1996) *J. Mol. Biol.* 263:800. Notably, the amino acids at positions 2, 48, 64 and 71 of the light chain and 26-30, 71 and 94 of the heavy chain (numbering according to Kabat) are known to be capable of interacting with the CDRs in many antibodies. The amino acids at positions 35 in the light chain and 93 and 103 in the heavy chain are also likely to interact with the CDRs. Additional residues which may effect conformation of the CDRs can be identified according to the methodology of Foote and Winter (1992) *J. Mol. Biol.* 224:487. Such residues are termed "vernier" residues and are those residues in the framework region closely underlying (*i.e.*, forming a "platform" under) the CDRs.

Residues which "participate in the VL-VH interface" or "packing residues" include those residues at the interface between VL and VH as defined, for example, by Novotny and Haber, *Proc. Natl. Acad. Sci. USA*, 82:4592-66 (1985) or Chothia *et al*, *supra*.

Occasionally, there is some ambiguity about whether a particular amino acid falls within one or more of the above-mentioned categories. In such instances, alternative variant antibodies are produced, one of which has that particular substitution, the other of which does not. Alternative variant antibodies so produced can be tested in any of the assays described herein for the desired activity, and the preferred antibody selected.

Additional candidates for substitution within the framework region are amino acids that are unusual or "rare" for an antibody at that position. These amino acids can be substituted with amino acids from the equivalent position of the human germline sequence or from the equivalent positions of more typical antibodies. For example, substitution may be desirable when the amino acid in a framework region of the antibody is rare for that position and the corresponding amino acid in the germline sequence is common for that position in immunoglobulin sequences; or when the amino acid in the antibody is rare for that position and the corresponding amino acid in the germline sequence is also rare, relative to other sequences. It is contemplated that by replacing an unusual amino acid with an amino acid from the germline sequence that happens to be typical for antibodies, the antibody may be made less immunogenic.

The term "rare", as used herein, indicates an amino acid occurring at that position in less than about 20%, preferably less than about 10%, more preferably less than about 5%, even more preferably less than about 3%, even more preferably less than about 2% and even more preferably less than about 1% of sequences in a representative sample of sequences, and the term "common", as used herein, indicates an amino acid occurring in more than about 25% but usually more than about 50% of sequences in a representative sample. For example, all light and heavy chain variable region sequences are respectively grouped into "subgroups" of sequences that are especially homologous to each other and have the same amino acids at certain critical positions (Kabat *et al.*, *supra*). When deciding whether an amino acid in an antibody sequence is "rare" or "common" among sequences, it will often be preferable to consider only those sequences in the same subgroup as the antibody sequence.

In general, the framework regions of antibodies are usually substantially identical, and more usually, identical to the framework regions of the human germline sequences from which they were derived. Of course, many of the amino acids in the framework region make little or no direct contribution to the specificity or affinity of an antibody. Thus, many individual conservative substitutions of framework residues can be tolerated without appreciable change of the specificity or affinity of the resulting immunoglobulin. Thus, in one embodiment the variable framework region of the antibody shares at least 85% sequence identity to a human germline variable framework region sequence or consensus of such sequences. In another embodiment, the variable framework region of the antibody shares at least 90%, 95%, 96%, 97%, 98% or 99% sequence identity to a human germline variable framework region sequence or consensus of such sequences.

In addition to simply binding DEC-205, an antibody may be selected for its retention of other functional properties of antibodies of the invention, such as, for example:

(a) binding to human DEC-205 with an affinity constant of at least 10^8 M^{-1} as measured by surface plasmon resonance;

(b) internalizing after binding to human dendritic cells expressing DEC-205;

(c) localizing to antigen processing compartments in the dendritic cells ;

(d) activating human dendritic cells expressing DEC-205;

(e) cross-reacting with DEC-205 on non-human primate dendritic cells or those of other species;

(f) generating or enhancing human T-cell responses, preferably T-cell responses mediated by both MHC Class I and Class II pathways;

(g) generating or enhancing human CD4+, CD8+ or NKT cell responses; and

(h) induces peripheral $CD8^+$ T cell tolerance.

Characterization of Monoclonal Antibodies to DEC-205

Monoclonal antibodies of the invention can be characterized for binding to DEC-205 using a variety of known techniques. Generally, the antibodies are initially characterized by ELISA. Briefly, microtiter plates can be coated with purified DEC-205 in PBS, and then blocked with irrelevant proteins such as bovine serum albumin (BSA) diluted in PBS. Dilutions of plasma from DEC-205-immunized mice are added to each well and incubated for 1-2 hours at 37°C. The plates are washed with PBS/Tween 20 and then incubated with a goat-anti-human IgG Fc-specific polyclonal reagent conjugated to alkaline phosphatase for 1 hour at 37°C. After washing, the plates are developed with ABTS substrate, and analyzed at OD of 405. Preferably, mice which develop the highest titers will be used for fusions.

An ELISA assay as described above can be used to screen for antibodies and, thus, hybridomas that produce antibodies that show positive reactivity with the DEC-205 immunogen. Hybridomas that bind, preferably with high affinity, to DEC-205 can than be subcloned and further characterized. One clone from each hybridoma, which retains the reactivity of the parent cells (by ELISA), can then be chosen for making a cell bank, and for antibody purification.

To purify anti-DEC-205 antibodies, selected hybridomas can be grown in roller bottles, two-liter spinner-flasks or other culture systems. Supernatants can be filtered and concentrated before affinity chromatography with protein A-sepharose (Pharmacia, Piscataway, NJ) to purify the protein. After buffer exchange to PBS, the concentration can be determined by OD_{280} using 1.43 extinction coefficient or preferably by nephelometric analysis. IgG can be checked by gel electrophoresis and by antigen specific method.

To determine if the selected anti-DEC-205 monoclonal antibodies bind to unique epitopes, each antibody can be biotinylated using commercially available reagents (Pierce, Rockford, IL). Biotinylated MAb binding can be detected with a streptavidin labeled probe. To determine the isotype of purified antibodies, isotype ELISAs can be performed using art recognized techniques. For example, wells of microtiter plates can be coated with 10 µg/ml of anti- Ig overnight at 4°C. After blocking with 5% BSA, the plates are reacted with 10 µg/ml of monoclonal antibodies or purified isotype controls, at ambient temperature for two hours. The wells can then be reacted with either IgGl or other isotype specific conjugated probes. Plates are developed and analyzed as described above.

To test the binding of monoclonal antibodies to live cells expressing DEC-205, flow cytometry can be used. Briefly, cell lines and/or human PBMCs expressing membrane-bound DEC-205 (grown under standard growth conditions) are mixed with various concentrations of monoclonal antibodies in PBS containing 0.1% BSA and 0.01% NaN3 at 4°C for 1 hour. After washing, the cells are reacted with Fluorescein-labeled anti- IgG antibody under the same conditions as the primary antibody staining. The samples can be analyzed by FACScan instrument using light and side scatter properties to gate on single cells and binding of the labeled antibodies is determined. An alternative assay using fluorescence microscopy may be used (in addition to or instead of) the flow cytometry assay. Cells can be stained exactly as described above and examined by fluorescence microscopy. This method allows visualization of individual cells, but may have diminished sensitivity depending on the density of the antigen.

Anti-DEC-205 IgGs can be further tested for reactivity with the DEC-205 antigen by Western blotting. Briefly, cell extracts from cells expressing DEC-205 can be prepared and subjected to sodium dodecyl sulfate polyacrylamide gel electrophoresis. After electrophoresis, the separated antigens will be transferred to nitrocellulose membranes, blocked with 20% mouse serum, and probed with the monoclonal antibodies to be tested. IgG binding can be detected using anti- IgG alkaline phosphatase and developed with BCIP/NBT substrate tablets (Sigma Chem. Co., St. Louis, MO).

Methods for analyzing binding affinity, cross-reactivity, and binding kinetics of various anti-DEC-205 antibodies include standard assays known in the art, for example, Biacore™ surface plasmon resonance (SPR) analysis using a Biacore™ 2000 SPR instrument (Biacore AB, Uppsala, Sweden), as described in Example 2 herein.

II. Molecular Conjugates/Immunotoxins

The present invention provides a variety of therapeutic molecular conjugates (*e.g.*, vaccine conjugates) which include an antigen, such as a tumor or viral antigen, linked to an antibody that binds to a receptor on an APC, for example, an antibody which binds to DEC-205. This allows for targeting of the antigen to APCs, such as cells expressing DEC-205 (*e.g.*, dendritic cells and B cells) to enhance processing, presentation and, ultimately, an immune response against the antigen(s), *e.g.*, a CTL response. A schematic representation of such a conjugate is shown in Figure 8. In the example shown, an antigen is genetically fused to the CH3 domain of each of the heavy chains of a substantially complete anti-DEC-205 antibody. However, it will be appreciated that the antigen may alternatively be joined to other parts of such an antibody or fragment thereof, and that other forms of conjugation, such as chemical conjugation, may also be employed, as discussed further below.

Suitable antigens for use in the present invention include, for example, infectious disease antigens and tumor antigens, against which protective or therapeutic immune responses are desired, *e.g.*, antigens expressed by a tumor cell or a pathogenic organism or infectious disease antigens. For example, suitable antigens include tumor-associated antigens for the prevention or treatment of cancers. Examples of tumor-associated antigens include, but are not limited to, sequences comprising all or part of the sequences of βhCG, gp100 or Pmel17, HER2/neu, WT1, mesothelin, CEA, gp100, MART1, TRP-2, melan-A, NY-ESO-1, NY-BR-1, NY-CO-58, MN (gp250), idiotype, MAGE-1, MAGE-3, MAGE-A3, Tyrosinase, Telomerase, SSX2 and MUC-1 antigens, and germ cell derived tumor antigens. Tumor associated antigens also include the blood group antigens, for example, Le^a, Le^b, LeX, LeY, H-2, B-1, B-2 antigens. Alternatively, more than one antigen can be included within the antigen-antibody constructs of the invention. For example, a MAGE antigen can be combined with other antigens such as melanin A, tyrosinase, and gp100 along with adjuvants such as GM-CSF or IL-12, and linked to an anti-APC antibody.

Other suitable antigens include viral antigens for the prevention or treatment of viral diseases. Examples of viral antigens include, but are not limited to, HIV-1 gag, HIV-1 env, HIV-1 nef, HBV (surface or core antigens), HPV, FAS, HSV-1, HSV-2, p17, ORF2 and ORF3 antigens. Examples of bacterial antigens include, but are not limited to, *Toxoplasma gondii* or *Treponema pallidum*. The antibody-bacterial antigen conjugates of the invention can be in the treatment or prevention of various bacterial diseases such as Anthrax, Botulism, Tetanus, Chlamydia, Cholera, Diphtheria, Lyme Disease, Syphilis and Tuberculosis.

Sequences of the foregoing antigens are well known in the art. For example, an example of a MAGE-3 cDNA sequence is provided in US 6,235,525 (Ludwig Institute for Cancer Research); examples of NY-ESO-1 nucleic acid and protein sequences are provided in US 5,804,381 and US 6,069,233 (Ludwig Institute for Cancer Research); examples of Melan-A nucleic acid and protein sequences are provided in US 5,620,886 and US 5,854,203 (Ludwig Institute for Cancer Research); examples of NY-BR-1 nucleic acid and protein sequences are provided in US 6,774,226 and US 6,911,529 (Ludwig Institute for Cancer Research) and examples of NY-CO-58 nucleic acid and protein sequences are provided in WO 02090986 (Ludwig Institute for Cancer Research); an example of an amino acid sequence for the HER-2/neu protein is available at GENBANK® Accession No. AAA58637; and a nucleotide sequence (mRNA) for human carcinoembryonic antigen-like 1 (CEA-1) is available at GENBANK® Accession No. NM__020219.

An HPV antigen that may be used in the pharmaceutical compositions and the methods of the invention may include, for example an HPV-16 antigen, an HPV-18 antigen, an HPV-31 antigen, an HPV-33 antigen and/or an HPV-35 antigen; and is suitably an HPV-16 antigen and/or HPV-18 antigen. A genome of HPV-16 is described in Virology, 145:181- 185 (1985) and DNA sequences encoding HPV-18 are described in US Patent No. 5,840,306, the disclosures of which are incorporated by reference herein in their entirety. HPV-16 antigens (e.g., seroreactive regions of the El and/or E2 proteins of HPV-16) are described in US Patent No. 6,531,127, and HPV-18 antigens (e.g., seroreactive regions of the Ll and/or L2 proteins of HPV-18) are described in US Patent No. 5,840,306, the disclosures of which are incorporated by reference herein.

Similarly, a complete genome for HBV is available at GENBANK® Accession No. NC_003977, the disclosure of which is incorporated herein. The genome of HCV is described in European Patent Application No. 318 216, the disclosure of which is incorporated herein. PCT/US90/01348, incorporated by reference herein, discloses sequence information of clones of the HCV genome, amino acid sequences of HCV viral proteins and methods of making and using such compositions for HCV vaccines comprising HCV proteins and peptides derived there from.

Antigenic peptides of proteins (*i.e.*, those containing T cell epitopes) can be identified in a variety of manners well known in the art. For example, T cell epitopes can be predicted by analyzing the sequence of the protein using web-based predictive algorithms (BIMAS & SYFPEITHI) to generate potential MHC class I and II- binding peptides that match an internal database of 10,000 well characterized MHC binding peptides previously defined by CTLs. High scoring peptides can be ranked and selected as "interesting" on the basis of high affinity to a given MHC molecule.

Another method for identifying antigenic peptides containing T cell epitopes is by dividing the protein into non-overlapping peptides of desired length or overlapping peptides of desired lengths which can be produced recombinantly, synthetically, or in certain limited situations, by chemical cleavage of the protein and tested for immunogenic properties, *e.g.*, eliciting a T cell response (*i.e.*, proliferation or lymphokine secretion).

In order to determine precise T cell epitopes of the protein by, for example, fine mapping techniques, a peptide having T cell stimulating activity and thus comprising at least one T cell epitope, as determined by T cell biology techniques, can be modified by addition or deletion of amino acid residues at either the amino or carboxy terminus of the peptide and tested to determine a change in T cell reactivity to the modified peptide. If two or more peptides which share an area of overlap in the native protein sequence are found to have human T cell stimulating activity, as determined by T cell biology techniques, additional peptides can be produced comprising all or a portion of such peptides and these additional peptides can be tested by a similar procedure. Following this technique, peptides are selected and produced recombinantly or synthetically. Peptides are selected based on various factors, including the strength of the T cell response to the peptide (*e.g.*, stimulation index). The physical and chemical properties of these selected peptides (*e.g.*, solubility, stability) can then be examined to determine whether the peptides are suitable for use in therapeutic compositions or whether the peptides require modification.

In addition, the vaccine conjugate can include one or more immunostimulatory agents that also enhance the immune response against the antigen. Antibody-antigen vaccine conjugates of the invention can be made genetically or chemically. In either case, the antibody portion of the conjugate may consist of the whole antibody or a portion of the antibody, such as the Fab fragment or single-chain Fv. In addition, more than one antigen and/or immunostimulatory agent can be included in the conjugate.

Chemically constructed antibody-antigen conjugates can be made using a variety of well known and readily available cross-linking reagents. These cross-linking reagents can be homofunctional or heterofunctional compounds, such as N-succinimidyl-3-(2-pyridyldithio)propionate (SPDP), N-succinimidyl-S-acetyl-thioacetate (SATA), sulfosuccinimidyl 4-(N-maleimidomethyl) cyclohaxane-1-carboxylate (sulfo-SMCC), 5,5'-dithiobis(2-nitrobenzoic acid) (DTNB), that form covalent linkages with different reactive amino acid or carbohydrate side chains on the anti-dendritic antibody and selected antigen. Other coupling and cross-linking agents also can be used to generate covalent linkages, such as protein A, carbodiimide, and o-phenylenedimaleimide (oPDM); (see *e.g.*, Karpovsky *et al.* (1984) J. Exp. Med. 160:1686; Liu, MA *et al.* (1985) Proc. Natl. Acad. Sci. USA 82:8648). Other methods include those described by Paulus (Behring Ins. Mitt. (1985) No. 78, 118-132); Brennan *et al.* (Science (1985) 229:81-83), and Glennie *et al.* (J. Immunol. (1987) 139: 2367-2375). Preferred conjugating agents are SATA and sulfo-SMCC, both available from Pierce Chemical Co. (Rockford, IL). Immunostimulatory agents can also be chemically linked to the molecular conjugates of the present invention using the same linking methods described above.

In another embodiment, the antibodies of the present invention are linked to a therapeutic moiety, such as a cytotoxin, a drug or a radioisotope. When conjugated to a cytotoxin, these antibody conjugates are referred to as "immunotoxins." A cytotoxin or cytotoxic agent includes any agent that is detrimental to (*e.g.*, kills) cells. Examples include taxol, cytochalasin B, gramicidin D, ethidium bromide, emetine, mitomycin, etoposide, tenoposide, vincristine, vinblastine, colchicin, doxorubicin, daunorubicin, dihydroxy anthracin dione, mitoxantrone, mithramycin, actinomycin D, 1-

dehydrotestosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, and puromycin and analogs or homologs thereof. Therapeutic agents include, but are not limited to, antimetabolites (*e.g.*, methotrexate, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil decarbazine), alkylating agents (*e.g.*, mechlorethamine, thioepa chlorambucil, melphalan, carmustine (BSNU) and lomustine (CCNU), cyclothosphamide, busulfan, dibromomannitol, streptozotocin, mitomycin C, and cis-dichlorodiamine platinum (II) (DDP) cisplatin), anthracyclines (*e.g.*, daunorubicin (formerly daunomycin) and doxorubicin), antibiotics (*e.g.*, dactinomycin (formerly actinomycin), bleomycin, mithramycin, and anthramycin (AMC)), and anti-mitotic agents (*e.g.*, vincristine and vinblastine). An antibody of the present invention can be conjugated to a radioisotope, *e.g.*, radioactive iodine, to generate cytotoxic radiopharmaceuticals for treating a dendritic-related disorder, such as an autoimmune or inflammatory disease, or graft versus host disease.

The antibody conjugates of the invention can be used to modify a given biological response, and the drug moiety is not to be construed as limited to classical chemical therapeutic agents. For example, the drug moiety may be a protein or polypeptide possessing a desired biological activity. Such proteins may include, for example, an enzymatically active toxin, or active fragment thereof, such as abrin, ricin A, pseudomonas exotoxin, or diphtheria toxin; a protein such as tumor necrosis factor or interferon-γ; or, biological response modifiers such as, for example, lymphokines, interleukin-1 ("IL-1"), interleukin-2 ("IL-2"), interleukin-6 ("IL-6"), granulocyte macrophage colony stimulating factor ("GM-CSF"), granulocyte colony stimulating factor ("G-CSF"), or other growth factors.

Techniques for conjugating such therapeutic moiety to antibodies are well known, see, *e.g.*, Arnon et al., "Monoclonal Antibodies For Immunotargeting Of Drugs In Cancer Therapy", in Monoclonal Antibodies And Cancer Therapy, Reisfeld *et al.* (eds.), pp. 243-56 (Alan R. Liss, Inc. 1985); Hellstrom et al., "Antibodies For Drug Delivery", in Controlled Drug Delivery (2nd Ed.), Robinson et al. (eds.), pp. 623-53 (Marcel Dekker, Inc. 1987); Thorpe, "Antibody Carriers Of Cytotoxic Agents In Cancer Therapy: A Review", in Monoclonal Antibodies '84: Biological And Clinical Applications, Pinchera et al. (eds.), pp. 475-506 (1985); "Analysis, Results, And Future Prospective Of The Therapeutic Use Of Radiolabeled Antibody In Cancer Therapy", in Monoclonal Antibodies For Cancer Detection And Therapy, Baldwin et al. (eds.), pp.

303-16 (Academic Press 1985), and Thorpe et al., "The Preparation And Cytotoxic Properties Of Antibody-Toxin Conjugates", Immunol. Rev., 62:119-58 (1982).

In another embodiment, the antibodies of the present invention can be used to directly target whole cells, *e.g.*, a tumor cell, an effector cell or a microbial pathogen, to dendritic cells. For example, anti-DEC-205 antibodies can be directly expressed on the surface of a cell, for example, by transfection or transduction of a cell with a vector containing nucleic acid sequences encoding an antibody of the invention. This can be done, for example, by transfecting the target cell with a nucleic acid encoding a fusion protein containing a transmembrane domain and a anti-dendritic cell antibody, or antigen binding fragment thereof. Methods for generating such nucleic acids, fusion proteins, and cells expressing such fusion proteins are described, for example, in U.S. Patent Application Serial No: 09/203,958, incorporated herein in its entirety by this reference. Alternatively, anti-dendritic cell antibodies, or antigen binding fragments thereof, can be bound to a cell or a pathogen by the use of chemical linkers, lipid tags, or other related methods (deKruif, J. *et al.* (2000) *Nat. Med.* 6:223-227; Nizard, P. *et al.* (1998) *FEBS Lett.* 433:83-88). Cells with surface-anchored anti-DEC-205 antibodies may be used to induce specific immune responses against the cell, *e.g.*, a tumor cell or microbial pathogen.

III. Pharmaceutical Compositions

In another embodiment, the present invention provides a composition, *e.g.*, a pharmaceutical composition, containing one or a combination of monoclonal antibodies of the present invention, formulated together with a pharmaceutically acceptable carrier. Compositions containing bispecific molecules or molecular conjugates which comprise an antibody of the present invention are also provided. In one embodiment, the compositions include a combination of multiple (*e.g.*, two or more) isolated antibodies of the invention. Preferably, each of the antibodies of the composition binds to a distinct, pre-selected epitope of DEC-205.

Pharmaceutical compositions of the invention also can be administered in combination therapy, *i.e.*, combined with other agents. For example, the combination therapy can include a composition of the present invention with at least one or more additional therapeutic agents, such as anti-inflammatory agents, DMARDs (disease-modifying anti-rheumatic drugs), immunosuppressive agents, and chemotherapeutics.

The pharmaceutical compositions of the invention can also be administered in conjunction with radiation therapy. Co-administration with other antibodies, such as CD4 specific antibodies, or IL-2 specific antibodies, are also encompassed by the invention. Such combinations with CD4 specific antibodies or IL-2 specific antibodies are considered particularly useful for treating autoimmune diseases and transplant rejections. Combinations with antibodies to CTLA4, CD40 etc particularly useful in cancer and infectious disease treatments.

In another embodiment, a vaccine conjugate that is rapidly internalized by APCs can be combined with a monoclonal antibody that enhances antigen presenting cell activities of dendritic cells, *e.g.*, release of immunostimulatory cytokines.

As used herein, "pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like that are physiologically compatible. Preferably, the carrier is suitable for intravenous, intramuscular, subcutaneous, parenteral, spinal or epidermal administration (*e.g.*, by injection or infusion). Depending on the route of administration, the active compound, *i.e.*, antibody, bispecific and multispecific molecule, may be coated in a material to protect the compound from the action of acids and other natural conditions that may inactivate the compound.

Examples of adjuvants which may be used with the antibodies and constructs of the present invention include: Freund's Incomplete Adjuvant and Complete Adjuvant (Difco Laboratories, Detroit, Mich.); Merck Adjuvant 65 (Merck and Company, Inc., Rahway, N.J.); AS-2 (SmithKline Beecham, Philadelphia, Pa.); aluminum salts such as aluminum hydroxide gel (alum) or aluminum phosphate; salts of calcium, iron or zinc; an insoluble suspension of acylated tyrosine; acylated sugars; cationically or anionically derivatised polysaccharides; polyphosphazenes; biodegradable microspheres; cytokines, such as GM-CSF, interleukin-2, -7, -12, and other like factors; 3D-MPL; CpG oligonucleotide; and monophosphoryl lipid A, for example 3-de-O-acylated monophosphoryl lipid A.

MPL adjuvants are available from Corixa Corporation (Seattle, Wash; see, for example, U.S. Pat. Nos. 4,436,727; 4,877,611; 4,866,034 and 4,912,094). CpG-containing oligonucleotides (in which the CpG dinucleotide is unmethylated) are well known and are described, for example, in WO 96/02555, WO 99/33488 and U.S. Pat.

Nos. 6,008,200 and 5,856,462. Immunostimulatory DNA sequences are also described, for example, by Sato et al., Science 273:352, 1996.

Further alternative adjuvants include, for example, saponins, such as Quil A, or derivatives thereof, including QS21 and QS7 (Aquila Biopharmaceuticals Inc., Framingham, Mass.); Escin; Digitonin; or Gypsophila or Chenopodium quinoa saponins; Montanide ISA 720 (Seppic, France); SAF (Chiron, California, United States); ISCOMS (CSL), MF-59 (Chiron); the SBAS series of adjuvants (e.g., SBAS-2 or SBAS-4, available from SmithKline Beecham, Rixensart, Belgium); Detox (Enhanzyn™) (Corixa, Hamilton, Mont.); RC-529 (Corixa, Hamilton, Mont.) and other aminoalkyl glucosaminide 4-phosphates (AGPs); polyoxyethylene ether adjuvants such as those described in WO 99/52549A1; synthetic imidazoquinolines such as imiquimod [S-26308, R-837], (Harrison, et al., Vaccine 19: 1820-1826, 2001; and resiquimod [S-28463, R-848] (Vasilakos, et al., Cellular immunology 204: 64-74, 2000; Schiff bases of carbonyls and amines that are constitutively expressed on antigen presenting cell and T-cell surfaces, such as tucaresol (Rhodes, J. et al., Nature 377: 71-75, 1995); cytokine, chemokine and co-stimulatory molecules as either protein or peptide, including for example pro-inflammatory cytokines such as Interferon, GM-CSF, IL-1 alpha, IL-1 beta, TGF-alpha and TGF-beta, Th1 inducers such as interferon gamma, IL-2, IL-12, IL-15, IL-18 and IL-21, Th2 inducers such as IL-4, IL-5, IL-6, IL-10 and IL-13 and other chemokine and co-stimulatory genes such as MCP-1, MIP-1 alpha, MIP-1 beta, RANTES, TCA-3, CD80, CD86 and CD40L; immunostimulatory agents targeting ligands such as CTLA-4 and L-selectin, apoptosis stimulating proteins and peptides such as Fas; synthetic lipid based adjuvants, such as vaxfectin, (Reyes et al., Vaccine 19: 3778-3786, 2001) squalene, alpha-tocopherol, polysorbate 80, DOPC and cholesterol; endotoxin, [LPS], (Beutler, B., Current Opinion in Microbiology 3: 23-30, 2000); ligands that trigger Toll receptors to produce Th1-inducing cytokines, such as synthetic Mycobacterial lipoproteins, Mycobacterial protein p19, peptidoglycan, teichoic acid and lipid A; and CT (cholera toxin, subunits A and B) and LT (heat labile enterotoxin from E. coli, subunits A and B), heat shock protein family (HSPs), and LLO (listeriolysin O; WO 01/72329). These and various further Toll-like Receptor (TLR) agonists are described for example in Kanzler et al, *Nature Medicine*, May 2007, Vol 13, No 5.

A "pharmaceutically acceptable salt" refers to a salt that retains the desired biological activity of the parent compound and does not impart any undesired toxicological effects (see *e.g.*, Berge, S.M., *et al.* (1977) J. Pharm. Sci. 66:1-19). Examples of such salts include acid addition salts and base addition salts. Acid addition salts include those derived from nontoxic inorganic acids, such as hydrochloric, nitric, phosphoric, sulfuric, hydrobromic, hydroiodic, phosphorous and the like, as well as from nontoxic organic acids such as aliphatic mono- and dicarboxylic acids, phenyl-substituted alkanoic acids, hydroxy alkanoic acids, aromatic acids, aliphatic and aromatic sulfonic acids and the like. Base addition salts include those derived from alkaline earth metals, such as sodium, potassium, magnesium, calcium and the like, as well as from nontoxic organic amines, such as N,N'-dibenzylethylenediamine, N-methylglucamine, chloroprocaine, choline, diethanolamine, ethylenediamine, procaine and the like.

A composition of the present invention can be administered by a variety of methods known in the art. As will be appreciated by the skilled artisan, the route and/or mode of administration will vary depending upon the desired results. The active compounds can be prepared with carriers that will protect the compound against rapid release, such as a controlled release formulation, including implants, transdermal patches, and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Many methods for the preparation of such formulations are patented or generally known to those skilled in the art. *See, e.g., Sustained and Controlled Release Drug Delivery Systems*, J.R. Robinson, ed., Marcel Dekker, Inc., New York, 1978.

To administer a compound of the invention by certain routes of administration, it may be necessary to coat the compound with, or co-administer the compound with, a material to prevent its inactivation. For example, the compound may be administered to a subject in an appropriate carrier, for example, liposomes, or a diluent. Pharmaceutically acceptable diluents include saline and aqueous buffer solutions. Liposomes include water-in-oil-in-water CGF emulsions as well as conventional liposomes (Strejan *et al.* (1984) *J. Neuroimmunol.* 7:27).

Pharmaceutically acceptable carriers include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. The use of such media and agents for pharmaceutically active substances is known in the art. Except insofar as any conventional media or agent is incompatible with the active compound, use thereof in the pharmaceutical compositions of the invention is contemplated. Supplementary active compounds can also be incorporated into the compositions.

Therapeutic compositions typically must be sterile and stable under the conditions of manufacture and storage. The composition can be formulated as a solution, microemulsion, liposome, or other ordered structure suitable to high drug concentration. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol, sorbitol, or sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent that delays absorption, for example, monostearate salts and gelatin.

Sterile injectable solutions can be prepared by incorporating the active compound in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by sterilization microfiltration. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle that contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and freeze-drying (lyophilization) that yield a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

Dosage regimens are adjusted to provide the optimum desired response (*e.g.*, a therapeutic response). For example, a single bolus may be administered, several divided doses may be administered over time or the dose may be proportionally reduced or increased as indicated by the exigencies of the therapeutic situation. For example, the antibodies of the invention may be administered once or twice weekly by subcutaneous injection or once or twice monthly by subcutaneous injection.

It is especially advantageous to formulate parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the subjects to be treated; each unit contains a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the invention are dictated by and directly dependent on (a) the unique characteristics of the active compound and the particular therapeutic effect to be achieved, and (b) the limitations inherent in the art of compounding such an active compound for the treatment of sensitivity in individuals.

Examples of pharmaceutically-acceptable antioxidants include: (1) water soluble antioxidants, such as ascorbic acid, cysteine hydrochloride, sodium bisulfate, sodium metabisulfite, sodium sulfite and the like; (2) oil-soluble antioxidants, such as ascorbyl palmitate, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), lecithin, propyl gallate, alpha-tocopherol, and the like; and (3) metal chelating agents, such as citric acid, ethylenediamine tetraacetic acid (EDTA), sorbitol, tartaric acid, phosphoric acid, and the like.

For the therapeutic compositions, formulations of the present invention include those suitable for oral, nasal, topical (including buccal and sublingual), rectal, vaginal and/or parenteral administration. The formulations may conveniently be presented in unit dosage form and may be prepared by any methods known in the art of pharmacy. The amount of active ingredient which can be combined with a carrier material to produce a single dosage form will vary depending upon the subject being treated, and the particular mode of administration. The amount of active ingredient which can be combined with a carrier material to produce a single dosage form will generally be that amount of the composition which produces a therapeutic effect. Generally, out of one hundred per cent, this amount will range from about 0.001 per cent to about ninety percent of active ingredient, preferably from about 0.005 per cent to about 70 per cent, most preferably from about 0.01 per cent to about 30 per cent.

Formulations of the present invention which are suitable for vaginal administration also include pessaries, tampons, creams, gels, pastes, foams or spray formulations containing such carriers as are known in the art to be appropriate. Dosage forms for the topical or transdermal administration of compositions of this invention include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches and inhalants. The active compound may be mixed under sterile conditions with a pharmaceutically acceptable carrier, and with any preservatives, buffers, or propellants which may be required.

The phrases "parenteral administration" and "administered parenterally" as used herein means modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal, epidural and intrasternal injection and infusion.

Examples of suitable aqueous and nonaqueous carriers which may be employed in the pharmaceutical compositions of the invention include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils, such as olive oil, and injectable organic esters, such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating materials, such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

These compositions may also contain adjuvants such as preservatives, wetting agents, emulsifying agents and dispersing agents. Prevention of presence of microorganisms may be ensured both by sterilization procedures, supra, and by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid, and the like. It may also be desirable to include isotonic agents, such as sugars, sodium chloride, and the like into the compositions. In addition, prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents which delay absorption such as aluminum monostearate and gelatin.

When the compounds of the present invention are administered as pharmaceuticals, to humans and animals, they can be given alone or as a pharmaceutical composition containing, for example, 0.001 to 90% (more preferably, 0.005 to 70%, such as 0.01 to 30%) of active ingredient in combination with a pharmaceutically acceptable carrier.

Regardless of the route of administration selected, the compounds of the present invention, which may be used in a suitable hydrated form, and/or the pharmaceutical compositions of the present invention, are formulated into pharmaceutically acceptable dosage forms by conventional methods known to those of skill in the art.

Actual dosage levels of the active ingredients in the pharmaceutical compositions of the present invention may be varied so as to obtain an amount of the active ingredient which is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration, without being toxic to the patient. The selected dosage level will depend upon a variety of pharmacokinetic factors including the activity of the particular compositions of the present invention employed, or the ester, salt or amide thereof, the route of administration, the time of administration, the rate of excretion of the particular compound being employed, the duration of the treatment, other drugs, compounds and/or materials used in combination with the particular compositions employed, the age, sex, weight, condition, general health and prior medical history of the patient being treated, and like factors well known in the medical arts. A physician or veterinarian having ordinary skill in the art can readily determine and prescribe the effective amount of the pharmaceutical composition required. For example, the physician or veterinarian could start doses of the compounds of the invention employed in the pharmaceutical composition at levels lower than that required in order to achieve the desired therapeutic effect and gradually increase the dosage until the desired effect is achieved. In general, a suitable daily dose of a composition of the invention will be that amount of the compound which is the lowest dose effective to produce a therapeutic effect. Such an effective dose will generally depend upon the factors described above. It is preferred that administration be intravenous, intramuscular, intraperitoneal, or subcutaneous, preferably administered proximal to the site of the target. If desired, the effective daily dose of a therapeutic composition may be administered as two, three, four, five, six or more sub-doses administered separately at appropriate intervals throughout the day, optionally, in unit dosage forms. While it is possible for a compound of the present invention to be administered alone, it is preferable to administer the compound as a pharmaceutical formulation (composition).

Therapeutic compositions can be administered with medical devices known in the art. For example, in a preferred embodiment, a therapeutic composition of the invention can be administered with a needleless hypodermic injection device, such as the devices disclosed in U.S. Patent Nos. 5,399,163, 5,383,851, 5,312,335, 5,064,413, 4,941,880, 4,790,824, or 4,596,556. Examples of well-known implants and modules useful in the present invention include: U.S. Patent No. 4,487,603, which discloses an implantable micro-infusion pump for dispensing medication at a controlled rate; U.S. Patent No. 4.,486,194, which discloses a therapeutic device for administering medicants through the skin; U.S. Patent No. 4,447,233, which discloses a medication infusion pump for delivering medication at a precise infusion rate; U.S. Patent No. 4,447,224, which discloses a variable flow implantable infusion apparatus for continuous drug delivery; U.S. Patent No. 4,439,196, which discloses an osmotic drug delivery system having multi-chamber compartments; and U.S. Patent No. 4,475,196, which discloses an osmotic drug delivery system. Many other such implants, delivery systems, and modules are known to those skilled in the art.

In certain embodiments, the antibodies of the invention can be formulated to ensure proper distribution *in vivo*. For example, the blood-brain barrier (BBB) excludes many highly hydrophilic compounds. To ensure that the therapeutic compounds of the invention cross the BBB (if desired), they can be formulated, for example, in liposomes. For methods of manufacturing liposomes, see, *e.g.*, U.S. Patents 4,522,811; 5,374,548; and 5,399,331. The liposomes may comprise one or more moieties which are selectively transported into specific cells or organs, thus enhance targeted drug delivery (*see, e.g.*, V.V. Ranade (1989) *J. Clin. Pharmacol.* 29:685). Exemplary targeting moieties include folate or biotin (see, *e.g.*, U.S. Patent 5,416,016 to Low *et al.*); mannosides (Umezawa *et al.*, (1988) *Biochem. Biophys. Res. Commun.* 153:1038); antibodies (P.G. Bloeman *et al.* (1995) *FEBS Lett.* 357:140; M. Owais *et al.* (1995) *Antimicrob. Agents Chemother.* 39:180); surfactant protein A receptor (Briscoe *et al.* (1995) *Am. J. Physiol.* 1233:134), different species of which may comprise the formulations of the inventions, as well as components of the invented molecules; p120 (Schreier *et al.* (1994) *J. Biol. Chem.* 269:9090); see also K. Keinanen; M.L. Laukkanen (1994) *FEBS Lett.* 346:123; J.J. Killion; I.J. Fidler (1994) *Immunomethods* 4:273. In one embodiment of the invention, the therapeutic compounds of the invention are formulated in liposomes; in a more preferred embodiment, the liposomes include a targeting moiety. In a most preferred embodiment, the therapeutic compounds in the liposomes are delivered by bolus injection to a site proximal to the tumor or infection. The composition must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi.

The ability of a compound to inhibit cancer can be evaluated in an animal model system predictive of efficacy in human tumors. Alternatively, this property of a composition can be evaluated by examining the ability of the compound to inhibit, such inhibition *in vitro* by assays known to the skilled practitioner. A therapeutically effective amount of a therapeutic compound can decrease tumor size, or otherwise ameliorate symptoms in a subject. One of ordinary skill in the art would be able to determine such amounts based on such factors as the subject's size, the severity of the subject's symptoms, and the particular composition or route of administration selected.

The ability of the antibodies to enhance antigen presentation or induce cytotoxic T cell (CTL) responses against a variety of target cells or pathogens can also be evaluated according to methods well known in the art.

The composition must be sterile and fluid to the extent that the composition is deliverable by syringe. In addition to water, the carrier can be an isotonic buffered saline solution, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyetheylene glycol, and the like), and suitable mixtures thereof. Proper fluidity can be maintained, for example, by use of coating such as lecithin, by maintenance of required particle size in the case of dispersion and by use of surfactants. In many cases, it is preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol or sorbitol, and sodium chloride in the composition. Long-term absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate or gelatin.

When the active compound is suitably protected, as described above, the compound may be orally administered, for example, with an inert diluent or an assimilable edible carrier.

IV. <u>Uses and Methods of the Invention</u>

In one embodiment, the antibodies, bispecific molecules, and molecular conjugates of the present invention can be used to treat and/or prevent (*e.g.*, immunize against) a variety of diseases and conditions.

One of the primary disease indications that can be treated using antibodies of the invention is cancer. This includes, but is not limited to, colon cancer, melanoma, lymphoma, prostate carcinoma, pancreatic carcinoma, bladder carcinoma, fibrosarcoma, rhabdomyosarcoma, mastocytoma, mammary adenocarcinoma, leukemia, or rheumatoid fibroblastsoma. Another primary disease indication is infectious diseases including, but not limited to, HIV, Hepatitis (*e.g.*, A, B, & C), Influenza, Herpes, Giardia, Malaria, Leishmania, Staphylococcus Aureus, Pseudomonas aeruginosa. Another primary disease indication includes autoimmune diseases.

For use in therapy, vaccine conjugates of the invention can be administered to a subject directly (*i.e.*, *in vivo*), either alone or with an immunostimulatory agent. In one aspect, the immunostimulatory agent is linked to the conjugate. Alternatively, the conjugates can be administered to a subject indirectly by first contacting the conjugates (*e.g.*, by culturing or incubating) with APCs, such as dendritic cells, and then administering the cells to the subject (*i.e.*, *ex vivo*). The contacting and delivering of the conjugates to APCs, such that they are processed and presented by the APCs prior to administration, is also referred to as antigen or cell "loading." Techniques for loading antigens to APCs are well known in the art and include, for example, Gunzer and Grabbe, Crit Rev Immunol 21 (1-3):133-45 (2001) and Steinman, Exp Hematol 24(8): 859-62 (1996).

In all cases, the vaccine conjugates and the immunostimulatory agents are administered in an effective amount to exert their desired therapeutic effect. The term "effective amount" refers to that amount necessary or sufficient to realize a desired biologic effect. For example, an effective amount could be that amount necessary to eliminate a tumor, cancer, or bacterial, viral or fungal infection. The effective amount for any particular application can vary depending on such factors as the disease or condition being treated, the particular conjugate being administered, the size of the subject, or the severity of the disease or condition. One of ordinary skill in the art can empirically determine the effective amount of a particular multispecific molecule without necessitating undue experimentation.

Preferred routes of administration for the vaccine conjugates include, for example, injection (*e.g.*, subcutaneous, intravenous, parenteral, intraperitoneal, intrathecal). The injection can be in a bolus or a continuous infusion. Other routes of administration include oral administration.

Vaccine conjugates of the invention also can be coadministered with adjuvants and other therapeutic agents. It will be appreciated that the term "coadministered" as used herein includes any or all of simultaneous, separate, or sequential administration of the antibodies and conjugates of the present invention with adjuvants and other agents, including administration as part of a dosing regimen. The conjugates are typically formulated in a pharmaceutically acceptable carrier alone or in combination with such agents. Examples of such carriers include solutions, solvents, dispersion media, delay agents, emulsions and the like. The use of such media for pharmaceutically active substances is well known in the art. Any other conventional carrier suitable for use with the molecules falls within the scope of the instant invention.

Suitable agents for coadministration with the vaccine conjugates include other antibodies, cytotoxins and/or drugs. In one embodiment, the agent is an anti-CTLA-4 antibody which is known to aid or induce immune responses. In another embodiment, the agent is a chemotherapeutic agent. The vaccine conjugates also can be administered in combination with radiation.

Chemotherapeutic agents suitable for coadministration with the antibodies and conjugates of the present invention in the treatment of tumors include, for example: taxol, cytochalasin B, gramicidin D, ethidium bromide, emetine, mitomycin, etoposide, tenoposide, vincristine, vinblastine, colchicin, doxorubicin, daunorubicin, dihydroxy anthracin dione, mitoxantrone, mithramycin, actinomycin D, 1-dehydrotestosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, and puromycin and analogs or homologs thereof. Further agents include, for example, antimetabolites (*e.g.*, methotrexate, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil decarbazine), alkylating agents (*e.g.*, mechlorethamine, thioepa chlorambucil, melphalan, carmustine (BSNU) and lomustine (CCNU), cyclothosphamide, busulfan, dibromomannitol, streptozotocin, mitomycin C, and cis-dichlorodiamine platinum (II) (DDP) cisplatin), anthracyclines (*e.g.*, daunorubicin (formerly daunomycin) and doxorubicin), antibiotics (*e.g.*, dactinomycin (formerly actinomycin), bleomycin, mithramycin, and anthramycin (AMC)), and anti-mitotic agents (*e.g.*, vincristine and vinblastine) and temozolomide.

Agents that delete or inhibit immunosuppressive activities, for example, by immune cells (for example regulatory T-cells, NKT cells, macrophages, myeloid-derived suppressor cells, immature or suppressive dendritic cells) or suppressive factors produced by the tumor or host cells in the local microenvironment of the tumor (for example, TGFbeta, indoleamine 2,3 dioxygenase – IDO), may also be administered with the antibodies and conjugates of the present invention. Such agents include antibodies and small molecule drugs such as IDO inhibitors such as 1 methyl tryptophan or derivatives.

In another embodiment, the antibodies of the present invention can be used to treat a subject with an autoimmune, immune system, or inflammatory disorder, *e.g.*, a disorder characterized by aberrant or unwanted immune activity associated with immunomodulation by dendritic cells. Autoimmune, immune system, and inflammatory disorders that may benefit from treatment with the anti-dendritic cells of the invention include rheumatoid arthritis, multiple sclerosis, immune-mediated or Type 1 diabetes mellitus, myasthenia gravis, pernicious anemia, Addison's disease, Sjogren's syndrome, psoriasis, lupus erythematosus, inflammatory bowel diseases such as Crohn's disease and ulcerative colitis, scleroderma/ Raynaud's syndrome, Reiter's syndrome, and autoimmune thyroid diseases such as Hashimoto's thyroiditis and Graves's disease. For example, a subject suffering from an autoimmune disorder may benefit from inhibition of dendritic cell mediated presentation of an autoantigen..

The antibodies of the present invention may also be used for preventing and treating all forms of allergy and allergic disorder, including without limitation: ophthalmic allergic disorders, including allergic conjunctivitis, vernal conjunctivitis, vernal keratoconjunctivitis, and giant papillary conjunctivitis; nasal allergic disorders, including allergic rhinitis and sinusitis; otic allergic disorders, including eustachian tube itching; allergic disorders of the upper and lower airways, including intrinsic and extrinsic asthma; allergic disorders of the skin, including dermatitis, eczema and urticaria; and allergic disorders of the gastrointestinal tract.

Suitable agents for coadministration with the antibodies of the present invention for treatment of such immune disorders include for example, immunosuppressive agents such as rapamycin, cyclosporin and FK506; anti-TNFa agents such as etanercept, adalimumab and infliximab; and steroids. Examples of specific natural and synthetic steroids include, for example: aldosterone, beclomethasone, betamethasone, budesonide, cloprednol, cortisone, cortivazol, deoxycortone, desonide, desoximetasone, dexamethasone, difluorocortolone, fluclorolone, flumethasone, flunisolide, fluocinolone, fluocinonide, fluocortin butyl, fluorocortisone, fluorocortolone, fluorometholone, flurandrenolone, fluticasone, halcinonide, hydrocortisone, icomethasone, meprednisone, methylprednisolone, paramethasone, prednisolone, prednisone, tixocortol and triamcinolone.

Other examples of diseases that can be treated using the anti-DEC-205 antibodies of the invention include transplant rejection and graft versus host disease.

<u>Transplant Rejection</u>

Over recent years there has been a considerable improvement in the efficiency of surgical techniques for transplanting tissues and organs such as skin, kidney, liver, heart, lung, pancreas and bone marrow. Perhaps the principal outstanding problem is the lack of satisfactory agents for inducing immune-tolerance in the recipient to the transplanted allograft or organ. When allogeneic cells or organs are transplanted into a host (*i.e.*, the donor and donee are different individual from the same species), the host immune system is likely to mount an immune response to foreign antigens in the transplant (host-versus-graft disease) leading to destruction of the transplanted tissue. CD8+ cells, CD4+ cells and monocytes are all involved in the rejection of transplant tissues. The antibodies of the present invention are useful to inhibit dendritic cell mediated alloantigen-induced immune responses in the donee thereby preventing such cells from participating in the destruction of the transplanted tissue or organ.

<u>Graft Versus Host Disease</u>

A related use for the antibodies of the present invention is in modulating the immune response involved in "graft versus host" disease (GVHD). GVHD is a potentially fatal disease that occurs when immunologically competent cells are transferred to an allogeneic recipient. In this situation, the donor's immunocompetent cells may attack tissues in the recipient. Tissues of the skin, gut epithelia and liver are frequent targets and may be destroyed during the course of GVHD. The disease presents an especially severe problem when immune tissue is being transplanted, such as in bone marrow transplantation; but less severe GVHD has also been reported in other cases as well, including heart and liver transplants. The therapeutic agents of the present invention are used to inhibit the activity of host antigen presenting cells, *e.g.*, dendritic cells.

The present invention is further illustrated by the following examples which should not be construed as further limiting. The contents of Sequence Listing, figures and all references, patents and published patent applications cited throughout this application are expressly incorporated herein by reference.

EXAMPLES

Example 1

Generation of DEC-205-Specific Human Monoclonal Antibodies (HuMabs)

Human anti-DEC-205 monoclonal antibodies were generated by immunizing the HC2/KCo7 strain of HuMAb® transgenic mice ("HuMab" is a Trade Mark of Medarex, Inc., Princeton, New Jersey) with a soluble human DEC-205 antigen. HC2/KCo7 HuMAb mice were generated as described in U.S. Pat. Nos. 5,770,429 and 5,545,806, the entire disclosures of which are hereby incorporated by reference.

Antigen and Immunization: The antigen was a soluble fusion protein comprising a DEC-205 extracellular domain (comprising all ten lectin-binding domains) fused with an antibody Fc domain. A nucleic acid and amino acid sequence of human DEC-205 is provided in PCT Patent Publication No WO 96023882 (Steinman). The antigen was mixed with Complete Freund's (Sigma) adjuvant for the first immunization. Thereafter, the antigen was mixed with Incomplete Freund's (Sigma). Additional mice were immunized with the soluble DEC-205 protein in RIBI MPL plus TDM adjuvant system (Sigma). 5-25 micrograms soluble recombinant DEC-205 antigen in PBS or 5 x 10^6 CHO cells transfected for surface expression of human DEC-205 in PBS were mixed 1:1 with the adjuvant. Mice were injected with 100 microliters of the prepared antigen into the peritoneal cavity every 14 days. Animals that developed anti-DEC-205 titers were given an iv injection of 10 micrograms soluble recombinant DEC-205 antigen three to four days prior to fusion. Mouse spleens were harvested, and the isolated splenocytes used for hybridoma preparation.

Hybridoma Preparation: The P3x63Ag8.653 murine myeloma cell line (ATCC CRL 1580) was used for the fusions. RPMI 1640 (Invitrogen) containing 10% FBS, and was used to culture the myeloma cells. Additional media supplements were added to the Hybridoma growth media, which included: 3% Origen-Hybridoma Cloning

Factor (Igen), 10% FBS (Sigma), L-glutamine (Gibco) 0.1% gentamycin (Gibco), 2-mercaptoethanol (Gibco), HAT (Sigma; 1.0 x 10^{4} M hypoxanthine, 4.0 x 10^{-7} M aminopterin, 1.6 x 10^{-5} M thymidine), or HT (Sigma; 1.0 x 10^{-4} M hypoxanthine, 1.6 x 10^{-5} M thymidine) media.

Spleen cells were mixed with the 653 myeloma cells in a 6:1 ratio and pelleted by centrifugation. Polyethylene glycol was added dropwise with careful mixing to facilitate fusion. Hybridomas were allowed to grow out for one to two weeks until visible colonies become established. Supernatant was harvested and used for initial screening for human IgG via ELISA using a human kappa chain specific capture and a human Fc specific detection. IgG positive supernatants were then assayed for DEC-205 specificity via flow cytometry or using a DEC-205 ELISA.

Hybridomas producing specific HuMab IgG were subcloned and expanded. The HuMabs produced were then purified by protein A column chromatography according to standard conditions which led to the isolation of a number of antibodies of particular interest.

Example 2

Determination of Affinity and Rate Constants of HuMabs by Surface Plasmon Resonance (SPR)

Binding affinity and binding kinetics of various human anti-DEC-205 antibodies from Example 1 were examined by Biacore™ surface plasmon resonance (SPR) analysis using a Biacore™ 2000 SPR instrument (Biacore AB, Uppsala, Sweden) according to the manufacturer's guidelines.

Purified recombinant human DEC-205 fusion (or control) protein was covalently linked to a Biacore™ CM5 sensor chip (carboxymethylated dextran covalently attached to a gold surface; Biacore Product No. BR-1000-14) using standard amine coupling chemistry with an Amine Coupling Kit provided by Biacore according to the manufacturer's guidelines (BIAcore Product No. BR-1000-50, comprising coupling reagents N-hydroxysuccinimide (NHS) and 1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDC)). Low levels of ligand were immobilised to limit any effects of mass transport of analyte on kinetic parameters, such that the R_{MAX} observed was in the order of 200 RU.

Binding was measured by flowing the antibodies over the sensor chip in HBS-NP buffer (HBS-N buffer, Biacore Product No. BR-1003-69: 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES) 0.24%, sodium chloride 0.88%, qs water, filtered/de-gassed and pre-equilibrated to room temperature with a 1:2000 dilution of Surfactant P20) at concentrations ranging from 1.25 to 200 nM and at a flow rate of 35 μl/minute. The antigen-antibody association and dissociation kinetics were followed for approximately 300 to 600 seconds in each case.

Corresponding controls were conducted in each case using an unrelated protein for "background" subtraction. A single injection of 18 mM NaOH for 17 seconds at 35 μl/min was used as the regeneration conditions throughout the study.

Biacore's kinetics wizard was used in each case to derive kinetic parameters from the concentration series of analyte diluted in HBS-NP running buffer. The association and dissociation curves were fitted to a 1:1 Langmuir binding model using Biacore™ kinetics wizard software (Biacore AB) according to the manufacturer's guidelines. The affinity and kinetic parameters (with background subtracted) as determined are shown in Table 1 below. For each antibody, the figures shown are the mean of two separate series of experiments, using separately prepared sensor chips in each case, (where ka = rate constant of association, kd = rate constant of dissociation, K_D = dissociation equilibrium constant (measure of affinity), K_A = association equilibrium constant, Rmax = maximum SPR response signal).

Table 1

mAb #	**mAb ID**	**ka (1/Ms)**	**kd (1/s)**	**K_A (1/M)**	**K_D (M)**	**RMax (RU)**
#1	3A4-1C10	1.5×10^{6}	9.6×10^{-5}	1.6×10^{10}	6.6×10^{-11}	278
#2	5A8-1F1	3.6×10^{5}	2.0×10^{-4}	2.1×10^{9}	1.5×10^{-9}	172
#3	3C7-3A3	1.7×10^{5}	7.6×10^{-4}	5.2×10^{8}	5.6×10^{-9}	133
#4	2D3-1F5	3.3×10^{5}	2.2×10^{-5}	1.5×10^{10}	6.8×10^{-11}	275
#5	3D6-2F4	1.8×10^{6}	1.2×10^{-4}	1.5×10^{10}	8.0×10^{-11}	294

#6	5D12-5G1	5.4×10^{5}	3.2×10^{-4}	2.0×10^{9}	7.0×10^{-10}	272
#7	1G6-1G6	1.4×10^{6}	3.0×10^{-4}	4.7×10^{9}	2.3×10^{-10}	249
#8	3G9-2D2	9.0×10^{5}	1.9×10^{-4}	4.7×10^{9}	2.4×10^{-10}	268

Example 3

Binding of HuMabs to cells expressing human DEC-205

The ability of anti-DEC-205 HuMabs to bind to DEC-205 on CHO-S cells expressing human DEC-205 on their surface was investigated by flow cytometry as follows.

Antibodies were tested for binding to CHO-S cells expressing human DEC-205 on their surface. Protein A purified HuMabs 3D6-2F4, 3D6-4C8, 3G9-2D2, 5A8-1F1, 2D3-1F5-2A9, 3C7-3A3, 5D12-5G1, 1G6-1G6 and 3A4-1C10 were incubated with the CHO-S cells expressing human DEC-205, as well as CHO-S control cells at 4°C. All antibodies were used at saturating concentrations. After 1 hour, the cells were washed with PBS containing 0.1% BSA and 0.05% NaN_3 (PBA) and the bound antibodies were detected by incubating the cells with a PE labeled goat anti-human IgG Fc-specific probe, at 4°C. The excess probe was washed from the cells with PBA and the cell associated fluorescence was determined by analysis using a LSR™ instrument (BD Biosciences, NJ, USA) according to the manufacturer's directions. Results are shown in Figure 1.

As shown in Figure 1, the HuMabs demonstrated high level binding to CHO-S cells expressing human DEC-205. These data demonstrate that these antibodies bind efficiently and specifically to human DEC-205 expressed on live CHO-S cells compared to the control cells.

Example 4

Binding of HuMabs to human dendritic cells

Human peripheral blood mononuclear cells (PBMCs) were obtained by density gradient centrifugation of Leukopak platelet apheresis preparations Monocytes were isolated by adherance to tissue culture flasks for two hours, and then differentiated into dendritic cells by incubation with 2 ng/ml GM-CSF and 10 ng/ml IL-4 in macrophage serum free media (Gibco) for 5 to 7 days.

The ability of anti-DEC-205 HuMabs to bind to DEC-205 on human dendritic cells prepared as above was investigated by flow cytometry as follows.

Protein A purified HuMabs 3D6-2F2, 3D6-4C8, 3G9-2D2, 5A8-1F1, 2D3-1F5-2A9, 3C7-3A3, 5D12-5G1, 1G6-1G6 and 3A4-1C10, and an isotype control (human IgG) were incubated with the human dendritic cells at 4°C. All antibodies were used at saturating concentrations. After 1 hour, the cells were washed with PBS containing 0.1% BSA and 0.05% NaN_3 (PBA) and the bound antibodies were detected by incubating the cells with a PE labeled goat anti-human IgG Fc-specific probe, at 4°C. The excess probe was washed from the cells with PBA and the cell associated fluorescence was determined by analysis using a LSR™ instrument (BD Biosciences, NJ, USA) according to the manufacturer's directions. Results are shown in Figure 2, which shows that the HuMabs demonstrated high level binding to human dendritic cells compared to the isotype control.

Example 5

ELISA Assay to Determine HuMAb Binding Characteristics on DEC-205

Microtiter plates were coated with soluble DEC-205/Fc fusion protein in PBS, and then blocked with 5% bovine serum albumin in PBS. Protein A purified HuMabs and an isotype control were added at saturating concentrations and incubated at 37°C. The plates were washed with PBS/Tween and then incubated with a goat-anti-human IgG Fc-specific polyclonal reagent conjugated to alkaline phosphatase at 37°C. After washing, the plates were developed with pNPP substrate (1 mg/ml), and analyzed at OD 405-650 using a microtiter plate reader. Results are shown in Figure 3, which shows that the HuMabs demonstrated high level binding compared to the isotype control.

Example 6

Antibody internalization assay

Human monocyte-derived dendritic cells 5 x 10^5 per aliquot were incubated with human IgG (1 mg/ml) to block non-specific binding. Cells were then incubated for 30 minutes on ice with 100 μg/ml of FITC-conjugated anti-Dec-205 HuMab 3G9-2D2 in blocking buffer for binding, and subsequently transferred to 37°C for 0, 10, 30, 60 and 120 minutes for internalization. FITC-conjugated human IgG1 at same concentration was used as control. Cells were then washed and fixed with 1% paraformaldehyde. Fixed cells were washed, resuspended in water, and cytospun onto microscope slides. Images were taken with a Zeiss LSM 510 Meta confocal microscope. Results are shown in Figure 4, which shows that the FITC-labelled HuMabs demonstrated efficient internalization into the dendritic cells compared to the control.

Example 7

Antibody Sequencing

As described above in Example 1, HuMabs from hybridomas producing specific HuMab IgG were purified by protein A column chromatography which led to the isolation of eight antibodies ("HuMabs") of particular interest. The V_H and V_L coding regions of HuMabs 3D6-2F4, 3D6-4C8, 3G9-2D2, 5A8-1F1, 2D3-1F5-2A9 (V_H region), 3C7-3A3, 1E6-3D10 (V_H region) and 5C3-2-3F6 were identified using RNA from the corresponding hybridomas. RNA was reverse transcribed to cDNA, the V coding regions were amplified by PCR and the PCR product was sequenced. The following are the nucleic and amino acid sequences of the V_H and V_L regions of the HuMabs (in the case of the amino acid sequences, the Complementarity Determining Regions (CDRs) are underlined).

3D6-2F4 V_H nucleic acid sequence (VH3, locus 3-33; JH4) (SEQ ID NO:2):
atggagtttgggctgagctgggttttcctcgttgctcttttaagaggtgtccagtgtcaggtgcagctggtggagtctgggggag
gcgtggtccagcctgggaggtccctgagactctcctgtgcagcgtctggattcatcttcagtatctatggcatgcactgggtccg
ccaggctccaggcaaggggctggagtgggtggcagttatatggtatgatggaagtaataaatactatgcagactccgtgaagg
gccgattcaccatctccagagacaattccaagaacacgctgtatctgcaaatgaacagcctgagagccgaggacacggctgtg
tattactgtgcgagagctcctcactttgactactggggccagggaaccctggtcaccgtctcctcagctagc

3D6-2F4 V_H amino acid sequence (SEQ ID NO:3) including signal peptide:
MEFGLSWVFLVALLRGVQCQVQLVESGGGVVQPGRSLRLSCAASGFIFSIYGM
HWVRQAPGKGLEWVAVIWYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSL
RAEDTAVYYCARAPHFDYWGQGTLVTVSS

3D6-2F4 V_H "mature" amino acid sequence (SEQ ID NO: 4) excluding signal peptide:
QVQLVESGGGVVQPGRSLRLSCAASGFIFSIYGMHWVRQAPGKGLEWVAVIWYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARAPHFDYWGQGTLVTVSS

3D6-2F4 V_H CDR1 (SEQ ID NO: 5): IYGMH

3D6-2F4 V_H CDR2 (SEQ ID NO: 6): VIWYDGSNKYYADSVKG

3D6-2F4 V_H CDR3 (SEQ ID NO: 7): APHFDY

3D6-2F4 V_L nucleic acid sequence (VK1, locus L15; JK2) (SEQ ID NO: 8):
atgggatggagctgtatcatcctgttcctcgtggccacagcaaccggtgtccactccgacatccagatgacccagtctccatcctcactgtctgcatctgttggagacagagtcaccatcacttgtcgggcgagtcagggtattagcagctggttagcctggtatcagcagaaaccagagaaagcccctaagtccctgatctatgctgcatccagtttgcaaagtggggtcccatcaaggttcagcggcagtggatctgggacagatttcactctcaccatcagcagcctgcagcctgaagattttgcaacttattactgccaacagtataatagttacccgtacacttttggccaggggaccaagctggagatcaaacgtacg

3D6-2F4 V_L amino acid sequence (SEQ ID NO: 9) including signal peptide:
MDMRVLAQLLGLLLLCFPGARCDIQMTQSPSSLSASVGDRVTITCRASQGISSWLAWYQQKPEKAPKSLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQYNSYPYTFGQGTKLEIK

3D6-2F4 V_L "mature" amino acid sequence (SEQ ID NO: 10) excluding signal peptide:
DIQMTQSPSSLSASVGDRVTITCRASQGISSWLAWYQQKPEKAPKSLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQYNSYPYTFGQGTKLEIK

3D6-2F4 V_L CDR1 (SEQ ID NO: 11): RASQGISSWLA

3D6-2F4 V_L CDR2 (SEQ ID NO: 12): AASSLQS

3D6-2F4 V_L CDR3 (SEQ ID NO: 13): QQYNSYPYT

3D6-4C8 V_H nucleic acid sequence (VH3, locus 3-33; JH4) (SEQ ID NO: 14):
atggagtttgggctgagctgggttttcctcgttgctcttttaagaggtgtccagtgtcaggtgcagctggtggagtctgggggaggcgtggtccagcctgggaggtccctgagactctcctgtgcagcgtctggattcatcttcagtatctatggcatgcactgggtccgccaggctccaggcaaggggctggagtgggtggcagttatatggtatgatggaagtaataaatactatgcagactccgtgaagggccgattcaccatctccagagacaattccaagaacacgctgtatctgcaaatgaacagcctgagagccgaggacacggctgtgtattactgtgcgagagctcctcactttgactactggggccagggaaccctggtcaccgtctcctcagcctccaccaagggcccatcggtcttccccctggcac

3D6-4C8 V_H amino acid sequence (SEQ ID NO: 15) including signal peptide:
MEFGLSWVFLVALLRGVQCQVQLVESGGGVVQPGRSLRLSCAASGFIFSIYGMHWVRQAPGKGLEWVAVIWYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARAPHFDYWGQGTLVTVSS

3D6-4C8 V_H "mature" amino acid sequence (SEQ ID NO: 16) excluding signal peptide:
QVQLVESGGGVVQPGRSLRLSCAASGFIFSIYGMHWVRQAPGKGLEWVAVIWYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARAPHFDYWGQGTLVTVSS

3D6-4C8 V_H CDR1 (SEQ ID NO: 17): IYGMH

3D6-4C8 V_H CDR2 (SEQ ID NO: 18): VIWYDGSNKYYADSVKG

3D6-4C8 V_H CDR3 (SEQ ID NO: 19): APHFDY

3D6-4C8 V_L nucleic acid sequence (VK1, locus L4; JK4) (SEQ ID NO: 20):
atggacatgagggtccccgctcagctcctggggcttctgctgctctggctcccaggtgccagatgtgccatccagttgacccagtctccatcctccctgtctgcatctgtaggagacagagtcaccatcacttgccgggcaagtcagggcattagcagtgctttagcctggtatcagcagaaaccagggaaagctcctaagctcctgatctatgatgcctccagtttggaaagtggggtcccatcaaggttcagcggcagtggatctgggacagatttcactctcaccatcagcagcctgcagcctgaagattttgcaacttattactgtcaacagtttaatagttaccctctcactttcggcggagggaccaaggtggagatcaaa

3D6-4C8 V_L amino acid sequence (SEQ ID NO: 21) including signal peptide:

MDMRVPAQLLGLLLLWLPGARCAIQLTQSPSSLSASVGDRVTITCRASQGISSALAWYQQKPGKAPKLLIYDASSLESGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQFNSYPLTFGGGTKVEIK

3D6-4C8 V_L "mature" amino acid sequence (SEQ ID NO: 22) excluding signal peptide:
AIQLTQSPSSLSASVGDRVTITCRASQGISSALAWYQQKPGKAPKLLIYDASSLESGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQFNSYPLTFGGGTKVEIK

3D6-4C8 V_L CDR1 (SEQ ID NO: 23): RASQGISSALA

3D6-4C8 V_L CDR2 (SEQ ID NO: 24): DASSLES

3D6-4C8 V_L CDR3 (SEQ ID NO: 25): QQFNSYPLT

3G9-2D2, V_H nucleic acid sequence (VH3, locus 3-33; D undetermined; JH4) (SEQ ID NO: 26):
atggagtttgggctgagctgggttttcctcgttgctcttttaagaggtgtccagtgtcaggtgcagctggtggagtctgggggaggcgtggtccagcctgggaggtccctgagactctcctgtgcagcgtctggattcaccttcagtaattatggcatgtactgggtccgccaggctccaggcaaggggctggagtgggtggcagttatatggtatgatggaagtaataaatactatgcagactccgtgaagggccgattcaccatctccagagacaattccaagaacacgctgtatctgcaaatgaacagcctgagagccgaggacacggctgtgtattactgtgcgagagatctctggggatggtactttgactattggggccagggaaccctggtcaccgtctcctcagctagc

3G9-2D2, V_H amino acid sequence (SEQ ID NO: 27) including signal peptide:
MEFGLSWVFLVALLRGVQCQVQLVESGGGVVQPGRSLRLSCAASGFTFSNYGMYWVRQAPGKGLEWVAVIWYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDLWGWYFDYWGQGTLVTVSSASTKGPSVFPLA

3G9-2D2, V_H "mature" amino acid sequence (SEQ ID NO: 28) excluding signal peptide:
QVQLVESGGGVVQPGRSLRLSCAASGFTFSNYGMYWVRQAPGKGLEWVAVIWYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDLWGWYFDYWGQGTLVTVSSASTKGPSVFPLA

3G9-2D2, V_H CDR1 (SEQ ID NO: 29): NYGMY

3G9-2D2, V_H CDR2 (SEQ ID NO: 30): VIWYDGSNKYYADSVKG

3G9-2D2, V_H CDR3 (SEQ ID NO: 31): DLWGWYFDY

3G9-2D2, V_L nucleic acid sequence (VK3, locus L6; JK4) (SEQ ID NO: 32):
atgggatggagctgtatcatcctgttcctcgtggccacagcaaccggtgtccactccgaaattgtgttgacacagtctccagccacccctgtctttgtctccaggggaaagagccaccctctcctgcagggccagtcagagtgttagcagctacttagcctggtaccaacagaaacctggccaggctcccaggctcctcatctatgatgcatccaacagggccactggcatcccagccaggttcagtggcagtgggtctgggacagacttcactctcaccatcagcagcctagagcctgaagattttgcagtttattactgtcagcagcgtcgcaactggccgctcactttcggcggagggaccaaggtggagatcaaacgtacg

3G9-2D2, V_L amino acid sequence (SEQ ID NO: 33) including signal peptide:
MEAPAQLLFLLLLWLPDTTGEIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRATGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQRRNWPLTFGGGTKVEIK

3G9-2D2, V_L "mature" amino acid sequence (SEQ ID NO: 34) excluding signal peptide:
EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRATGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQRRNWPLTFGGGTKVEIK

3G9-2D2, V_L CDR1 (SEQ ID NO: 35): RASQSVSSYLA

3G9-2D2, V_L CDR2 (SEQ ID NO: 36): DASNRAT

3G9-2D2, V_L CDR3 (SEQ ID NO: 37): QQRRNWPLT

5A8-1F1, V_H nucleic acid sequence (VH3, locus 3-33; JH2) (SEQ ID NO: 38):
atggagtttgggctgacctgggttttcctcgttgctcttttaagaggtgtccagtgtcaggtgcagctggtggagtctgggggaggcgtggtccagcctgggaggtccctgagactctcctgtgcagcgtctggattcaccttcagtacctatggcatgcactgggtccgccaggctccaggcaaggggctggagtgggtggcaattatatggtatgatggaggtaataaatactatgcagactccgtgaagggccgattcaccatctccagagacaattccaagaacacgctgtatctgcaaatgaacagcctgagagccgaggacacggctgtg

tattactgtgcgagagacttctactggtacttcgatctctggggccgtggcaccctggtcactgtctcctcagcctccaccaaggg
cccatcggtcttcccccctggcaagg

5A8-1F1, V_H amino acid sequence (SEQ ID NO: 39) including signal peptide:
MEFGLTWVFLVALLRGVQCQVQLVESGGGVVQPGRSLRLSCAASGFTFSTYGM
HWVRQAPGKGLEWVAIIWYDGGNKYYADSVKGRFTISRDNSKNTLYLQMNSL
RAEDTAVYYCARDFYWYFDLWGRGTLVTVSSASTKGPSVFPLA

5A8-1F1, V_H “mature” amino acid sequence (SEQ ID NO: 40) excluding signal peptide:
QVQLVESGGGVVQPGRSLRLSCAASGFTFSTYGMHWVRQAPGKGLEWVAIIW
YDGGNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDFYWYF
DLWGRGTLVTVSSASTKGPSVFPLA

5A8-1F1, V_HCDR1 (SEQ ID NO: 41): TYGMH

5A8-1F1, V_HCDR2 (SEQ ID NO: 42): IIWYDGGNKYYADSVKG

5A8-1F1, V_HCDR3 (SEQ ID NO: 43): DFYWYFDL

5A8-1F1, V_L nucleic acid sequence (VK3, locus L6; JK1) (SEQ ID NO: 44):
atggaagccccagctcagcttctcttcctcctgctactctggctcccagataccaccggagaaattgtgttgacacagtctccagc
caccctgtctttgtctccaggggaaagagccaccctctcctgcagggccagtcagagtgttagcagctacttagcctggtacca
acagaaacctggccaggctcccaggctcctcatctatgatgcatccaacagggccactggcatcccagccaggttcagtggca
gtgggtctgggacagacttcactctcaccatcagcagcctagagcctgaagattttgcagtttattactgtcagcagcgtaggac
gttcggccaagggaccaaggtggaaatcaaacga

5A8-1F1, V_L amino acid sequence (SEQ ID NO: 45) including signal peptide:
MEAPAQLLFLLLLWLPDTTGEIVLTQSPATLSLSPGERATLSCRASQSVSSYLAW
YQQKPGQAPRLLIYDASNRATGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQ
RRTFGQGTKVEIK

5A8-1F1, V_L "mature" amino acid sequence (SEQ ID NO: 46) excluding signal peptide:
EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRATGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQRRTFGQGTKVEIK

5A8-1F1, V_L CDR1 (SEQ ID NO: 47): RASQSVSSYLA

5A8-1F1, V_L CDR2 (SEQ ID NO: 48): DASNRAT

5A8-1F1, V_L CDR3 (SEQ ID NO: 49): QQRRT

3C7-3A3, V_H nucleic acid sequence (VH3, locus 3-33; JH2) (SEQ ID NO: 50):
atggagtttgggctgagctgggttttcctcgttgctcttttaagaggtgtccagtgtcaggtgcagctggtggagtctgggggaggcgtggtccagcctgggaggtccctgagactctcctgtgcagcgtctggattcaccttcagtagctataacatgcactgggtccgccaggctccaggcaaggggctggagtgggtggcatttatatggtatgatggaagtaataaatactatggagactccgtgaagggccgattcaccatctccagagacaattccaaaaacacgctgtatctgcaaatgaacagcctgagagccgaggacacggctgtgtattactgtgcgagagaagagctggggatcgggtggtacttcgatctctggggccgtggcaccctggtcactgtctcctcagcctccaccaagggcccatcggtcttccccctggcac

3C7-3A3, V_H amino acid sequence (SEQ ID NO: 51) including signal peptide:
MEFGLSWVFLVALLRGVQCQVQLVESGGGVVQPGRSLRLSCAASGFTFSSYNMHWVRQAPGKGLEWVAFIWYDGSNKYYGDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAREELGIGWYFDLWGRGTLVTVSSASTKGPSVFPLA

3C7-3A3, V_H "mature" amino acid sequence (SEQ ID NO: 52) excluding signal peptide:
QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYNMHWVRQAPGKGLEWVAFIWYDGSNKYYGDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAREELGIGWYFDLWGRGTLVTVSSASTKGPSVFPLA

3C7-3A3, V_H CDR1 (SEQ ID NO: 53): SYNMH

3C7-3A3, V_H CDR2 (SEQ ID NO: 54): FIWYDGSNKYYGDSVKG

3C7-3A3, V_H CDR3 (SEQ ID NO: 55): EELGIGWYFDL

3C7-3A3, V_L nucleic acid sequence (VK3, locus L6; JK1) (SEQ ID NO: 56):
atggaagccccagctcagcttctcttcctcctgctactctggctcccagataccaccggagaaattgtgttgacacagtctccagccaccctgtctttgtctccaggggaaagagccaccctctcctgcagggccagtcagagtgttagcagctacttagcctggtaccaacagaaacctggccaggctcccaggctcctcatctatgatgcatccaacagggccactggcatcccagccaggttcagtggcagtgggtctgggacagacttcactctcaccatcagcagcctagagcctgaagattttgcagtttattactgtcagcagcgtaggacgttcggccaagggaccaaggtggaaatcaaacgaactgtggctgcaccatctgtcttcatcttcccgccatctgatgagcagttgaaatctggaactgcctctgttgtgtgcctgc

3C7-3A3, V_L amino acid sequence (SEQ ID NO: 57) including signal peptide:
MEAPAQLLFLLLLWLPDTTGEIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRATGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQRRTFGQGTKVEIK

3C7-3A3, V_L “mature” amino acid sequence (SEQ ID NO: 58) excluding signal peptide:
EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRATGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQRRTFGQGTKVEIK

3C7-3A3, V_L CDR1 (SEQ ID NO: 59): RASQSVSSYLA

3C7-3A3, V_L CDR2 (SEQ ID NO: 60): DASNRAT

3C7-3A3, V_L CDR3 (SEQ ID NO: 61): QQRRT

2D3-1F5-2A9, V_H nucleic acid sequence (VH3, locus Orph-C16; JH3) (SEQ ID NO: 62):
atggagtttgtgctgagctgggttctccttgttgctatattaaaaggtgtccagtgtgaggttcagctggtgcagtctgggggaggcttggtacatcctggggggtccctgagactctcctgtgcaggctctggattcaccttcagtaactatgctatgcactgggttcgccaggctccaggaaaaggtctggagtgggtatcaactattggtactggtggtggcacaccctatgcagactccgtgaagggccgcttcaccatctccagagacaatgccaagaactccttgtatcttcaaatgaacagcctgagagccgaggacatggctgtgtattactgtgcattaagtgcttttgatgtctggggccaagggacaatggtcaccgtctcttcagcctccaccaagggcccatcggtcttccccctggcac

2D3-1F5-2A9, V_H amino acid sequence (SEQ ID NO: 63) including signal peptide:
MEFVLSWVLLVAILKGVQCEVQLVQSGGGLVHPGGSLRLSCAGSGFTFSNYAM
HWVRQAPGKGLEWVSTIGTGGGTPYADSVKGRFTISRDNAKNSLYLQMNSLRA
EDMAVYYCALSAFDVWGQGTMVTVSSASTKGPSVFPLA

2D3-1F5-2A9, V_H "mature" amino acid sequence (SEQ ID NO: 64) excluding signal peptide:
EVQLVQSGGGLVHPGGSLRLSCAGSGFTFSNYAMHWVRQAPGKGLEWVSTIGT
GGGTPYADSVKGRFTISRDNAKNSLYLQMNSLRAEDMAVYYCALSAFDVWGQ
GTMVTVSSASTKGPSVFPLA

2D3-1F5-2A9, V_H CDR1 (SEQ ID NO: 65): NYAMH

2D3-1F5-2A9, V_H CDR2 (SEQ ID NO: 66): TIGTGGGTPYADSVKG

2D3-1F5-2A9, V_H CDR3 (SEQ ID NO: 67): SAFDV

1E6-3D10 V_H nucleic acid sequence (VH3, locus Orph-HC16; JH4) (SEQ ID NO: 68):
Atggagtttgtgctgagctgggttttccttgttgctatattaaaaggtgtccagtgtgaggttcagctggtgcagtctgggggagg
cttggtacatcctggggggtccctgagactctcctgtgcaggctctggattcaccttcagtagctatgctatgcactgggttcgcc
aggctccaggaaaaggtctggagtgggtatcagctattggtactggtggttacacatactatgtagactccgtgaagggccgatt
caccatctccagagacaatgccaagaagtccttgtatcttcaaatgaacagcctgagagccgaggacatggctgtgtattactgt
gcaagagagccgttttacgatattttgactggttattccccatactttgactactggggccagggaaccctggtcaccgtctcctca
gcctccaccaagggcccatcggtcttcccctggcac

1E6-3D10 V_H amino acid sequence (SEQ ID NO: 69) including signal peptide:
MEFVLSWVFLVAILKGVQCEVQLVQSGGGLVHPGGSLRLSCAGSGFTFSSYAM
HWVRQAPGKGLEWVSAIGTGGYTYYVDSVKGRFTISRDNAKKSLYLQMNSLR
AEDMAVYYCAREPFYDILTGYSPYFDYWGQGTLVTVSS

1E6-3D10 V_H "mature" amino acid sequence (SEQ ID NO: 70) excluding signal peptide:

EVQLVQSGGGLVHPGGSLRLSCAGSGFTFSSYAMHWVRQAPGKGLEWVSAIGTGGYTYYVDSVKGRFTISRDNAKKSLYLQMNSLRAEDMAVYYCAREPFYDILTGYSPYFDYWGQGTLVTVSS

1E6-3D10 V_H CDR1: (SEQ ID NO: 71):SYAMH

1E6-3D10 V_H CDR2 (SEQ ID NO: 72): AIGTGGYTYYVDSVKG

1E6-3D10 V_H CDR3 (SEQ ID NO: 73): EPFYDILTGYSPYFDY

5C3-2-3F6 V_H nucleic acid sequence (VH3, locus 3-33; JH2) (SEQ ID NO: 74):

Atggagtttgggctgagctgggttttcctcgttgctcttttaagaggtgtccagtgtcaggtgcagctggtggagtctgggggaggcgtggtccagcctgggaggtccctgagactctcctgtgcagcgtctggattcaccttcagtagctataacatgcactgggtccgccaggctccaggcaaggggctggagtgggtggcagttatatggtatgatggaagtaataaatactatggagactccgtgaagggccgattcaccatctccagagacaattccaagaacacgctgtatctgcaaatgaacagcctgagagccgaggacacggctgtgtattactgtgcgagagaagagctggggatcgggtggtacttcgatctctggggccgtggcaccctggtcactgtctcctcagcctccaccaagggcccatcggtcttcccectggcac

5C3-2-3F6 V_H amino acid sequence (SEQ ID NO: 75) including signal peptide:

MEFGLSWVFLVALLRGVQCQVQLVESGGGVVQPGRSLRLSCAASGFTFSSYNMHWVRQAPGKGLEWVAVIWYDGSNKYYGDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAREELGIGWYFDLWGRGTLVTVSS

5C3-2-3F6 V_H "mature" amino acid sequence (SEQ ID NO: 76) excluding signal peptide:

QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYNMHWVRQAPGKGLEWVAVIWYDGSNKYYGDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAREELGIGWYFDLWGRGTLVTVSS

5C3-2-3F6 V_H CDR1 (SEQ ID NO: 77): SYNMH

5C3-2-3F6 V_H CDR2 (SEQ ID NO: 78): VIWYDGSNKYYGDSVKG

5C3-2-3F6 V_H CDR3 (SEQ ID NO: 79): EELGIGWYFDL

5C3-2-3F6 VK V_L nucleic acid sequence (VK1, locus L18; JK5) (SEQ ID NO: 80):
Atggacatgagggtccccgctcagctcctggggcttctgctgctctggctcccaggtgccagatgtgccatccagttgaccca gtctccatcctccctgtctgcatctgtaggagacagagtcaccatcacttgccgggcaagtcagggcattagcagtgctttagcc tggtatcagcagaaaccagggaaagctcctaagctcctgatctatgatgcctccagtttggaaagtggggtcccatcaaggttc agcggcagtggatctgggacagatttcactctcaccatcagcagcctgcagcctgaagattttgcaacttattactgtcaacagtt taatagttaccctcacttcggccaagggacacgactggagattaaacgaactgtggctgcaccatctgtcttcatcttcccgccat ctgatgagcagttgaaatctggaactgcctctgttgtgtgcctgcaagggc

5C3-2-3F6 VK V_L amino acid sequence (SEQ ID NO: 81) including signal peptide:
MDMRVPAQLLGLLLLWLPGARCAIQLTQSPSSLSASVGDRVTITCRASQGISSAL AWYQQKPGKAPKLLIYDASSLESGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC QQFNSYPHFGQGTRLEIK

5C3-2-3F6 VK V_L "mature" amino acid sequence (SEQ ID NO: 82) excluding signal peptide:
AIQLTQSPSSLSASVGDRVTITCRASQGISSALAWYQQKPGKAPKLLIYDASSLES GVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQFNSYPHFGQGTRLEIK

5C3-2-3F6 V_L CDR1 (SEQ ID NO: 83): RASQGISSALA

5C3-2-3F6 V_L CDR2 (SEQ ID NO: 84): DASSLES

5C3-2-3F6 V_L CDR3 (SEQ ID NO: 85): QQFNSYPH

5D12-5G1 VH nucleic acid sequence (VH3, locus 3-33; JH2) (SEQ ID NO: 86):
Atggagtttgggctgagctgggttttcctcgttgctcttttaagaggtgtccagtgtcaggtgcagctggtggagtctgggggag gcgtggtccagcctgggaggtccctgagactctcctgtgcagcgtctggattcaccttcagtagctatggcatgcactgggtcc gccaggctccaggcaaggggctggagtgggtggcagttatatggtatgatggaagtaataaatactatgcagactccgtgaag ggccgattcaccatctccagagacaattccaagaacacgctgtatctgcaaatgaacagcctgagagccgaggacacggctgt

gtattactgtgcgagaggcccccctcggtacttcgatctctggggccgtggcaccctggtcactgtctcctcagcctccaccaa gggcccatcggtcttccccctggcac

5D12-5G1 VH amino acid sequence (SEQ ID NO: 87) including signal peptide:
MEFGLSWVFLVALLRGVQCQVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVIWYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARGPPRYFDLWGRGTLVTVSS

5D12-5G1 VH "mature" amino acid sequence (SEQ ID NO: 88) excluding signal peptide:
QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVIWYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARGPPRYFDLWGRGTLVTVSS

5D12-5G1 VH CDR1 (SEQ ID NO: 89): SYGMH

5D12-5G1 VH CDR2 (SEQ ID NO: 90): VIWYDGSNKYYADSVKG

5D12-5G1 VH CDR3 (SEQ ID NO: 91): GPPRYFDL

For reference, the amino acid sequences of the proposed corresponding germline sequences (assigned without prejudice) are as follows:

Germline L6 (SEQ ID NO: 92):
EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRATGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQRSNWP

Germline L4 (SEQ ID NO: 93):
AIQLTQSPSSLSASVGDRVTITCRASQGISSALAWYQQKPGKAPKLLIYDASSLESGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQFNSYP

Germline L15 (SEQ ID NO: 94):

DIQMTQSPSSLSASVGDRVTITCRARQGISSWLAWYQQKPEKAPKSLIYAASSLQ SGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQYNSYP

Germline V_H3-33 (SEQ ID NO: 95):
QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVIW YDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR

Germline Orph-C16 (SEQ ID NO: 96):
EVQLVQSGGGLVHPGGSLRLSCAGSGFTFSSYAMHWVRQAPGKGLEWV SAIGTGGGTYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDMAVYYCAR

Sequence alignments of the V_L and V_H sequences against the proposed corresponding germline sequences are shown in Figure 5, for illustration purposes only.

Example 8

3G9-βhCG APC-targeted vaccine conjugate

A DEC-205 targeted vaccine conjugate was generated by linking the βhCG antigen to HuMab 3G9-2D2 (also determined to be cross-reactive with cynomologous DEC-205) from Example 7 above. Linkage was accomplished by covalently attaching the antigen to the heavy chain of the antibody by genetic fusion.

A plasmid containing neomycin and dihydrofolate reductase genes was generated containing the βhCG coding sequence fused to antibody 3G9-2D2 heavy chain at the CH3 domain and the 3G9-2D2 light chain. The resulting plasmid construct was transfected into CHO cells using a standardized protocol (Qiagen Inc, Valencia, CA). Transfected cells were selected in media containing the antibiotic G418. After selection, the cells were cloned by limiting dilution, and stable clonal lines were used to generate cell banks for further studies. To confirm expression of the 3G9-βhCG constructs, Western Blot analysis of proteins run on SDS-PAGE under reducing and non-reducing conditions was performed. This fusion protein was observed to be of the expected molecular weight and to be properly assembled (*i.e.*, to contain both the heavy chain fusion and the light chain). Specifically, the vaccine conjugate and the antibody alone were analyzed by SDS-PAGE using denaturing conditions and detected by Western blot analysis. The blot was then probed separately using goat anti-human IgG, and with a mAb (US Biologicals) specific to the βhCG C-terminal peptide. The results confirmed that the transformed CHO cells specifically expressed the 3G9-βhCG vaccine conjugate as evidenced by the appropriate size and composition of the fusion product.

Example 9

Antigen-specific activity using 3G9-βhCG APC-targeted vaccine conjugate

Cells capable of antigen presentation were human in origin and varied from peripheral blood mononuclear cells (PBMC), monocytes (THP-1), B lymphoblastoid cells (C1R.A2, 1518 B-LCL) and monocyte-derived DCs. All cells were positive for cell surface expression of DEC-205 as assessed by flow cytometry.

The vector pk: 3G9-hCGβ was transfected into CHO cells. Stable clones were selected with G418 and subsequently subcloned. The fusion protein produced by the cells (3G9-βhCG vaccine conjugate; Example 8) was collected in the supernatant and purified over Protein A column.

T cells were obtained from leukopacks of normal healthy donors. Antigen-specific T cells were generated in vitro by 2-3 weekly Stimulations with autologous DCs targeted with 3G9-hCGβ and enriched for CD8+ and CD4+ T cells before testing for antigen-specific activity with a variety of APCs (as described above) by GrB or IFNγ ELISpot assays (MabTech). Cytokines IL-7 and IL-2 were added to maintain effector propagation and activity every 3-4 days. Antigen-specific T cells were expanded on Miltenyi-MACS T cell expansion kit for 10-12 days in the presence of low dose of IL-2. CD40L (Alexis Biochemicals) was used to induce maturation of DCs. As shown in Figure 9A, CD8+ T cell responses were achieved in DCs and monocytes (THP-1), as well as B lymphoblastoid cells (Figure 9B). Accordingly, antigen targeting via the DEC-205 receptor to B cells resulted in the stimulation of MHC-class I restricted T cells.

Equivalents

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents of the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.

The claims defining the invention are as follows:-

1. An isolated human monoclonal antibody, which binds to human Dendritic and Epithelial Cell 205 receptor (DEC-205) and comprises heavy and light chain variable region CDR1, CDR2 and CDR3 sequences, wherein:

(i) the heavy chain variable region CDR1 comprises an amino acid sequence selected from the consensus sequence: (I,N,T,S) Y (G,N,A) M (H,Y) (SEQ ID NO: 97);

(ii) the heavy chain variable region CDR2 comprises an amino acid sequence selected from the consensus sequence: (V,I,F,T,A) I (W,G) (Y,T) (D,G) G (S,G,Y) (N,T) (K,P) Y (Y,A,V) (A,G,-) D S V K G (SEQ ID NO: 98);

(iii) the heavy chain variable region CDR3 comprises an amino acid sequence selected from the consensus sequence: (A,G,Y,S,P,-) (P,W,S,R) (Y,A,H) F D (Y,L,V) (SEQ ID NO: 99);

(iv) the light chain variable region CDR1 comprises an amino acid sequence selected from the consensus sequence: R A S Q (S,G) (I,V) S S (Y,W,A) L A (SEQ ID NO: 100);

(v) the light chain variable region CDR2 comprises an amino acid sequence selected from the consensus sequence: (D,A) A S (N,S) (R,L) (A,Q,E) (T,S) (SEQ ID NO: 101); and

(vi) the light chain variable region CDR3 comprises an amino acid sequence selected from the consensus sequence: Q Q (R,Y,F) (R,N) (T,S,N) (Y,W,-) (P,-) (Y,L,H,-) (T,-) (SEQ ID NO: 102); and

wherein "-" denotes the option of no amino acid residue being present at that consensus position.

2. The isolated monoclonal antibody of claim 1, wherein the antibody exhibits at least one of the following properties:

(a) binds to human DEC-205 with an affinity constant of at least 10^8 M^{-1} as determined by surface Plasmon resonance;
(b) is internalized after binding to human dendritic cells expressing DEC-205;
(c) generates or enhances human CD4+ T-cell responses to an antigen;
(d) generates or enhances human CTL or NKT responses to an antigen;
(e) localizes to antigen processing compartments in dendritic cells; or
(f) induces peripheral $CD8^+$ T cell tolerance.

3. The isolated monoclonal antibody of claim 1 or claim 2, wherein, the human T-cell response is mediated by either MHC Class I or Class II pathways or both.

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4. The isolated monoclonal antibody of claim 1 comprising a heavy chain variable region selected from the group consisting of: SEQ ID NOs: 28, 4, 16, 40, 52, 76, 64, and 70.

5. The isolated monoclonal antibody of claim 1 comprising a light chain variable region selected from the group consisting of: SEQ ID NOs: 34, 10, 22, 46, 58, and 82.

6. The isolated monoclonal antibody of claim 1 comprising heavy and light chain variable regions selected from the group consisting of:

(a) a heavy chain variable region comprising SEQ ID NO:28 and a light chain variable region comprising SEQ ID NO:34;

(b) a heavy chain variable region comprising SEQ ID NO:4 and a light chain variable region comprising SEQ ID NO:10;

(c) a heavy chain variable region comprising SEQ ID NO:16 and a light chain variable region comprising SEQ ID NO:22;

(d) a heavy chain variable region comprising SEQ ID NO:40 and a light chain variable region comprising SEQ ID NO:46;

(e) a heavy chain variable region comprising SEQ ID NO:52 and a light chain variable region comprising SEQ ID NO:58; and

(f) a heavy chain variable region comprising SEQ ID NO:76 and a light chain variable region comprising SEQ ID NO:82.

7. The isolated monoclonal antibody of claim 1 comprising heavy and light chain variable region CDR1, CDR2 and CDR3 sequences selected from the group consisting of:

(i) a heavy chain variable region CDR1 comprising SEQ ID NO: 29;
a heavy chain variable region CDR2 comprising SEQ ID NO: 30;
a heavy chain variable region CDR3 comprising SEQ ID NO: 31;
a light chain variable region CDR1 comprising SEQ ID NO: 35;
a light chain variable region CDR2 comprising SEQ ID NO: 36;
a light chain variable region CDR3 comprising SEQ ID NO: 37;

(ii) a heavy chain variable region CDR1 comprising SEQ ID NO: 17;
a heavy chain variable region CDR2 comprising SEQ ID NO: 18;
a heavy chain variable region CDR3 comprising SEQ ID NO: 19;
a light chain variable region CDR1 comprising SEQ ID NO: 23;
a light chain variable region CDR2 comprising SEQ ID NO: 24;
a light chain variable region CDR3 comprising SEQ ID NO: 25;

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(iii) a heavy chain variable region CDR1 comprising SEQ ID NO: 5;
a heavy chain variable region CDR2 comprising SEQ ID NO: 6;
a heavy chain variable region CDR3 comprising SEQ ID NO: 7;
a light chain variable region CDR1 comprising SEQ ID NO: 11;
a light chain variable region CDR2 comprising SEQ ID NO: 12;
a light chain variable region CDR3 comprising SEQ ID NO: 13;

(iv) a heavy chain variable region CDR1 comprising SEQ ID NO: 41;
a heavy chain variable region CDR2 comprising SEQ ID NO: 42;
a heavy chain variable region CDR3 comprising SEQ ID NO: 43;
a light chain variable region CDR1 comprising SEQ ID NO: 47;
a light chain variable region CDR2 comprising SEQ ID NO: 48;
a light chain variable region CDR3 comprising SEQ ID NO: 49;

(v) a heavy chain variable region CDR1 comprising SEQ ID NO: 53;
a heavy chain variable region CDR2 comprising SEQ ID NO: 54;
a heavy chain variable region CDR3 comprising SEQ ID NO: 55;
a light chain variable region CDR1 comprising SEQ ID NO: 59;
a light chain variable region CDR2 comprising SEQ ID NO: 60;
a light chain variable region CDR3 comprising SEQ ID NO: 61; and

(vi) a heavy chain variable region CDR1 comprising SEQ ID NO: 77;
a heavy chain variable region CDR2 comprising SEQ ID NO: 78;
a heavy chain variable region CDR3 comprising SEQ ID NO: 79;
a light chain variable region CDR1 comprising SEQ ID NO: 83;
a light chain variable region CDR2 comprising SEQ ID NO: 84;
a light chain variable region CDR3 comprising SEQ ID NO: 85.

8. The isolated monoclonal antibody of claim 1 comprising a heavy chain variable region and a light chain variable region encoded by nucleic acid sequences selected form the group consisting of:

(a) SEQ ID NOs: 26 and 32, respectively;
(b) SEQ ID NOs: 14 and 20, respectively;
(c) SEQ ID NOs: 2 and 8, respectively;
(d) SEQ ID NOs: 38 and 44, respectively;
(e) SEQ ID NOs: 50 and 56, respectively; and
(f) SEQ ID NOs: 74 and 80, respectively.

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9. The isolated monoclonal antibody of claim 1 comprising a heavy chain variable region comprising SEQ ID NO:28 and a light chain variable region comprising SEQ ID NO:34.

10. The isolated monoclonal antibody of claim 1 comprising:

(a) a heavy chain variable region CDR1 comprising SEQ ID NO: 29;
(b) a heavy chain variable region CDR2 comprising SEQ ID NO: 30;
(c) a heavy chain variable region CDR3 comprising SEQ ID NO: 31;
(d) a light chain variable region CDR1 comprising SEQ ID NO: 35;
(e) a light chain variable region CDR2 comprising SEQ ID NO: 36; and
(f) a light chain variable region CDR3 comprising SEQ ID NO: 37.

11. The isolated monoclonal antibody of claim 1 comprising a heavy chain variable region encoded by a nucleic acid sequence comprising SEQ ID NO:26 and a light chain variable region encoded by a nucleic acid sequence comprising SEQ ID NO:32.

12. An isolated antibody that competes for binding with the isolated monoclonal antibody of claim 6 or claim 7.

13. An isolated antibody which binds to an epitope bound by the isolated monoclonal antibody of claim 6 or claim 7.

14. The isolated monoclonal antibody of any one of claims 1 to 11, wherein the antibody is a human antibody or a chimeric antibody.

15. The isolated monoclonal antibody of claim 14, wherein the antibody is selected from the group consisting of an IgG1, an IgG2, an IgG3, an IgG4, an IgM, an IgA1, an IgA2, an IgAsec, an IgD, and an IgE antibody.

16. An expression vector comprising a nucleotide sequence encoding the antibody according to any one of claims 1 to 15.

17. A cell transformed with an expression vector as claimed in claim 16.

18. A molecular conjugate comprising the antibody according to any one of claims 1 to 15, linked to an antigen.

19. The molecular conjugate of claim 18, wherein the antigen is selected from the group consisting of a component of a pathogen, a tumor antigen, an allergen and an autoantigen.

20. The molecular conjugate of claim 18, wherein the tumor antigen is selected from the group consisting of βhCG, gp100 or Pmel17, HER2/neu, WT1, mesothelin, CEA, gp100, MART1, TRP-2, NY-BR-1, NY-CO-58, MN (gp250), idiotype, Tyrosinase, Telomerase, SSX2, MUC-1, MART1, melan-A, NY-ESO-1, MAGE-1, MAGE-3, MAGE-A3, and high molecular weight-melanoma associated antigen (HMW-MAA).

21. The molecular conjugate of claim 18, wherein the antigen is from HIV, HPV, HBV or HCV.

22. The molecular conjugate of claim 18, further comprising a therapeutic agent selected from the group consisting of a cytotoxic agent, an immunosuppressive agent, and a chemotherapeutic agent.

23. A bispecific molecule comprising the antibody according to any one of claims 1 to 15 linked to a molecule having a binding specificity which is different from the antibody.

24. A composition comprising the antibody according to any one of claims 1 to 15 and a pharmaceutically effective carrier.

25. The composition of claim 24, further comprising a therapeutic agent.

26. Use of the antibody according to any one of claims 1 to 15 in the preparation of a medicament for targeting an antigen to DEC-205 in a subject.

27. Use of the antibody according to any one of claims 1 to 15 in the preparation of a medicament for inducing or enhancing an immune response against an antigen in a subject.

28. Use of the antibody according to any one of claims 1 to 15 in the preparation of a medicament for inducing or enhancing a T cell-mediated immune response in a subject against an antigen.

29. Use of the antibody according to any one of claims 1 to 15 in the preparation of a medicament for immunizing a subject.

30. Use of the antibody according to any one of claims 1 to 15 in the preparation of a medicament for treating a disorder in a subject.

31. A method for detecting the presence or absence of DEC-205 in a biological sample, comprising:

(a) contacting a biological sample with the antibody of any one of claims 1 to 15, wherein the antibody is labeled with a detectable substance; and

(b) detecting the antibody bound to DEC-205 to thereby detect the presence or absence of DEC-205 in the biological sample.

32. Use of a molecular conjugate comprising the antibody according to any one of claims 1 to 15 linked to an antigen in the preparation of a medicament for targeting the antigen to a B cell in a subject.

33. Use of a molecular conjugate comprising the antibody according to any one of claims 1 to 15 linked to an antigen in the preparation of a medicament for inducing or enhancing an immune response against the antigen in a subject.

34. Use of a molecular conjugate comprising the antibody of according to any one of claims 1 to 15 linked to an antigen in the preparation of a medicament for immunizing a subject against the antigen.

35. A method for targeting an antigen to DEC-205 in a subject, said method comprising the step of administering to the subject the antibody according to any one of claims 1 to 15 or the composition according to claim 24 or claim 25.

36. A method for inducing or enhancing an immune response against an antigen in a subject, said method comprising the step of administering to the subject the antibody according to any one of claims 1 to 15 or the composition according to claim 24 or claim 25.

37. A method for inducing or enhancing a T cell-mediated immune response in a subject, said method comprising the step of administering to the subject the antibody according to any one of claims 1 to 15 or the composition according to claim 24 or claim 25.

38. A method for immunizing a subject, said method comprising the step of administering to the subject antibody according to any one of claims 1 to 15 or the composition according to claim 24 or claim 25.

39. A method for treating a disorder in a subject, said method comprising the step of administering to the subject antibody according to any one of claims 1 to 15 or the composition according to claim 24 or claim 25.

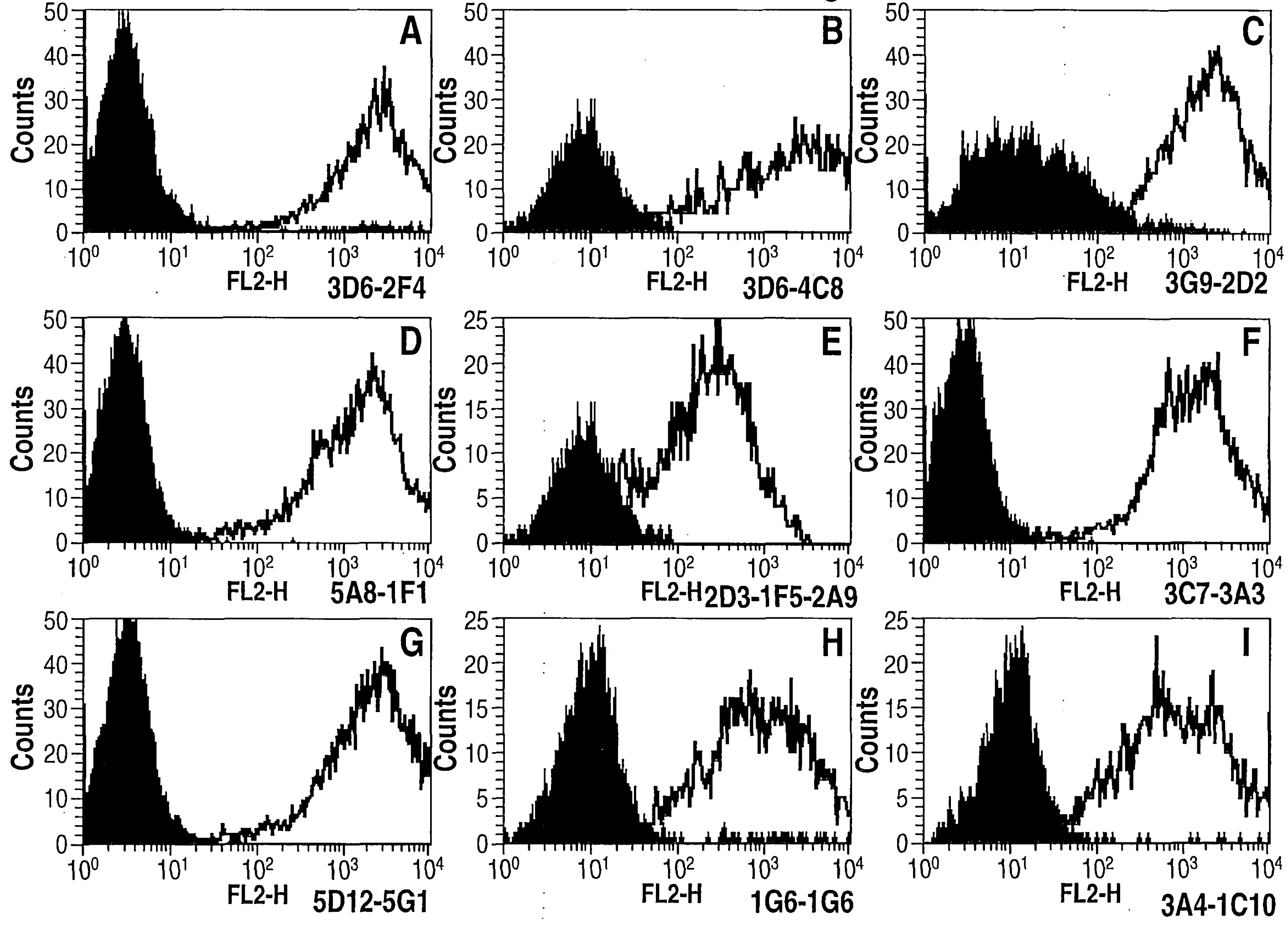
40. A method for targeting an antigen to a B cell in a subject, said method comprising the step of administering to the subject a molecular conjugate comprising the antibody according to any one of claims 1 to 15 linked to the antigen.

41. A method for inducing or enhancing an immune response against an antigen in a subject, said method comprising the step of administering to the subject the antibody according to any one of claims 1 to 15 linked to the antigen.

42. A method for immunizing a subject against an antigen, said method comprising the step of administering to the subject the antibody according to any one of claims 1 to 15 linked to the antigen.

43. An isolated human monoclonal antibody according to claim 1; an isolated antibody according to claim 12 or claim 13; an expression vector according to claim 16; a cell according to claim 17; a molecular conjugate according to claim 18; a bispecific molecule according to claim 23; a composition according to claim 24; use according to any one of claims 26-30 or 32-34; or a method according to any one of claims 31 or 35-42, substantially as herein described with reference to any one or more of the examples but excluding comparative examples.

Human anti-DEC205 Antibodies Binding to CHO cells



Filled histogram = control CHO-S cells

Open histograms = CHO-S cells expressing huDEC-205

All antibodies used at saturating concentrations

Fig. 1

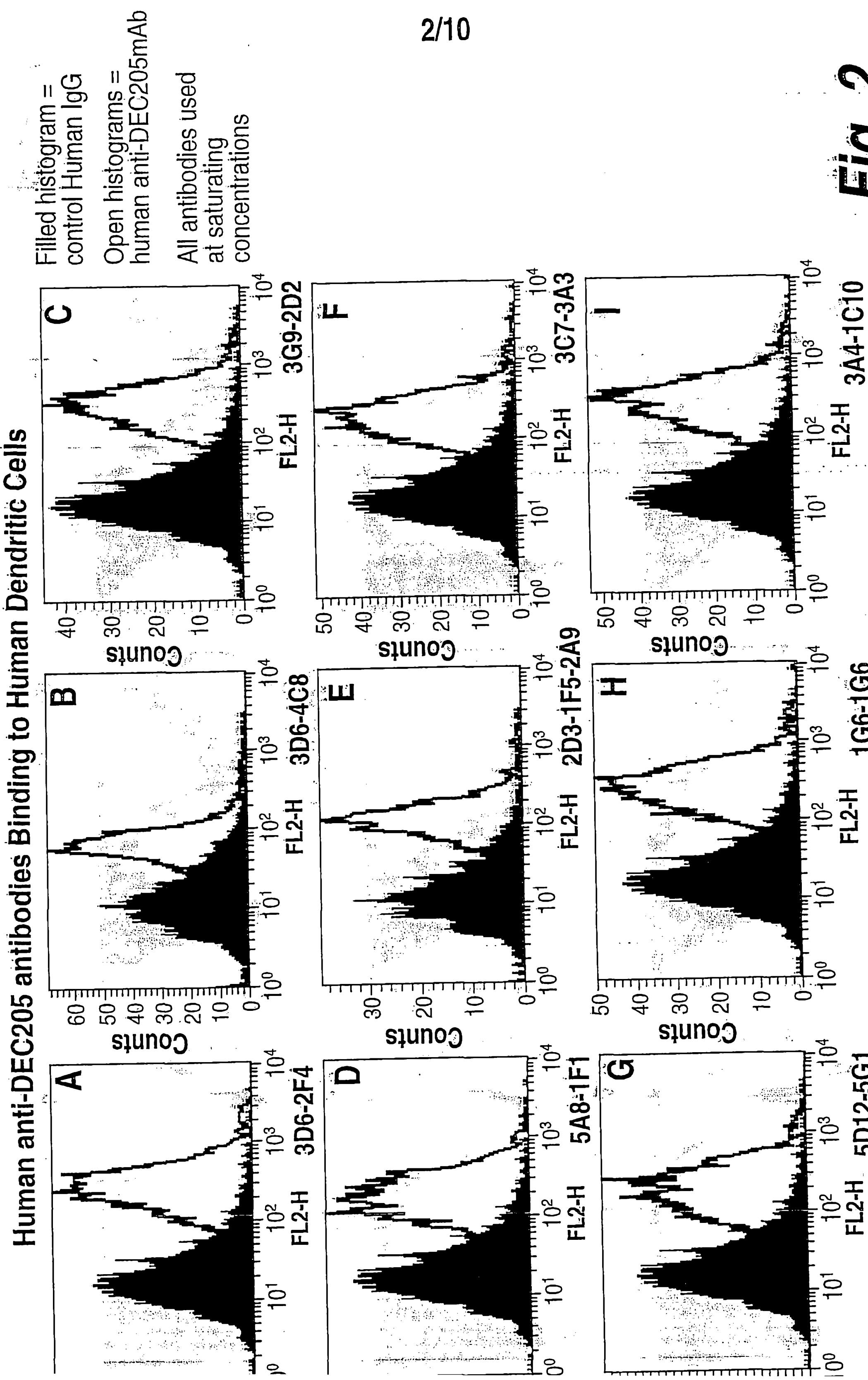

Human anti-DEC205 antibodies Binding to Human Dendritic Cells
Filled histogram = control Human IgG
Open histograms = human anti-DEC205mAb
All antibodies used at saturating concentrations
A
B
C
D
E
F
G
H
I
Counts
FL2-H
3D6-2F4
3D6-4C8
3G9-2D2
5A8-1F1
2D3-1F5-2A9
3C7-3A3
5D12-5G1
1G6-1G6
3A4-1C10

Fig. 2

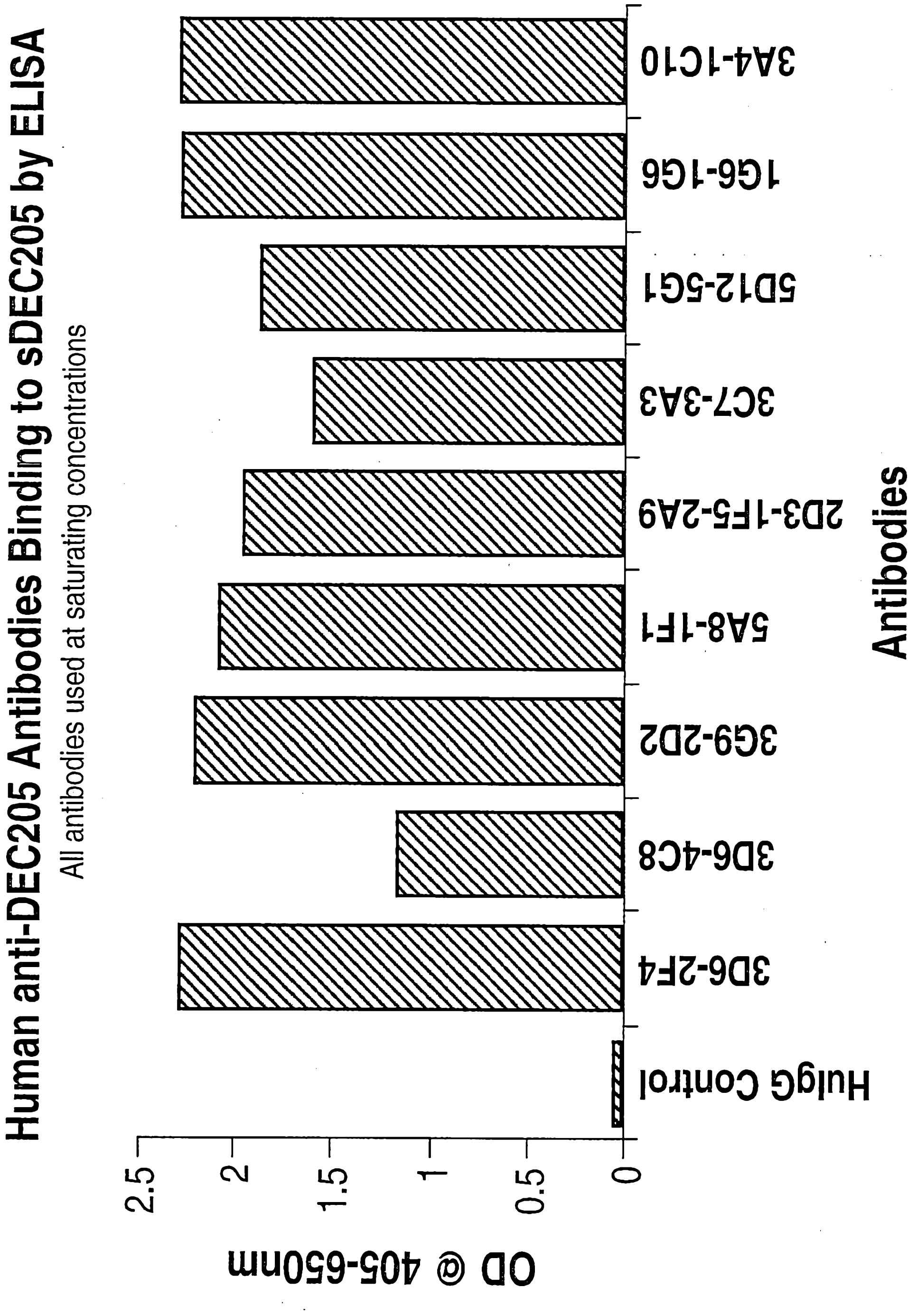
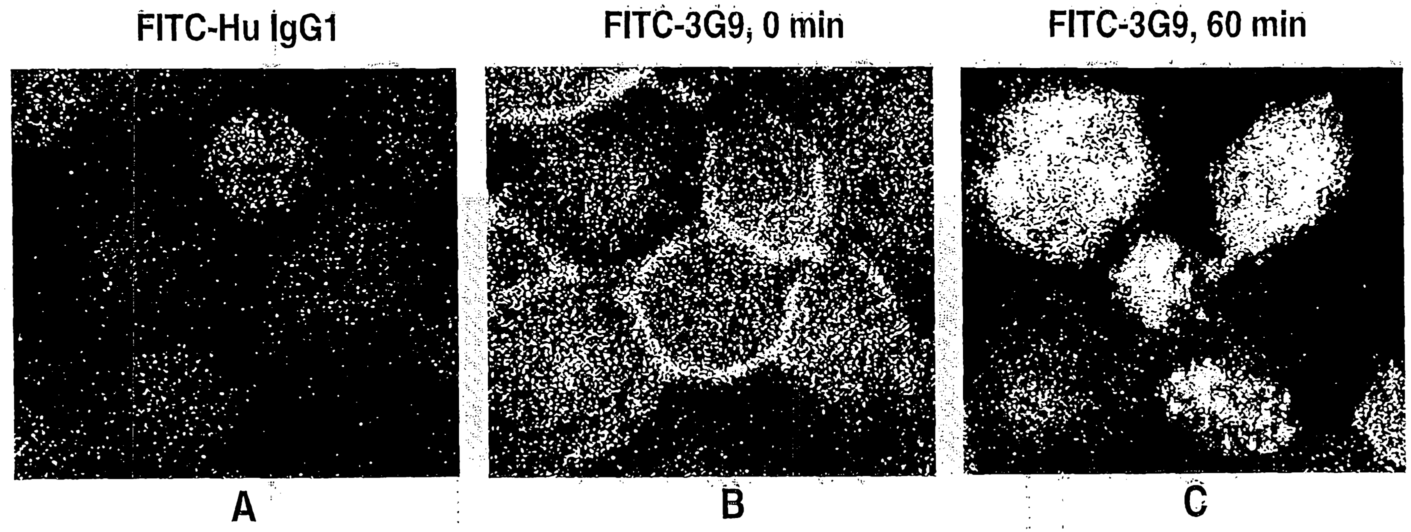

Human anti-DEC205 Antibodies Binding to sDEC205 by ELISA
All antibodies used at saturating concentrations
OD @ 405-650nm
2.5
2
1.5
1
0.5
0
HuIgG Control
3D6-2F4
3D6-4C8
3G9-2D2
5A8-1F1
2D3-1F5-2A9
3C7-3A3
5D12-5G1
1G6-1G6
3A4-1C10
Antibodies

Fig. 3

Dec205 mAb Binding and Internalization in Dendritic Cells



Monocyte-derived human DCs were pulsed with FITC-3G9-2D2 or FITC-human IgG1 for 30 minutes on ice. Cells were then incubated at 37°C for the indicated periods to allow for internalization. Images were captured by confocal microscopy, and green staining revealed the presence of FITC-labeled molecules.

Fig. 4

Human V_H and V_K Alignments and Germline Sequences

Vκ Alignments

	Sequence (CDR1, CDR2, CDR3, V, J)	J	
L6 germ.	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRATGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQRSNWP		
3G9-2D2	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRATGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQRRNWP	LTFGGGTKVEIK	JK4
5A8-1F1	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRATGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQRR___	_TFGQGTKVEIK	JK1
3C7-3A3	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRATGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQRR___	_TFGQGTKVEIK	JK1
L4 germ.	AIQLTQSPSSLSASVGDRVTITCRASQGISSALAWYQQKPGKAPKLLIYDASSLESGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQFNSYP		
5C3-2-3F6	AIQLTQSPSSLSASVGDRVTITCRASQGISSALAWYQQKPGKAPKLLIYDASSLESGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQFNSYP	H_FGQGTRLEIK	JK5
3D6-4C8	AIQLTQSPSSLSASVGDRVTITCRASQGISSALAWYQQKPGKAPKLLIYDASSLESGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQFNSYP	LTFGGGTKVEIK	JK4
L15 germ.	DIQMTQSPSSLSASVGDRVTITCRARQGISSWLAWYQQKPEKAPKSLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQYNSYP		
3D6-2F4	DIQMTQSPSSLSASVGDRVTITCRASQGISSWLAWYQQKPEKAPKSLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQYNSYP	YTFGQGTKLEIK	JK2

VH Alignments

	Sequence (CDR1, CDR2, V)	CDR3 D	J	
3-33 germ.	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVIWYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR			
3D6-2F4	QVQLVESGGGVVQPGRSLRLSCAASGFIFSIYGMHWVRQAPGKGLEWVAVIWYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR	APH	FDYWGQGTLVTVSS	JH4
3D6-4C8	QVQLVESGGGVVQPGRSLRLSCAASGFIFSIYGMHWVRQAPGKGLEWVAVIWYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR	APH	FDYWGQGTLVTVSS	JH4
3G9-2D2	QVQLVESGGGVVQPGRSLRLSCAASGFTFSNYGMYWVRQAPGKGLEWVAVIWYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR	DLWGW	YFDYWGQGTLVTVSS	JH4
5A8-1F1	QVQLVESGGGVVQPGRSLRLSCAASGFTFSTYGMHWVRQAPGKGLEWVAIIWYDGGNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR	DF	YWYFDLWGRGTLVTVSS	JH2
3C7-3A3	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYNMHWVRQAPGKGLEWVAFIWYDGSNKYYGDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR	EELGIG	WYFDLWGRGTLVTVSS	JH2
5C3-2-3F6	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYNMHWVRQAPGKGLEWVAVIWYDGSNKYYGDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR	EELGIG	WYFDLWGRGTLVTVSS	JH2
5D12-5G1	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVIWYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR	GPPR	YFDLWGRGTLVTVSS	JH2
Orph-HC16	EVQLVQSGGGLVHPGGSLRLSCAGSGFTFSSYAMHWVRQAPGKGLEWVSAIGTGGGTYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDMAVYYCAR			
2D3-1F5-2A9	EVQLVQSGGGLVHPGGSLRLSCAGSGFTFSNYAMHWVRQAPGKGLEWVSTIGTGGGTPYADSVKGRFTISRDNAKNSLYLQMNSLRAEDMAVYYCAL	S	AFDVWGQGTMVTVSS	JH3
1E6-3D10	EVQLVQSGGGLVHPGGSLRLSCAGSGFTFSSYAMHWVRQAPGKGLEWVSAIGTGGYTYYVDSVKGRFTISRDNAKKSLYLQMNSLRAEDMAVYYCAR	EPFYDILTGYSP (D3-9)	YFDYWGQGTLVTVSS	JH4

Fig. 5

Human V_H CDR Consensus Sequences

3D6-2F4 VH CDR1 (SEQ ID NO:5):	IYGMH
3D6-4C8 VH CDR1 (SEQ ID NO:17):	IYGMH
3G9-2D2 VH CDR1 (SEQ ID NO: 29):	NYGMY
5A8-1F1 VH CDR1 (SEQ ID NO: 41):	TYGMH
3C7-3A3, VH CDR1 (SEQ ID NO: 53):	SYNMH
2D3-1F5-2A9, VH CDR1 (SEQ ID NO: 65):	NYAMH
1E6-3D10 VH CDR1: (SEQ ID NO: 71):	SYAMH
5C3-2-3F6 VH CDR1 (SEQ ID NO: 77):	SYNMH
5D12-5G1 VH CDR1 (SEQ ID NO: 89):	SYGMH

VH CDR1 CONSENSUS (SEQ ID NO: 97): (I,N,T,S) Y (G,N,A) M (H,Y)

3D6-2F4 VH CDR2 (SEQ ID NO: 6):	VIWYDGSNKYYADSVKG
3D6-4C8 VH CDR2 (SEQ ID NO: 18):	VIWYDGSNKYYADSVKG
3G9-2D2, VH CDR2 (SEQ ID NO: 30):	VIWYDGSNKYYADSVKG
5A8-1F1, VH CDR2 (SEQ ID NO: 42):	IIWYDGGNKYYADSVKG
3C7-3A3, VH CDR2 (SEQ ID NO: 54):	FIWYDGSNKYYGDSVKG
2D3-1F5-2A9, VH CDR2 (SEQ ID NO: 66):	TIGTGGGTPYA-DSVKG
1E6-3D10 VH CDR2 (SEQ ID NO: 72):	AIGTGGYTYYV-DSVKG
5C3-2-3F6 VH CDR2 (SEQ ID NO: 78):	VIWYDGSNKYYGDSVKG
5D12-5G1 VH CDR2 (SEQ ID NO: 90):	VIWYDGSNKYYADSVKG

VH CDR2 CONSENSUS (SEQ ID NO: 98): (V,I,F,T,A) I (W,G) (Y,T) (D,G) G (S,G,Y) (N,T) (K,P) Y (Y,A,V) (A,G,-) D S V K G

3D6-2F4 VH CDR3 (SEQ ID NO: 7):	APHFDY
3D6-4C8 VH CDR3 (SEQ ID NO: 19):	APHFDY
3G9-2D2, VH CDR3 (SEQ ID NO: 31):	DLWGWYFDY
5A8-1F1, VH CDR3 (SEQ ID NO: 43):	DFYWYFDL
3C7-3A3, VH CDR3 (SEQ ID NO: 55):	EELGIGWYFDL
2D3-1F5-2A9, VH CDR3 (SEQ ID NO: 67):	SAFDV
1E6-3D10 VH CDR3 (SEQ ID NO: 73):	EPFYDILTGYSPYFDY
5C3-2-3F6 VH CDR3 (SEQ ID NO: 79):	EELGIGWYFDL
5D12-5G1 VH CDR3 (SEQ ID NO: 91):	GPPRYFDL

VH CDR3 (CORE) CONSENSUS (SEQ ID NO: 99): (A,G,Y,S,P,-) (P,W,S,R) (Y,A,H) F D (Y,L,V)
(Where "-" denotes option of no amino acid residue present at that position)

Fig. 6

Human V_L CDR Consensus Sequences

3D6-2F4 VL CDR1 (SEQ ID NO: 11):	RASQGISSWLA
3D6-4C8 VL CDR1 (SEQ ID NO: 23):	RASQGISSALA
3G9-2D2, VL CDR1 (SEQ ID NO: 35):	RASQSVSSYLA
5A8-1F1, VL CDR1 (SEQ ID NO: 47):	RASQSVSSYLA
3C7-3A3, VL CDR1 (SEQ ID NO: 59):	RASQSVSSYLA
5C3-2-3F6 VL CDR1 (SEQ ID NO: 83):	RASQGISSALA

VL CDR1 CONSENSUS (SEQ ID NO: 100): R A S Q (S,G) (I,V) S S (Y,W,A) L A

3D6-2F4 VL CDR2 (SEQ ID NO: 12):	AASSLQS
3D6-4C8 VL CDR2 (SEQ ID NO: 24):	DASSLES
3G9-2D2, VL CDR2 (SEQ ID NO: 36):	DASNRAT
5A8-1F1, VL CDR2 (SEQ ID NO: 48):	DASNRAT
3C7-3A3, VL CDR2 (SEQ ID NO: 60):	DASNRAT
5C3-2-3F6 VL CDR2 (SEQ ID NO: 84):	DASSLES

VL CDR2 CONSENSUS (SEQ ID NO: 101): (D,A) A S (N,S) (R,L) (A,Q,E) (T,S)

3D6-2F4 VL CDR3 (SEQ ID NO: 13):	QQYNSYPYT
3D6-4C8 VL CDR3 (SEQ ID NO: 25):	QQFNSYPLT
3G9-2D2, VL CDR3 (SEQ ID NO: 37):	QQRRNWPLT
5A8-1F1, VL CDR3 (SEQ ID NO: 49):	QQRRT----
3C7-3A3, VL CDR3 (SEQ ID NO: 61):	QQRRT----
5C3-2-3F6 VL CDR3 (SEQ ID NO: 85):	QQFNSYPH-

VL CDR3 CONSENSUS (SEQ ID NO: 102): Q Q (R,Y,F) (R,N) (T,S,N) (Y,W,-) (P,-) (Y,L,H,-) (T,-)

(Where "-" denotes option of no amino acid residue present at that position)

Fig. 7

Example of anti-DEC-205/antigen fusion
APC targeted vaccine construct (schematic representation)

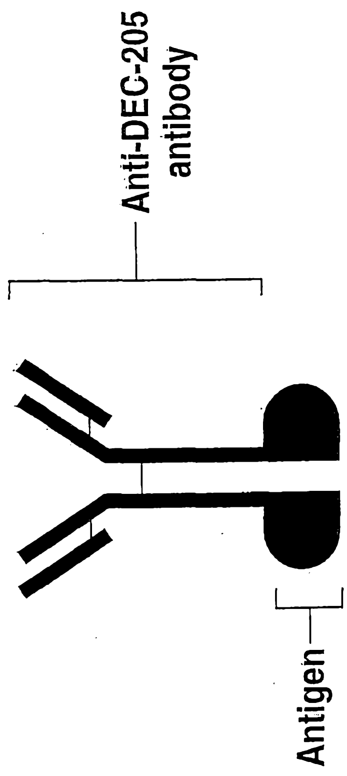


Fig. 8

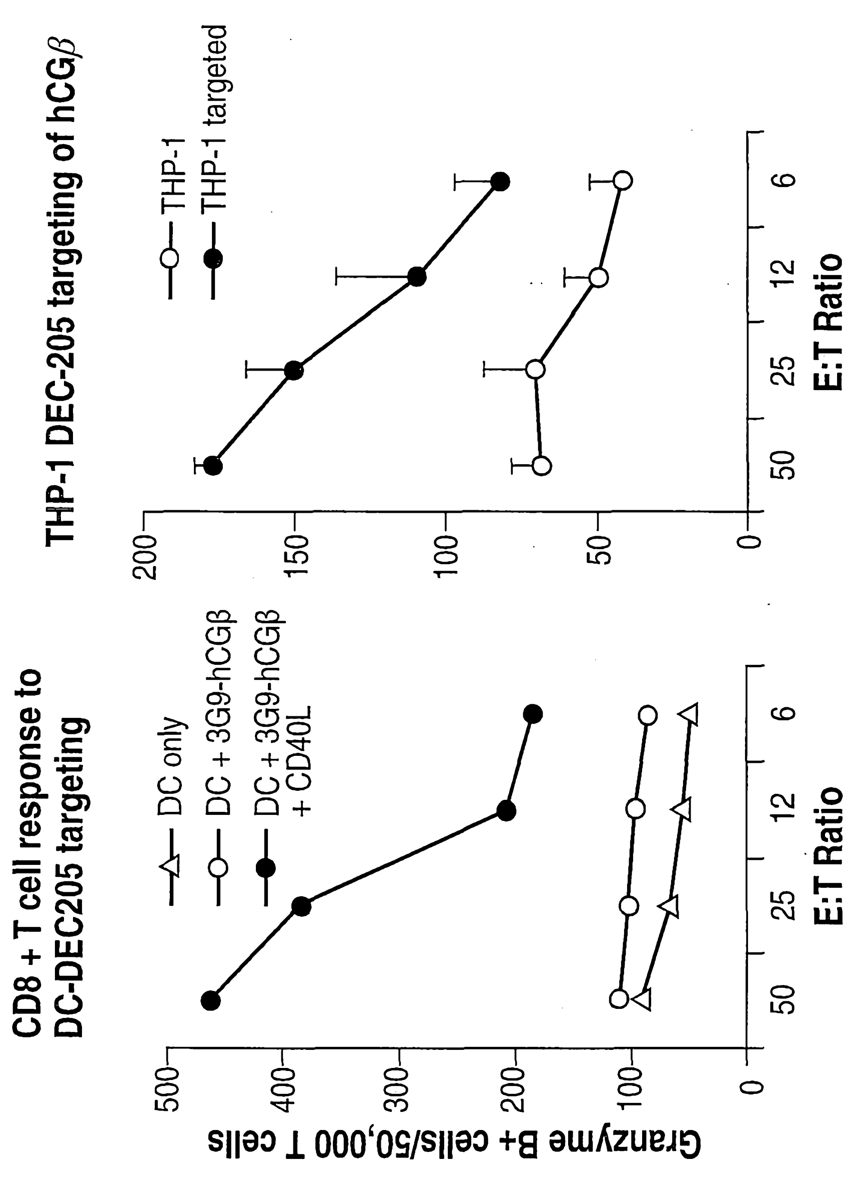

CD8 + T cell response to
DC-DEC205 targeting
DC only
DC + 3G9-hCGβ
DC + 3G9-hCGβ + CD40L
Granzyme B+ cells/50,000 T cells
500
400
300
200
100
0
50
25
12
6
E:T Ratio
THP-1 DEC-205 targeting of hCGβ
THP-1
THP-1 targeted
200
150
100
50
0
50
25
12
6
E:T Ratio

Fig. 9A

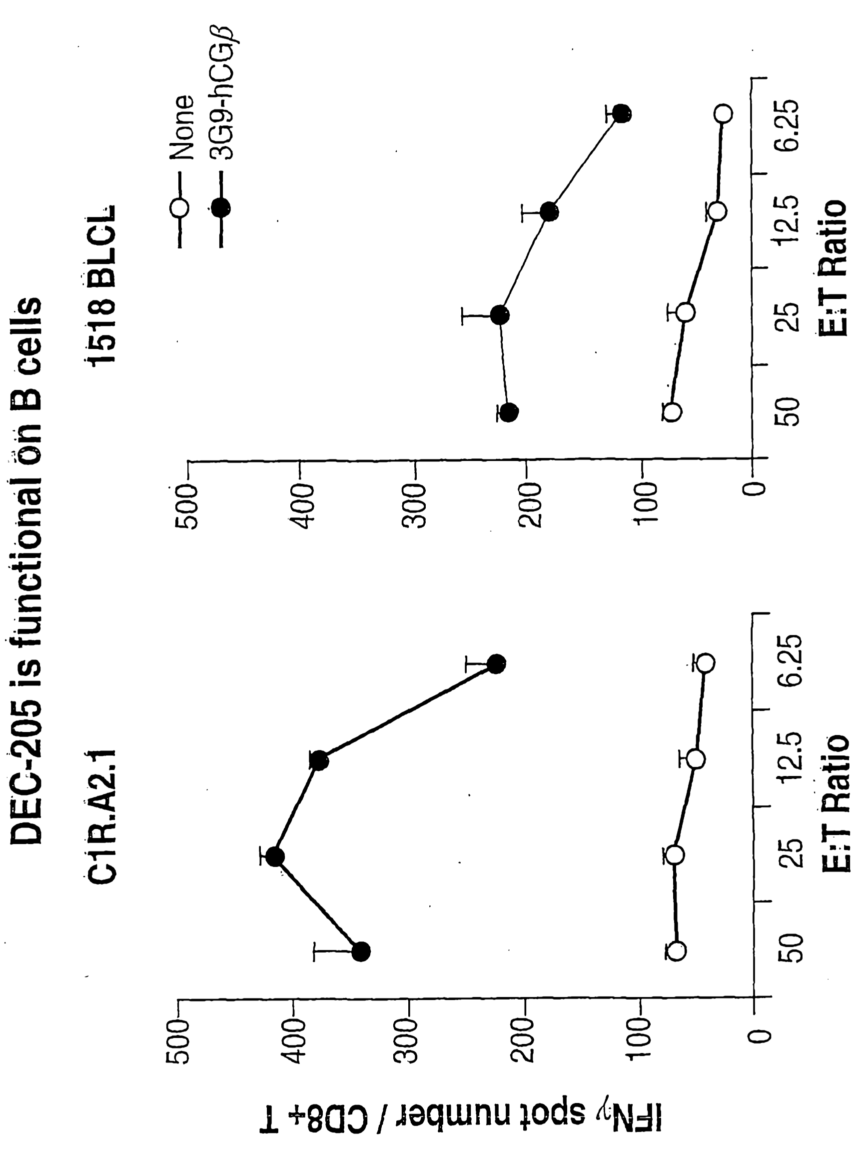

DEC-205 is functional on B cells
C1R.A2.1
1518 BLCL
None
3G9-hCGβ
IFNγ spot number / CD8+ T
500
400
300
200
100
0
50
25
12.5
6.25
E:T Ratio

Fig. 9B

SEQUENCE LISTING

<110> Celldex Therapeutics Inc., et al.

<120> ANTIBODIES THAT BIND HUMAN DENDRITIC AND EPITHELIAL CELL 205 (DEC-205)

<130> CDJ-346PC

<140> Not Yet Assigned
<141> Concurrently Herewith

<150> 61/002,253
<151> 2007-11-07

<150> 61/191,551
<151> 2008-09-10

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<170> PatentIn version 3.5

<210> 1
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20 25 30

Asn Asp Pro Phe Thr Ile Val His Gly Asn Thr Gly Lys Cys Ile Lys
35 40 45

Pro Val Tyr Gly Trp Ile Val Ala Asp Asp Cys Asp Glu Thr Glu Asp
50 55 60

Lys Leu Trp Lys Trp Val Ser Gln His Arg Leu Phe His Leu His Ser
65 70 75 80

Gln Lys Cys Leu Gly Leu Asp Ile Thr Lys Ser Val Asn Glu Leu Arg
85 90 95

Met Phe Ser Cys Asp Ser Ser Ala Met Leu Trp Trp Lys Cys Glu His
100 105 110

His Ser Leu Tyr Gly Ala Ala Arg Tyr Arg Leu Ala Leu Lys Asp Gly
115 120 125

His Gly Thr Ala Ile Ser Asn Ala Ser Asp Val Trp Lys Lys Gly Gly
130 135 140

Ser Glu Glu Ser Leu Cys Asp Gln Pro Tyr His Glu Ile Tyr Thr Arg
145 150 155 160

```
Asp Gly Asn Ser Tyr Gly Arg Pro Cys Glu Phe Pro Phe Leu Ile Asp
                165                 170                 175

Gly Thr Trp His His Asp Cys Ile Leu Asp Glu Asp His Ser Gly Pro
            180                 185                 190

Trp Cys Ala Thr Thr Leu Asn Tyr Glu Tyr Asp Arg Lys Trp Gly Ile
        195                 200                 205

Cys Leu Lys Pro Glu Asn Gly Cys Glu Asp Asn Trp Glu Lys Asn Glu
    210                 215                 220

Gln Phe Gly Ser Cys Tyr Gln Phe Asn Thr Gln Thr Ala Leu Ser Trp
225                 230                 235                 240

Lys Glu Ala Tyr Val Ser Cys Gln Asn Gln Gly Ala Asp Leu Leu Ser
                245                 250                 255

Ile Asn Ser Ala Ala Glu Leu Thr Tyr Leu Lys Glu Lys Glu Gly Ile
            260                 265                 270

Ala Lys Ile Phe Trp Ile Gly Leu Asn Gln Leu Tyr Ser Ala Arg Gly
        275                 280                 285

Trp Glu Trp Ser Asp His Lys Pro Leu Asn Phe Leu Asn Trp Asp Pro
    290                 295                 300

Asp Arg Pro Ser Ala Pro Thr Ile Gly Gly Ser Ser Cys Ala Arg Met
305                 310                 315                 320

Asp Ala Glu Ser Gly Leu Trp Gln Ser Phe Ser Cys Glu Ala Gln Leu
                325                 330                 335

Pro Tyr Val Cys Arg Lys Pro Leu Asn Asn Thr Val Glu Leu Thr Asp
            340                 345                 350

Val Trp Thr Tyr Ser Asp Thr Arg Cys Asp Ala Gly Trp Leu Pro Asn
        355                 360                 365

Asn Gly Phe Cys Tyr Leu Leu Val Asn Glu Ser Asn Ser Trp Asp Lys
    370                 375                 380

Ala His Ala Lys Cys Lys Ala Phe Ser Ser Asp Leu Ile Ser Ile His
385                 390                 395                 400

Ser Leu Ala Asp Val Glu Val Val Val Thr Lys Leu His Asn Glu Asp
                405                 410                 415

Ile Lys Glu Glu Val Trp Ile Gly Leu Lys Asn Ile Asn Ile Pro Thr
            420                 425                 430
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        435   440   445

Glu Asn Glu Pro Asn Val Pro Tyr Asn Lys Thr Pro Asn Cys Val Ser
    450   455   460

Tyr Leu Gly Glu Leu Gly Gln Trp Lys Val Gln Ser Cys Glu Glu Lys
465   470   475   480

Leu Lys Tyr Val Cys Lys Arg Lys Gly Glu Lys Leu Asn Asp Ala Ser
                485   490   495

Ser Asp Lys Met Cys Pro Pro Asp Glu Gly Trp Lys Arg His Gly Glu
            500   505   510

Thr Cys Tyr Lys Ile Tyr Glu Asp Glu Val Pro Phe Gly Thr Asn Cys
        515   520   525

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    530   535   540

Met Lys Lys Tyr Asp Lys Ser Leu Arg Lys Tyr Phe Trp Thr Gly Leu
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Arg Asp Val Asp Ser Cys Gly Glu Tyr Asn Trp Ala Thr Val Gly Gly
                565   570   575

Arg Arg Arg Ala Val Thr Phe Ser Asn Trp Asn Phe Leu Glu Pro Ala
            580   585   590

Ser Pro Gly Gly Cys Val Ala Met Ser Thr Gly Lys Ser Val Gly Lys
        595   600   605

Trp Glu Val Lys Asp Cys Arg Ser Phe Lys Ala Leu Ser Ile Cys Lys
    610   615   620

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

Asp Pro Cys Pro Glu Gly Trp Gln Ser Phe Pro Ala Ser Leu Ser Cys
                645   650   655

Tyr Lys Val Phe His Ala Glu Arg Ile Val Arg Lys Arg Asn Trp Glu
            660   665   670

Glu Ala Glu Arg Phe Cys Gln Ala Leu Gly Ala His Leu Ser Ser Phe
        675   680   685

Ser His Val Asp Glu Ile Lys Glu Phe Leu His Phe Leu Thr Asp Gln
    690   695   700

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Phe Ser Gly Gln His Trp Leu Trp Ile Gly Leu Asn Lys Arg Ser Pro
705                 710                 715                 720

Asp Leu Gln Gly Ser Trp Gln Trp Ser Asp Arg Thr Pro Val Ser Thr
                725                 730                 735

Ile Ile Met Pro Asn Glu Phe Gln Gln Asp Tyr Asp Ile Arg Asp Cys
            740                 745                 750

Ala Ala Val Lys Val Phe His Arg Pro Trp Arg Arg Gly Trp His Phe
        755                 760                 765

Tyr Asp Asp Arg Glu Phe Ile Tyr Leu Arg Pro Phe Ala Cys Asp Thr
    770                 775                 780

Lys Leu Glu Trp Val Cys Gln Ile Pro Lys Gly Arg Thr Pro Lys Thr
785                 790                 795                 800

Pro Asp Trp Tyr Asn Pro Asp Arg Ala Gly Ile His Gly Pro Pro Leu
                805                 810                 815

Ile Ile Glu Gly Ser Glu Tyr Trp Phe Val Ala Asp Leu His Leu Asn
            820                 825                 830

Tyr Glu Glu Ala Val Leu Tyr Cys Ala Ser Asn His Ser Phe Leu Ala
        835                 840                 845

Thr Ile Thr Ser Phe Val Gly Leu Lys Ala Ile Lys Asn Lys Ile Ala
    850                 855                 860

Asn Ile Ser Gly Asp Gly Gln Lys Trp Trp Ile Arg Ile Ser Glu Trp
865                 870                 875                 880

Pro Ile Asp Asp His Phe Thr Tyr Ser Arg Tyr Pro Trp His Arg Phe
                885                 890                 895

Pro Val Thr Phe Gly Glu Glu Cys Leu Tyr Met Ser Ala Lys Thr Trp
            900                 905                 910

Leu Ile Asp Leu Gly Lys Pro Thr Asp Cys Ser Thr Lys Leu Pro Phe
        915                 920                 925

Ile Cys Glu Lys Tyr Asn Val Ser Ser Leu Glu Lys Tyr Ser Pro Asp
    930                 935                 940

Ser Ala Ala Lys Val Gln Cys Ser Glu Gln Trp Ile Pro Phe Gln Asn
945                 950                 955                 960

Lys Cys Phe Leu Lys Ile Lys Pro Val Ser Leu Thr Phe Ser Gln Ala
                965                 970                 975
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            980                 985                 990

Gln Ile Glu Gln Asp Phe Ile Thr  Ser Leu Leu Pro Asp  Met Glu Ala
        995                 1000                 1005

Thr Leu  Trp Ile Gly Leu Arg  Trp Thr Ala Tyr Glu  Lys Ile Asn
    1010                 1015                 1020

Lys Trp  Thr Asp Asn Arg Glu  Leu Thr Tyr Ser Asn  Phe His Pro
    1025                 1030                 1035

Leu Leu  Val Ser Gly Arg Leu  Arg Ile Pro Glu Asn  Phe Phe Glu
    1040                 1045                 1050

Glu Glu  Ser Arg Tyr His Cys  Ala Leu Ile Leu Asn  Leu Gln Lys
    1055                 1060                 1065

Ser Pro  Phe Thr Gly Thr Trp  Asn Phe Thr Ser Cys  Ser Glu Arg
    1070                 1075                 1080

His Phe  Val Ser Leu Cys Gln  Lys Tyr Ser Glu Val  Lys Ser Arg
    1085                 1090                 1095

Gln Thr  Leu Gln Asn Ala Ser  Glu Thr Val Lys Tyr  Leu Asn Asn
    1100                 1105                 1110

Leu Tyr  Lys Ile Ile Pro Lys  Thr Leu Thr Trp His  Ser Ala Lys
    1115                 1120                 1125

Arg Glu  Cys Leu Lys Ser Asn  Met Gln Leu Val Ser  Ile Thr Asp
    1130                 1135                 1140

Pro Tyr  Gln Gln Ala Phe Leu  Ser Val Gln Ala Leu  Leu His Asn
    1145                 1150                 1155

Ser Ser  Leu Trp Ile Gly Leu  Phe Ser Gln Asp Asp  Glu Leu Asn
    1160                 1165                 1170

Phe Gly  Trp Ser Asp Gly Lys  Arg Leu His Phe Ser  Arg Trp Ala
    1175                 1180                 1185

Glu Thr  Asn Gly Gln Leu Glu  Asp Cys Val Val Leu  Asp Thr Asp
    1190                 1195                 1200

Gly Phe  Trp Lys Thr Val Asp  Cys Asn Asp Asn Gln  Pro Gly Ala
    1205                 1210                 1215

Ile Cys  Tyr Tyr Ser Gly Asn  Glu Thr Glu Lys Glu  Val Lys Pro
    1220                 1225                 1230
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Val Asp Ser Val Lys Cys Pro Ser Pro Val Leu Asn Thr Pro Trp
1235 1240 1245

Ile Pro Phe Gln Asn Cys Cys Tyr Asn Phe Ile Ile Thr Lys Asn
1250 1255 1260

Arg His Met Ala Thr Thr Gln Asp Glu Val His Thr Lys Cys Gln
1265 1270 1275

Lys Leu Asn Pro Lys Ser His Ile Leu Ser Ile Arg Asp Glu Lys
1280 1285 1290

Glu Asn Asn Phe Val Leu Glu Gln Leu Leu Tyr Phe Asn Tyr Met
1295 1300 1305

Ala Ser Trp Val Met Leu Gly Ile Thr Tyr Arg Asn Asn Ser Leu
1310 1315 1320

Met Trp Phe Asp Lys Thr Pro Leu Ser Tyr Thr His Trp Arg Ala
1325 1330 1335

Gly Arg Pro Thr Ile Lys Asn Glu Lys Phe Leu Ala Gly Leu Ser
1340 1345 1350

Thr Asp Gly Phe Trp Asp Ile Gln Thr Phe Lys Val Ile Glu Glu
1355 1360 1365

Ala Val Tyr Phe His Gln His Ser Ile Leu Ala Cys Lys Ile Glu
1370 1375 1380

Met Val Asp Tyr Lys Glu Glu His Asn Thr Thr Leu Pro Gln Phe
1385 1390 1395

Met Pro Tyr Glu Asp Gly Ile Tyr Ser Val Ile Gln Lys Lys Val
1400 1405 1410

Thr Trp Tyr Glu Ala Leu Asn Met Cys Ser Gln Ser Gly Gly His
1415 1420 1425

Leu Ala Ser Val His Asn Gln Asn Gly Gln Leu Phe Leu Glu Asp
1430 1435 1440

Ile Val Lys Arg Asp Gly Phe Pro Leu Trp Val Gly Leu Ser Ser
1445 1450 1455

His Asp Gly Ser Glu Ser Ser Phe Glu Trp Ser Asp Gly Ser Thr
1460 1465 1470

Phe Asp Tyr Ile Pro Trp Lys Gly Gln Thr Ser Pro Gly Asn Cys
1475 1480 1485

Val Leu Leu Asp Pro Lys Gly Thr Trp Lys His Glu Lys Cys Asn
    1490   1495   1500

Ser Val Lys Asp Gly Ala Ile Cys Tyr Lys Pro Thr Lys Ser Lys
    1505   1510   1515

Lys Leu Ser Arg Leu Thr Tyr Ser Ser Arg Cys Pro Ala Ala Lys
    1520   1525   1530

Glu Asn Gly Ser Arg Trp Ile Gln Tyr Lys Gly His Cys Tyr Lys
    1535   1540   1545

Ser Asp Gln Ala Leu His Ser Phe Ser Glu Ala Lys Lys Leu Cys
    1550   1555   1560

Ser Lys His Asp His Ser Ala Thr Ile Val Ser Ile Lys Asp Glu
    1565   1570   1575

Asp Glu Asn Lys Phe Val Ser Arg Leu Met Arg Glu Asn Asn Asn
    1580   1585   1590

Ile Thr Met Arg Val Trp Leu Gly Leu Ser Gln His Ser Val Asp
    1595   1600   1605

Gln Ser Trp Ser Trp Leu Asp Gly Ser Glu Val Thr Phe Val Lys
    1610   1615   1620

Trp Glu Asn Lys Ser Lys Ser Gly Val Gly Arg Cys Ser Met Leu
    1625   1630   1635

Ile Ala Ser Asn Glu Thr Trp Lys Lys Val Glu Cys Glu His Gly
    1640   1645   1650

Phe Gly Arg Val Val Cys Lys Val Pro Leu Gly Pro Asp Tyr Thr
    1655   1660   1665

Ala Ile Ala Ile Ile Val Ala Thr Leu Ser Ile Leu Val Leu Met
    1670   1675   1680

Gly Gly Leu Ile Trp Phe Leu Phe Gln Arg His Arg Leu His Leu
    1685   1690   1695

Ala Gly Phe Ser Ser Val Arg Tyr Ala Gln Gly Val Asn Glu Asp
    1700   1705   1710

Glu Ile Met Leu Pro Ser Phe His Asp
    1715   1720

<210> 2
<211> 408
<212> DNA
<213> Homo sapiens

<400> 2
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gtgcagctgg tggagtctgg gggaggcgtg gtccagcctg ggaggtccct gagactctcc 120

tgtgcagcgt ctggattcat cttcagtatc tatggcatgc actgggtccg ccaggctcca 180

ggcaaggggc tggagtgggt ggcagttata tggtatgatg gaagtaataa atactatgca 240

gactccgtga agggccgatt caccatctcc agagacaatt ccaagaacac gctgtatctg 300

caaatgaaca gcctgagagc cgaggacacg gctgtgtatt actgtgcgag agctcctcac 360

tttgactact ggggccaggg aaccctggtc accgtctcct cagctagc 408

<210> 3
<211> 134
<212> PRT
<213> Homo sapiens

<400> 3
Met Glu Phe Gly Leu Ser Trp Val Phe Leu Val Ala Leu Leu Arg Gly
1 5 10 15

Val Gln Cys Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln
20 25 30

Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ile Phe
35 40 45

Ser Ile Tyr Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
50 55 60

Glu Trp Val Ala Val Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala
65 70 75 80

Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn
85 90 95

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

Tyr Tyr Cys Ala Arg Ala Pro His Phe Asp Tyr Trp Gly Gln Gly Thr
115 120 125

Leu Val Thr Val Ser Ser
130

<210> 4
<211> 115
<212> PRT
<213> Homo sapiens

<400> 4
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

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Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ile Phe Ser Ile Tyr
            20                  25                  30


Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45


Ala Val Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
    50                  55                  60


Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80


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


Ala Arg Ala Pro His Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr
            100                 105                 110


Val Ser Ser
        115


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

<400> 5
Ile Tyr Gly Met His
1               5


<210> 6
<211> 17
<212> PRT
<213> Homo sapiens

<400> 6
Val Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val Lys
1               5                   10                  15


Gly



<210> 7
<211> 6
<212> PRT
<213> Homo sapiens

<400> 7
Ala Pro His Phe Asp Tyr
1               5


<210> 8
<211> 384
<212> DNA
<213> Homo sapiens
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<400> 8
atgggatgga gctgtatcat cctgttcctc gtggccacag caaccggtgt ccactccgac 60

atccagatga cccagtctcc atcctcactg tctgcatctg ttggagacag agtcaccatc 120

acttgtcggg cgagtcaggg tattagcagc tggttagcct ggtatcagca gaaaccagag 180

aaagccccta agtccctgat ctatgctgca tccagtttgc aaagtggggt cccatcaagg 240

ttcagcggca gtggatctgg gacagatttc actctcacca tcagcagcct gcagcctgaa 300

gattttgcaa cttattactg ccaacagtat aatagttacc cgtacacttt tggccagggg 360

accaagctgg agatcaaacg tacg 384

<210> 9
<211> 129
<212> PRT
<213> Homo sapiens

<400> 9
Met Asp Met Arg Val Leu Ala Gln Leu Leu Gly Leu Leu Leu Leu Cys
1   5   10   15

Phe Pro Gly Ala Arg Cys Asp Ile Gln Met Thr Gln Ser Pro Ser Ser
            20   25   30

Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser
        35   40   45

Gln Gly Ile Ser Ser Trp Leu Ala Trp Tyr Gln Gln Lys Pro Glu Lys
    50   55   60

Ala Pro Lys Ser Leu Ile Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val
65   70   75   80

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
                85   90   95

Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln
            100   105   110

Tyr Asn Ser Tyr Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile
        115   120   125

Lys

<210> 10
<211> 107
<212> PRT
<213> Homo sapiens

<400> 10
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1   5   10   15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Trp
            20   25   30

Leu Ala Trp Tyr Gln Gln Lys Pro Glu Lys Ala Pro Lys Ser Leu Ile
        35   40   45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50   55   60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65   70   75   80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asn Ser Tyr Pro Tyr
                85   90   95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
            100   105

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

<400> 11
Arg Ala Ser Gln Gly Ile Ser Ser Trp Leu Ala
1   5   10

<210> 12
<211> 7
<212> PRT
<213> Homo sapiens

<400> 12
Ala Ala Ser Ser Leu Gln Ser
1   5

<210> 13
<211> 9
<212> PRT
<213> Homo sapiens

<400> 13
Gln Gln Tyr Asn Ser Tyr Pro Tyr Thr
1   5

<210> 14
<211> 439
<212> DNA
<213> Homo sapiens

<400> 14
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gtgcagctgg tggagtctgg gggaggcgtg gtccagcctg ggaggtccct gagactctcc 120

tgtgcagcgt ctggattcat cttcagtatc tatggcatgc actgggtccg ccaggctcca 180

ggcaaggggc tggagtgggt ggcagttata tggtatgatg gaagtaataa atactatgca 240 gactccgtga agggccgatt caccatctcc agagacaatt ccaagaacac gctgtatctg 300

caaatgaaca gcctgagagc cgaggacacg gctgtgtatt actgtgcgag agctcctcac 360

tttgactact ggggccaggg aaccctggtc accgtctcct cagcctccac caagggccca 420

tcggtcttcc ccctggcac 439

<210> 15
<211> 134
<212> PRT
<213> Homo sapiens

<400> 15
Met Glu Phe Gly Leu Ser Trp Val Phe Leu Val Ala Leu Leu Arg Gly
1 5 10 15

Val Gln Cys Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln
20 25 30

Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ile Phe
35 40 45

Ser Ile Tyr Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
50 55 60

Glu Trp Val Ala Val Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala
65 70 75 80

Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn
85 90 95

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

Tyr Tyr Cys Ala Arg Ala Pro His Phe Asp Tyr Trp Gly Gln Gly Thr
115 120 125

Leu Val Thr Val Ser Ser
130

<210> 16
<211> 115
<212> PRT
<213> Homo sapiens

<400> 16
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ile Phe Ser Ile Tyr
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Val Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
    50   55   60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80

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

Ala Arg Ala Pro His Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr
            100   105   110

Val Ser Ser
        115

<210> 17
<211> 5
<212> PRT
<213> Homo sapiens

<400> 17
Ile Tyr Gly Met His
1   5

<210> 18
<211> 17
<212> PRT
<213> Homo sapiens

<400> 18
Val Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val Lys
1   5   10   15

Gly

<210> 19
<211> 6
<212> PRT
<213> Homo sapiens

<400> 19
Ala Pro His Phe Asp Tyr
1   5

<210> 20
<211> 387
<212> DNA
<213> Homo sapiens

<400> 20
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agatgtgcca tccagttgac ccagtctcca tcctccctgt ctgcatctgt aggagacaga 120

gtcaccatca cttgccgggc aagtcagggc attagcagtg ctttagcctg gtatcagcag 180

aaaccaggga aagctcctaa gctcctgatc tatgatgcct ccagtttgga aagtggggtc 240 ccatcaaggt tcagcggcag tggatctggg acagatttca ctctcaccat cagcagcctg 300

cagcctgaag attttgcaac ttattactgt caacagttta atagttaccc tctcactttc 360

ggcggaggga ccaaggtgga gatcaaa 387

<210> 21
<211> 129
<212> PRT
<213> Homo sapiens

<400> 21
Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

Leu Pro Gly Ala Arg Cys Ala Ile Gln Leu Thr Gln Ser Pro Ser Ser
20 25 30

Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser
35 40 45

Gln Gly Ile Ser Ser Ala Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys
50 55 60

Ala Pro Lys Leu Leu Ile Tyr Asp Ala Ser Ser Leu Glu Ser Gly Val
65 70 75 80

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
85 90 95

Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln
100 105 110

Phe Asn Ser Tyr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile
115 120 125

Lys

<210> 22
<211> 107
<212> PRT
<213> Homo sapiens

<400> 22
Ala Ile Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Ala
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Ser Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly
    50   55   60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65   70   75   80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Phe Asn Ser Tyr Pro Leu
                85   90   95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100   105

<210> 23
<211> 11
<212> PRT
<213> Homo sapiens

<400> 23
Arg Ala Ser Gln Gly Ile Ser Ser Ala Leu Ala
1   5   10

<210> 24
<211> 7
<212> PRT
<213> Homo sapiens

<400> 24
Asp Ala Ser Ser Leu Glu Ser
1   5

<210> 25
<211> 9
<212> PRT
<213> Homo sapiens

<400> 25
Gln Gln Phe Asn Ser Tyr Pro Leu Thr
1   5

<210> 26
<211> 417
<212> DNA
<213> Homo sapiens

<400> 26
atggagtttg ggctgagctg ggttttcctc gttgctcttt taagaggtgt ccagtgtcag   60

gtgcagctgg tggagtctgg gggaggcgtg gtccagcctg ggaggtccct gagactctcc   120

tgtgcagcgt ctggattcac cttcagtaat tatggcatgt actgggtccg ccaggctcca   180

ggcaaggggc tggagtgggt ggcagttata tggtatgatg gaagtaataa atactatgca   240

gactccgtga agggccgatt caccatctcc agagacaatt ccaagaacac gctgtatctg   300

caaatgaaca gcctgagagc cgaggacacg gctgtgtatt actgtgcgag agatctctgg   360

ggatggtact ttgactattg gggccaggga accctggtca ccgtctcctc agctagc   417

<210> 27

<211> 149
<212> PRT
<213> Homo sapiens

<400> 27
Met Glu Phe Gly Leu Ser Trp Val Phe Leu Val Ala Leu Leu Arg Gly
1   5   10   15

Val Gln Cys Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln
            20   25   30

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

Ser Asn Tyr Gly Met Tyr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
    50   55   60

Glu Trp Val Ala Val Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala
65   70   75   80

Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn
                85   90   95

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

Tyr Tyr Cys Ala Arg Asp Leu Trp Gly Trp Tyr Phe Asp Tyr Trp Gly
        115   120   125

Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
    130   135   140

Val Phe Pro Leu Ala
145

<210> 28
<211> 130
<212> PRT
<213> Homo sapiens

<400> 28
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1   5   10   15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
            20   25   30

Gly Met Tyr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45

Ala Val Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
    50   55   60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr

65 70 75 80

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

Ala Arg Asp Leu Trp Gly Trp Tyr Phe Asp Tyr Trp Gly Gln Gly Thr
100 105 110

Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
115 120 125

Leu Ala
130

<210> 29
<211> 5
<212> PRT
<213> Homo sapiens

<400> 29
Asn Tyr Gly Met Tyr
1 5

<210> 30
<211> 17
<212> PRT
<213> Homo sapiens

<400> 30
Val Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 31
<211> 9
<212> PRT
<213> Homo sapiens

<400> 31
Asp Leu Trp Gly Trp Tyr Phe Asp Tyr
1 5

<210> 32
<211> 384
<212> DNA
<213> Homo sapiens

<400> 32
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attgtgttga cacagtctcc agccaccctg tctttgtctc caggggaaag agccaccctc 120

tcctgcaggg ccagtcagag tgttagcagc tacttagcct ggtaccaaca gaaacctggc 180

caggctccca ggctcctcat ctatgatgca tccaacaggg ccactggcat cccagccagg 240

ttcagtggca gtgggtctgg gacagacttc actctcacca tcagcagcct agagcctgaa 300 gattttgcag tttattactg tcagcagcgt cgcaactggc cgctcacttt cggcggaggg 360

accaaggtgg agatcaaacg tacg 384

<210> 33
<211> 127
<212> PRT
<213> Homo sapiens

<400> 33
Met Glu Ala Pro Ala Gln Leu Leu Phe Leu Leu Leu Leu Trp Leu Pro
1   5   10   15

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

Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser
        35   40   45

Val Ser Ser Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro
    50   55   60

Arg Leu Leu Ile Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala
65   70   75   80

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
                85   90   95

Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Arg
            100   105   110

Asn Trp Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
        115   120   125

<210> 34
<211> 107
<212> PRT
<213> Homo sapiens

<400> 34
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1   5   10   15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
            20   25   30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        35   40   45

Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
    50   55   60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65   70   75   80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Arg Asn Trp Pro Leu
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 35
<211> 11
<212> PRT
<213> Homo sapiens

<400> 35
Arg Ala Ser Gln Ser Val Ser Ser Tyr Leu Ala
1 5 10

<210> 36
<211> 7
<212> PRT
<213> Homo sapiens

<400> 36
Asp Ala Ser Asn Arg Ala Thr
1 5

<210> 37
<211> 9
<212> PRT
<213> Homo sapiens

<400> 37
Gln Gln Arg Arg Asn Trp Pro Leu Thr
1 5

<210> 38
<211> 447
<212> DNA
<213> Homo sapiens

<400> 38
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gtgcagctgg tggagtctgg gggaggcgtg gtccagcctg ggaggtccct gagactctcc 120

tgtgcagcgt ctggattcac cttcagtacc tatggcatgc actgggtccg ccaggctcca 180

ggcaaggggc tggagtgggt ggcaattata tggtatgatg gaggtaataa atactatgca 240

gactccgtga agggccgatt caccatctcc agagacaatt ccaagaacac gctgtatctg 300

caaatgaaca gcctgagagc cgaggacacg gctgtgtatt actgtgcgag agacttctac 360

tggtacttcg atctctgggg ccgtggcacc ctggtcactg tctcctcagc ctccaccaag 420

ggcccatcgg tcttccccct ggcaagg 447

<210> 39
<211> 148
<212> PRT
<213> Homo sapiens

<400> 39
Met Glu Phe Gly Leu Thr Trp Val Phe Leu Val Ala Leu Leu Arg Gly
1   5   10   15

Val Gln Cys Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln
            20   25   30

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

Ser Thr Tyr Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
    50   55   60

Glu Trp Val Ala Ile Ile Trp Tyr Asp Gly Gly Asn Lys Tyr Tyr Ala
65   70   75   80

Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn
                85   90   95

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

Tyr Tyr Cys Ala Arg Asp Phe Tyr Trp Tyr Phe Asp Leu Trp Gly Arg
        115   120   125

Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
    130   135   140

Phe Pro Leu Ala
145

<210> 40
<211> 129
<212> PRT
<213> Homo sapiens

<400> 40
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1   5   10   15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Thr Tyr
            20   25   30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45

Ala Ile Ile Trp Tyr Asp Gly Gly Asn Lys Tyr Tyr Ala Asp Ser Val
    50   55   60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys

                85   90   95

Ala Arg Asp Phe Tyr Trp Tyr Phe Asp Leu Trp Gly Arg Gly Thr Leu
            100   105   110

Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
        115   120   125

Ala

<210> 41
<211> 5
<212> PRT
<213> Homo sapiens

<400> 41
Thr Tyr Gly Met His
1   5

<210> 42
<211> 17
<212> PRT
<213> Homo sapiens

<400> 42
Ile Ile Trp Tyr Asp Gly Gly Asn Lys Tyr Tyr Ala Asp Ser Val Lys
1   5   10   15

Gly

<210> 43
<211> 8
<212> PRT
<213> Homo sapiens

<400> 43
Asp Phe Tyr Trp Tyr Phe Asp Leu
1   5

<210> 44
<211> 372
<212> DNA
<213> Homo sapiens

<400> 44
atggaagccc cagctcagct tctcttcctc ctgctactct ggctcccaga taccaccgga 60

gaaattgtgt tgacacagtc tccagccacc ctgtctttgt ctccagggga aagagccacc 120

ctctcctgca gggccagtca gagtgttagc agctacttag cctggtacca acagaaacct 180

ggccaggctc ccaggctcct catctatgat gcatccaaca gggccactgg catcccagcc 240

aggttcagtg gcagtgggtc tgggacagac ttcactctca ccatcagcag cctagagcct 300

gaagattttg cagtttatta ctgtcagcag cgtaggacgt tcggccaagg gaccaaggtg 360

gaaatcaaac ga 372

<210> 45
<211> 123
<212> PRT
<213> Homo sapiens

<400> 45
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Met Glu Ala Pro Ala Gln Leu Leu Phe Leu Leu Leu Leu Trp Leu Pro
1               5                   10                  15

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

Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser
        35                  40                  45

Val Ser Ser Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro
    50                  55                  60

Arg Leu Leu Ile Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala
65                  70                  75                  80

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
                85                  90                  95

Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Arg
            100                 105                 110

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
        115                 120
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<210> 46
<211> 103
<212> PRT
<213> Homo sapiens

<400> 46
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Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1               5                   10                  15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
            20                  25                  30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        35                  40                  45

Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65                  70                  75                  80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Arg Thr Phe Gly Gln
                85                  90                  95
```

Gly Thr Lys Val Glu Ile Lys
            100

<210> 47
<211> 11
<212> PRT
<213> Homo sapiens

<400> 47
Arg Ala Ser Gln Ser Val Ser Ser Tyr Leu Ala
1   5   10

<210> 48
<211> 7
<212> PRT
<213> Homo sapiens

<400> 48
Asp Ala Ser Asn Arg Ala Thr
1   5

<210> 49
<211> 5
<212> PRT
<213> Homo sapiens

<400> 49
Gln Gln Arg Arg Thr
1   5

<210> 50
<211> 454
<212> DNA
<213> Homo sapiens

<400> 50
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gtgcagctgg tggagtctgg gggaggcgtg gtccagcctg ggaggtccct gagactctcc   120

tgtgcagcgt ctggattcac cttcagtagc tataacatgc actgggtccg ccaggctcca   180

ggcaaggggc tggagtgggt ggcatttata tggtatgatg gaagtaataa atactatgga   240

gactccgtga agggccgatt caccatctcc agagacaatt ccaaaaacac gctgtatctg   300

caaatgaaca gcctgagagc cgaggacacg gctgtgtatt actgtgcgag agaagagctg   360

gggatcgggt ggtacttcga tctctggggc cgtggcaccc tggtcactgt ctcctcagcc   420

tccaccaagg gcccatcggt cttccccctg gcac   454

<210> 51
<211> 151
<212> PRT
<213> Homo sapiens

<400> 51
Met Glu Phe Gly Leu Ser Trp Val Phe Leu Val Ala Leu Leu Arg Gly
1   5   10   15

Val Gln Cys Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln
20 25 30

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

Ser Ser Tyr Asn Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
50 55 60

Glu Trp Val Ala Phe Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Gly
65 70 75 80

Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn
85 90 95

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

Tyr Tyr Cys Ala Arg Glu Glu Leu Gly Ile Gly Trp Tyr Phe Asp Leu
115 120 125

Trp Gly Arg Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly
130 135 140

Pro Ser Val Phe Pro Leu Ala
145 150

<210> 52
<211> 132
<212> PRT
<213> Homo sapiens

<400> 52
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Asn Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Phe Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Gly Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

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

Ala Arg Glu Glu Leu Gly Ile Gly Trp Tyr Phe Asp Leu Trp Gly Arg

100 105 110

Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
115 120 125

Phe Pro Leu Ala
130

<210> 53
<211> 5
<212> PRT
<213> Homo sapiens

<400> 53
Ser Tyr Asn Met His
1 5

<210> 54
<211> 17
<212> PRT
<213> Homo sapiens

<400> 54
Phe Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Gly Asp Ser Val Lys
1 5 10 15

Gly

<210> 55
<211> 11
<212> PRT
<213> Homo sapiens

<400> 55
Glu Glu Leu Gly Ile Gly Trp Tyr Phe Asp Leu
1 5 10

<210> 56
<211> 454
<212> DNA
<213> Homo sapiens

<400> 56
atggaagccc cagctcagct tctcttcctc ctgctactct ggctcccaga taccaccgga 60

gaaattgtgt tgacacagtc tccagccacc ctgtctttgt ctccagggga aagagccacc 120

ctctcctgca gggccagtca gagtgttagc agctacttag cctggtacca acagaaacct 180

ggccaggctc ccaggctcct catctatgat gcatccaaca gggccactgg catcccagcc 240

aggttcagtg gcagtgggtc tgggacagac ttcactctca ccatcagcag cctagagcct 300

gaagattttg cagtttatta ctgtcagcag cgtaggacgt tcggccaagg gaccaaggtg 360

gaaatcaaac gaactgtggc tgcaccatct gtcttcatct tcccgccatc tgatgagcag 420

ttgaaatctg gaactgcctc tgttgtgtgc ctgc 454

<210> 57
<211> 123
<212> PRT
<213> Homo sapiens

<400> 57
Met Glu Ala Pro Ala Gln Leu Leu Phe Leu Leu Leu Leu Trp Leu Pro
1   5   10   15

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

Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser
        35   40   45

Val Ser Ser Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro
    50   55   60

Arg Leu Leu Ile Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala
65   70   75   80

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
                85   90   95

Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Arg
            100   105   110

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
        115   120

<210> 58
<211> 103
<212> PRT
<213> Homo sapiens

<400> 58
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1   5   10   15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
            20   25   30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        35   40   45

Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
    50   55   60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65   70   75   80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Arg Thr Phe Gly Gln
                85   90   95

Gly Thr Lys Val Glu Ile Lys
            100

<210> 59
<211> 11
<212> PRT
<213> Homo sapiens

<400> 59
Arg Ala Ser Gln Ser Val Ser Ser Tyr Leu Ala
1   5   10

<210> 60
<211> 7
<212> PRT
<213> Homo sapiens

<400> 60
Asp Ala Ser Asn Arg Ala Thr
1   5

<210> 61
<211> 5
<212> PRT
<213> Homo sapiens

<400> 61
Gln Gln Arg Arg Thr
1   5

<210> 62
<211> 433
<212> DNA
<213> Homo sapiens

<400> 62
atggagtttg tgctgagctg ggttctcctt gttgctatat taaaaggtgt ccagtgtgag   60

gttcagctgg tgcagtctgg gggaggcttg gtacatcctg gggggtccct gagactctcc   120

tgtgcaggct ctggattcac cttcagtaac tatgctatgc actgggttcg ccaggctcca   180

ggaaaaggtc tggagtgggt atcaactatt ggtactggtg gtggcacacc ctatgcagac   240

tccgtgaagg gccgcttcac catctccaga gacaatgcca agaactcctt gtatcttcaa   300

atgaacagcc tgagagccga ggacatggct gtgtattact gtgcattaag tgcttttgat   360

gtctggggcc aagggacaat ggtcaccgtc tcttcagcct ccaccaaggg cccatcggtc   420

ttcccccctgg cac   433

<210> 63
<211> 144
<212> PRT
<213> Homo sapiens

<400> 63
Met Glu Phe Val Leu Ser Trp Val Leu Leu Val Ala Ile Leu Lys Gly
1   5   10   15

Val Gln Cys Glu Val Gln Leu Val Gln Ser Gly Gly Gly Leu Val His

20 25 30

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

Ser Asn Tyr Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
50 55 60

Glu Trp Val Ser Thr Ile Gly Thr Gly Gly Gly Thr Pro Tyr Ala Asp
65 70 75 80

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser
85 90 95

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

Tyr Cys Ala Leu Ser Ala Phe Asp Val Trp Gly Gln Gly Thr Met Val
115 120 125

Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
130 135 140

<210> 64
<211> 125
<212> PRT
<213> Homo sapiens

<400> 64
Glu Val Gln Leu Val Gln Ser Gly Gly Gly Leu Val His Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Gly Ser Gly Phe Thr Phe Ser Asn Tyr
20 25 30

Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

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

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr Leu
65 70 75 80

Gln Met Asn Ser Leu Arg Ala Glu Asp Met Ala Val Tyr Tyr Cys Ala
85 90 95

Leu Ser Ala Phe Asp Val Trp Gly Gln Gly Thr Met Val Thr Val Ser
100 105 110

Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
115 120 125

<210> 65
<211> 5
<212> PRT
<213> Homo sapiens

<400> 65
Asn Tyr Ala Met His
1   5

<210> 66
<211> 16
<212> PRT
<213> Homo sapiens

<400> 66
Thr Ile Gly Thr Gly Gly Gly Thr Pro Tyr Ala Asp Ser Val Lys Gly
1   5   10   15

<210> 67
<211> 5
<212> PRT
<213> Homo sapiens

<400> 67
Ser Ala Phe Asp Val
1   5

<210> 68
<211> 466
<212> DNA
<213> Homo sapiens

<400> 68
atggagtttg tgctgagctg ggttttcctt gttgctatat taaaaggtgt ccagtgtgag   60

gttcagctgg tgcagtctgg gggaggcttg gtacatcctg gggggtccct gagactctcc   120

tgtgcaggct ctggattcac cttcagtagc tatgctatgc actgggttcg ccaggctcca   180

ggaaaaggtc tggagtgggt atcagctatt ggtactggtg gttacacata ctatgtagac   240

tccgtgaagg gccgattcac catctccaga gacaatgcca agaagtcctt gtatcttcaa   300

atgaacagcc tgagagccga ggacatggct gtgtattact gtgcaagaga gccgttttac   360

gatattttga ctggttattc cccatacttt gactactggg gccagggaac cctggtcacc   420

gtctcctcag cctccaccaa gggcccatcg gtcttccccc tggcac   466

<210> 69
<211> 143
<212> PRT
<213> Homo sapiens

<400> 69
Met Glu Phe Val Leu Ser Trp Val Phe Leu Val Ala Ile Leu Lys Gly
1   5   10   15

Val Gln Cys Glu Val Gln Leu Val Gln Ser Gly Gly Gly Leu Val His
            20   25   30

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

Ser Ser Tyr Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
    50   55   60

Glu Trp Val Ser Ala Ile Gly Thr Gly Gly Tyr Thr Tyr Tyr Val Asp
65   70   75   80

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Lys Ser
                85   90   95

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

Tyr Cys Ala Arg Glu Pro Phe Tyr Asp Ile Leu Thr Gly Tyr Ser Pro
        115   120   125

Tyr Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
    130   135   140

<210> 70
<211> 124
<212> PRT
<213> Homo sapiens

<400> 70
Glu Val Gln Leu Val Gln Ser Gly Gly Gly Leu Val His Pro Gly Gly
1   5   10   15

Ser Leu Arg Leu Ser Cys Ala Gly Ser Gly Phe Thr Phe Ser Ser Tyr
            20   25   30

Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45

Ser Ala Ile Gly Thr Gly Gly Tyr Thr Tyr Tyr Val Asp Ser Val Lys
    50   55   60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Lys Ser Leu Tyr Leu
65   70   75   80

Gln Met Asn Ser Leu Arg Ala Glu Asp Met Ala Val Tyr Tyr Cys Ala
                85   90   95

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

Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
        115   120

<210> 71
<211> 5

<212> PRT
<213> Homo sapiens

<400> 71
Ser Tyr Ala Met His
1   5

<210> 72
<211> 16
<212> PRT
<213> Homo sapiens

<400> 72
Ala Ile Gly Thr Gly Gly Tyr Thr Tyr Tyr Val Asp Ser Val Lys Gly
1   5   10   15

<210> 73
<211> 16
<212> PRT
<213> Homo sapiens

<400> 73
Glu Pro Phe Tyr Asp Ile Leu Thr Gly Tyr Ser Pro Tyr Phe Asp Tyr
1   5   10   15

<210> 74
<211> 454
<212> DNA
<213> Homo sapiens

<400> 74
atggagtttg ggctgagctg ggttttcctc gttgctcttt taagaggtgt ccagtgtcag   60

gtgcagctgg tggagtctgg gggaggcgtg gtccagcctg ggaggtccct gagactctcc   120

tgtgcagcgt ctggattcac cttcagtagc tataacatgc actgggtccg ccaggctcca   180

ggcaaggggc tggagtgggt ggcagttata tggtatgatg gaagtaataa atactatgga   240

gactccgtga agggccgatt caccatctcc agagacaatt ccaagaacac gctgtatctg   300

caaatgaaca gcctgagagc cgaggacacg gctgtgtatt actgtgcgag agaagagctg   360

gggatcgggt ggtacttcga tctctggggc cgtggcaccc tggtcactgt ctcctcagcc   420

tccaccaagg gcccatcggt cttccccctg gcac   454

<210> 75
<211> 139
<212> PRT
<213> Homo sapiens

<400> 75
Met Glu Phe Gly Leu Ser Trp Val Phe Leu Val Ala Leu Leu Arg Gly
1   5   10   15

Val Gln Cys Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln
            20   25   30

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

Ser Ser Tyr Asn Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
    50   55   60

Glu Trp Val Ala Val Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Gly
65   70   75   80

Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn
                85   90   95

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

Tyr Tyr Cys Ala Arg Glu Glu Leu Gly Ile Gly Trp Tyr Phe Asp Leu
        115   120   125

Trp Gly Arg Gly Thr Leu Val Thr Val Ser Ser
    130   135

<210> 76
<211> 120
<212> PRT
<213> Homo sapiens

<400> 76
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1   5   10   15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20   25   30

Asn Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45

Ala Val Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Gly Asp Ser Val
    50   55   60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80

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

Ala Arg Glu Glu Leu Gly Ile Gly Trp Tyr Phe Asp Leu Trp Gly Arg
            100   105   110

Gly Thr Leu Val Thr Val Ser Ser
        115   120

<210> 77
<211> 5
<212> PRT
<213> Homo sapiens

<400> 77
Ser Tyr Asn Met His
1   5

<210> 78
<211> 17
<212> PRT
<213> Homo sapiens

<400> 78
Val Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Gly Asp Ser Val Lys
1   5   10   15

Gly

<210> 79
<211> 11
<212> PRT
<213> Homo sapiens

<400> 79
Glu Glu Leu Gly Ile Gly Trp Tyr Phe Asp Leu
1   5   10

<210> 80
<211> 475
<212> DNA
<213> Homo sapiens

<400> 80
atggacatga gggtccccgc tcagctcctg gggcttctgc tgctctggct cccaggtgcc   60

agatgtgcca tccagttgac ccagtctcca tcctccctgt ctgcatctgt aggagacaga   120

gtcaccatca cttgccgggc aagtcagggc attagcagtg ctttagcctg gtatcagcag   180

aaaccaggga aagctcctaa gctcctgatc tatgatgcct ccagtttgga aagtggggtc   240

ccatcaaggt tcagcggcag tggatctggg acagatttca ctctcaccat cagcagcctg   300

cagcctgaag attttgcaac ttattactgt caacagttta atagttaccc tcacttcggc   360

caagggacac gactggagat taaacgaact gtggctgcac catctgtctt catcttcccg   420

ccatctgatg agcagttgaa atctggaact gcctctgttg tgtgcctgca agggc   475

<210> 81
<211> 128
<212> PRT
<213> Homo sapiens

<400> 81
Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1   5   10   15

Leu Pro Gly Ala Arg Cys Ala Ile Gln Leu Thr Gln Ser Pro Ser Ser
            20   25   30

Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser
        35   40   45

Gln Gly Ile Ser Ser Ala Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys
    50   55   60

Ala Pro Lys Leu Leu Ile Tyr Asp Ala Ser Ser Leu Glu Ser Gly Val
65   70   75   80

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
                85   90   95

Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln
            100   105   110

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

<210> 82
<211> 106
<212> PRT
<213> Homo sapiens

<400> 82
Ala Ile Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1   5   10   15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Ala
            20   25   30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35   40   45

Tyr Asp Ala Ser Ser Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly
    50   55   60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65   70   75   80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Phe Asn Ser Tyr Pro His
                85   90   95

Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
            100   105

<210> 83
<211> 11
<212> PRT
<213> Homo sapiens

<400> 83
Arg Ala Ser Gln Gly Ile Ser Ser Ala Leu Ala
1   5   10

<210> 84
<211> 7

<212> PRT
<213> Homo sapiens

<400> 84
Asp Ala Ser Ser Leu Glu Ser
1   5

<210> 85
<211> 8
<212> PRT
<213> Homo sapiens

<400> 85
Gln Gln Phe Asn Ser Tyr Pro His
1   5

<210> 86
<211> 445
<212> DNA
<213> Homo sapiens

<400> 86
atggagtttg ggctgagctg ggttttcctc gttgctcttt taagaggtgt ccagtgtcag   60

gtgcagctgg tggagtctgg gggaggcgtg gtccagcctg ggaggtccct gagactctcc   120

tgtgcagcgt ctggattcac cttcagtagc tatggcatgc actgggtccg ccaggctcca   180

ggcaaggggc tggagtgggt ggcagttata tggtatgatg gaagtaataa atactatgca   240

gactccgtga agggccgatt caccatctcc agagacaatt ccaagaacac gctgtatctg   300

caaatgaaca gcctgagagc cgaggacacg gctgtgtatt actgtgcgag aggcccccct   360

cggtacttcg atctctgggg ccgtggcacc ctggtcactg tctcctcagc ctccaccaag   420

ggcccatcgg tcttccccct ggcac   445

<210> 87
<211> 136
<212> PRT
<213> Homo sapiens

<400> 87
Met Glu Phe Gly Leu Ser Trp Val Phe Leu Val Ala Leu Leu Arg Gly
1   5   10   15

Val Gln Cys Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln
            20   25   30

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

Ser Ser Tyr Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
    50   55   60

Glu Trp Val Ala Val Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala
65   70   75   80

Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn

                85   90   95

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

Tyr Tyr Cys Ala Arg Gly Pro Pro Arg Tyr Phe Asp Leu Trp Gly Arg
        115   120   125

Gly Thr Leu Val Thr Val Ser Ser
    130   135

<210> 88
<211> 117
<212> PRT
<213> Homo sapiens

<400> 88
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1   5   10   15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20   25   30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45

Ala Val Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
    50   55   60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80

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

Ala Arg Gly Pro Pro Arg Tyr Phe Asp Leu Trp Gly Arg Gly Thr Leu
            100   105   110

Val Thr Val Ser Ser
        115

<210> 89
<211> 5
<212> PRT
<213> Homo sapiens

<400> 89
Ser Tyr Gly Met His
1   5

<210> 90
<211> 17
<212> PRT
<213> Homo sapiens

<400> 90
Val Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val Lys
1   5   10   15

Gly

<210> 91
<211> 8
<212> PRT
<213> Homo sapiens

<400> 91
Gly Pro Pro Arg Tyr Phe Asp Leu
1   5

<210> 92
<211> 95
<212> PRT
<213> Homo sapiens

<400> 92
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1   5   10   15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
            20   25   30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        35   40   45

Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
    50   55   60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65   70   75   80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro
                85   90   95

<210> 93
<211> 95
<212> PRT
<213> Homo sapiens

<400> 93
Ala Ile Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1   5   10   15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Ala
            20   25   30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35   40   45

Tyr Asp Ala Ser Ser Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly

    50   55   60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65   70   75   80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Phe Asn Ser Tyr Pro
                85   90   95

<210> 94
<211> 95
<212> PRT
<213> Homo sapiens

<400> 94
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1   5   10   15

Asp Arg Val Thr Ile Thr Cys Arg Ala Arg Gln Gly Ile Ser Ser Trp
            20   25   30

Leu Ala Trp Tyr Gln Gln Lys Pro Glu Lys Ala Pro Lys Ser Leu Ile
        35   40   45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50   55   60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65   70   75   80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asn Ser Tyr Pro
                85   90   95

<210> 95
<211> 98
<212> PRT
<213> Homo sapiens

<400> 95
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1   5   10   15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20   25   30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45

Ala Val Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
    50   55   60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys

                85   90   95

Ala Arg

<210> 96
<211> 97
<212> PRT
<213> Homo sapiens

<400> 96
Glu Val Gln Leu Val Gln Ser Gly Gly Gly Leu Val His Pro Gly Gly
1   5   10   15

Ser Leu Arg Leu Ser Cys Ala Gly Ser Gly Phe Thr Phe Ser Ser Tyr
            20   25   30

Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45

Ser Ala Ile Gly Thr Gly Gly Gly Thr Tyr Tyr Ala Asp Ser Val Lys
    50   55   60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr Leu
65   70   75   80

Gln Met Asn Ser Leu Arg Ala Glu Asp Met Ala Val Tyr Tyr Cys Ala
                85   90   95

Arg

<210> 97
<211> 5
<212> PRT
<213> Artificial sequence

<220>
<221> source
<223> /note="Description of artificial sequence: Synthetic
      consensus sequence"

<220>
<221> VARIANT
<222> (1)..(1)
<223> /replace="Asn" or "Thr" or "Ser"

<220>
<221> misc_feature
<222> (1)..(1)
<223> /note="Residue given in the sequence has no preference
      with respect to those in the annotation for said position"

<220>
<221> VARIANT
<222> (3)..(3)
<223> /replace="Asn" or "Ala"

<220>
<221> misc_feature
<222> (3)..(3)
<223> /note="Residue given in the sequence has no preference
with respect to those in the annotation for said position"

<220>
<221> VARIANT
<222> (5)..(5)
<223> /replace="Tyr"

<220>
<221> misc_feature
<222> (5)..(5)
<223> /note="Residue given in the sequence has no preference
with respect to those in the annotation for said position"

<400> 97
Ile Tyr Gly Met His
1   5

<210> 98
<211> 17
<212> PRT
<213> Artificial sequence

<220>
<221> source
<223> /note="Description of artificial sequence: Synthetic
consensus sequence"

<220>
<221> VARIANT
<222> (1)..(1)
<223> /replace="Ile" or "Phe" or "Thr" or "Ala"

<220>
<221> misc_feature
<222> (1)..(1)
<223> /note="Residue given in the sequence has no preference
with respect to those in the annotation for said position"

<220>
<221> VARIANT
<222> (3)..(3)
<223> /replace="Gly"

<220>
<221> VARIANT
<222> (4)..(4)
<223> /replace="Thr"

<220>
<221> VARIANT
<222> (5)..(5)
<223> /replace="Gly"

<220>
<221> misc_feature
<222> (3)..(5)
<223> /note="Residues given in the sequence have no preference
with respect to those in the annotations for said positions"

<220>
<221> VARIANT
<222> (7)..(7)

<223> /replace="Gly" or "Tyr"

<220>
<221> VARIANT
<222> (8)..(8)
<223> /replace="Thr"

<220>
<221> VARIANT
<222> (9)..(9)
<223> /replace="Pro"

<220>
<221> misc_feature
<222> (7)..(9)
<223> /note="Residues given in the sequence have no preference
with respect to those in the annotations for said positions"

<220>
<221> VARIANT
<222> (11)..(11)
<223> /replace="Ala" or "Val"

<220>
<221> VARIANT
<222> (12)..(12)
<223> /replace="Gly" or " "

<220>
<221> misc_feature
<222> (11)..(12)
<223> /note="Residues given in the sequence have no preference
with respect to those in the annotations for said positions"

<400> 98
Val Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val Lys
1   5   10   15

Gly

<210> 99
<211> 6
<212> PRT
<213> Artificial sequence

<220>
<221> source
<223> /note="Description of artificial sequence: Synthetic
consensus sequence"

<220>
<221> VARIANT
<222> (1)..(1)
<223> /replace="Gly" or "Tyr" or "Ser" or "Pro" or " "

<220>
<221> VARIANT
<222> (2)..(2)
<223> /replace="Trp" or "Ser" or "Arg"

<220>
<221> VARIANT
<222> (3)..(3)
<223> /replace="Ala" or "His"

<220>
<221> misc_feature
<222> (1)..(3)
<223> /note="Residues given in the sequence have no preference
with respect to those in the annotations for said positions"

<220>
<221> VARIANT
<222> (6)..(6)
<223> /replace="Leu" or "Val"

<220>
<221> misc_feature
<222> (6)..(6)
<223> /note="Residue given in the sequence has no preference
with respect to those in the annotation for said position"

<400> 99
Ala Pro Tyr Phe Asp Tyr
1   5

<210> 100
<211> 11
<212> PRT
<213> Artificial sequence

<220>
<221> source
<223> /note="Description of artificial sequence: Synthetic
consensus sequence"

<220>
<221> VARIANT
<222> (5)..(5)
<223> /replace="Gly"

<220>
<221> VARIANT
<222> (6)..(6)
<223> /replace="Val"

<220>
<221> misc_feature
<222> (5)..(6)
<223> /note="Residues given in the sequence have no preference
with respect to those in the annotations for said positions"

<220>
<221> VARIANT
<222> (9)..(9)
<223> /replace="Trp" or "Ala"

<220>
<221> misc_feature
<222> (9)..(9)
<223> /note="Residue given in the sequence has no preference
with respect to those in the annotation for said position"

<400> 100
Arg Ala Ser Gln Ser Ile Ser Ser Tyr Leu Ala
1   5   10

<210> 101
<211> 7

<212> PRT
<213> Artificial sequence

<220>
<221> source
<223> /note="Description of artificial sequence: Synthetic
consensus sequence"

<220>
<221> VARIANT
<222> (1)..(1)
<223> /replace="Ala"

<220>
<221> misc_feature
<222> (1)..(1)
<223> /note="Residue given in the sequence has no preference
with respect to those in the annotation for said position"

<220>
<221> VARIANT
<222> (4)..(4)
<223> /replace="Ser"

<220>
<221> VARIANT
<222> (5)..(5)
<223> /replace="Leu"

<220>
<221> VARIANT
<222> (6)..(6)
<223> /replace="Gln" or "Glu"

<220>
<221> VARIANT
<222> (7)..(7)
<223> /replace="Ser"

<220>
<221> misc_feature
<222> (4)..(7)
<223> /note="Residues given in the sequence have no preference
with respect to those in the annotations for said positions"

<400> 101
Asp Ala Ser Asn Arg Ala Thr
1   5

<210> 102
<211> 9
<212> PRT
<213> Artificial sequence

<220>
<221> source
<223> /note="Description of artificial sequence: Synthetic
consensus sequence"

<220>
<221> VARIANT
<222> (3)..(3)
<223> /replace="Tyr" or "Phe"

<220>

<221> VARIANT
<222> (4)..(4)
<223> /replace="Asn"

<220>
<221> VARIANT
<222> (5)..(5)
<223> /replace="Ser" or "Asn"

<220>
<221> VARIANT
<222> (6)..(6)
<223> /replace="Trp" or " "

<220>
<221> VARIANT
<222> (7)..(7)
<223> /replace=" "

<220>
<221> VARIANT
<222> (8)..(8)
<223> /replace="Leu" or "His" or " "

<220>
<221> VARIANT
<222> (9)..(9)
<223> /replace=" "

<220>
<221> misc_feature
<222> (3)..(9)
<223> /note="Residues given in the sequence have no preference
with respect to those in the annotations for said positions"

<400> 102
Gln Gln Arg Arg Thr Tyr Pro Tyr Thr
1   5

<210> 103
<211> 118
<212> PRT
<213> Homo sapiens

<400> 103
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1   5   10   15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
            20   25   30

Gly Met Tyr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45

Ala Val Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
    50   55   60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80

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

Ala Arg Asp Leu Trp Gly Trp Tyr Phe Asp Tyr Trp Gly Gln Gly Thr
            100   105   110

Leu Val Thr Val Ser Ser
        115

<210> 104
<211> 117
<212> PRT
<213> Homo sapiens

<400> 104
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1   5   10   15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Thr Tyr
            20   25   30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45

Ala Ile Ile Trp Tyr Asp Gly Gly Asn Lys Tyr Tyr Ala Asp Ser Val
    50   55   60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80

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

Ala Arg Asp Phe Tyr Trp Tyr Phe Asp Leu Trp Gly Arg Gly Thr Leu
            100   105   110

Val Thr Val Ser Ser
        115

<210> 105
<211> 120
<212> PRT
<213> Homo sapiens

<400> 105
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1   5   10   15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20   25   30

Asn Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45

Ala Phe Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Gly Asp Ser Val
    50   55   60

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Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

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

Ala Arg Glu Glu Leu Gly Ile Gly Trp Tyr Phe Asp Leu Trp Gly Arg
            100                 105                 110

Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210> 106
<211> 113
<212> PRT
<213> Homo sapiens

<400> 106
Glu Val Gln Leu Val Gln Ser Gly Gly Gly Leu Val His Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Gly Ser Gly Phe Thr Phe Ser Asn Tyr
            20                  25                  30

Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

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

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr Leu
65                  70                  75                  80

Gln Met Asn Ser Leu Arg Ala Glu Asp Met Ala Val Tyr Tyr Cys Ala
                85                  90                  95

Leu Ser Ala Phe Asp Val Trp Gly Gln Gly Thr Met Val Thr Val Ser
            100                 105                 110

Ser
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