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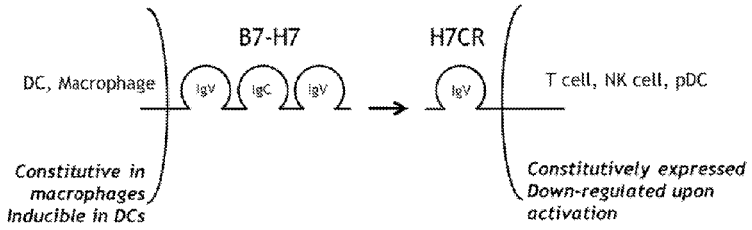

Figure 1

(57) Abstract: Antibodies and humanized variants thereof and their antigen-binding fragments and to other molecules that are capable of immunospecifically binding to the B7-H7 counter-receptor, H7CR, and their uses in enhancing immune responses and the treatment and diagnosis of cancer and other diseases are provided.

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ANTI-H7CR ANTIBODIES

CROSS-REFERNCE TO RELATED APPLICATIONS

[0001] This application is a PCT application claiming benefit of and priority to US Provisional Patent Application No. 61/745,296 filed on December 21, 2012, US Provisional Patent Application No. 61/745,312 filed on December 21, 2012, US Provisional Patent Application No. 61/827,269 filed on May 24, 2013, and US Provisional Patent Application No. 61/827,279 filed on May 24, 2013 all of which are incorporated by referenced in their entireties, where permissible.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT:

[0002] This invention was made, in part, with United States Government support under award numbers R01 CA097085-10 and ROl A172592 from the National Institutes of Health (NIH), and U19 CA113341 from the National Cancer Institute (NCI). The United States Government may have certain rights in this invention.

REFERENCE TO SEQUENCE LISTING

[0003] This application includes one or more Sequence Listings pursuant to 37 C.F.R. 1.821 *et seq*., which are disclosed in both paper and computer-readable media, and which paper and computer-readable disclosures are herein incorporated by reference in their entirety.

BACKGROUND OF THE INVENTION

Field of the Invention

[0004] The present invention relates to antibodies and their antigen-binding fragments and to other molecules that are capable of immunospecifically binding to the B7-H7 counter-receptor, H7CR, and their uses in the treatment and diagnosis of cancer and other diseases.

Description of Related Art

[0005] The immune system of humans and other mammals is responsible for providing protection against infection and disease. Such protection is provided both by a humoral immune response and by a cell-mediated immune response. The humoral response results in the production of antibodies and other biomolecules that are capable of recognizing and neutralizing foreign targets (antigens). In contrast, the cell-mediated immune response involves the activation of macrophages, natural killer cells (NK), and antigen-specific

cytotoxic T-lymphocytes by T cells, and the release of various cytokines in response to the recognition of an antigen (Dong, C. *et al.* (2003) "*Immune Regulation by Novel Costimulatory Molecules*," Immunolog. Res. 28(1):39-48).

[0006] The ability of T cells to optimally mediate an immune response against an antigen requires two distinct signaling interactions (Viglietta, V. *et al.* (2007) "*Modulating Co-Stimulation*," Neurotherapeutics 4:666-675; Korman, A.J. *et al.* (2007) "*Checkpoint Blockade in Cancer Immunotherapy*," Adv. Immunol. 90:297-339). First, antigen that has been displayed on the surface of antigen-presenting cells (APC) must be presented to an antigen-specific naive $CD4^+$ T cell. Such presentation delivers a signal via the T cell receptor (TCR) that directs the T cell to initiate an immune response that will be specific to the presented antigen. Second, a series of co-stimulatory and inhibitory signals, mediated through interactions between the APC and distinct T cell surface molecules, triggers first the activation and proliferation of the T cells and ultimately their inhibition. Thus, the first signal confers specificity to the immune response; whereas, the second signal serves to determine the nature, magnitude and duration of the response.

[0007] The immune system is tightly controlled by co-stimulatory and co-inhibitory ligands and receptors. These molecules provide the second signal for T cell activation and provide a balanced network of positive and negative signals to maximize immune responses against infection while limiting immunity to self (Wang, L. *et al.* (March 7, 2011) "*VISTA, A Novel Mouse Ig Superfamily Ligand That Negatively Regulates T Cell Responses*," J. Exp. Med. 10.1084/jem.20100619:1-16; Lepenies, B. *et al.* (2008) "*The Role Of Negative Costimulators During Parasitic Infections*," Endocrine, Metabolic & Immune Disorders - Drug Targets 8:279-288). Of particular importance is binding between the B7.1 (CD80) and B7.2 (CD86) ligands of the Antigen Presenting Cell and the CD28 and CLTA-4 receptors of the $CD4^+$ T-lymphocyte (Sharpe, A.H. *et al.* (2002) "*The B7-CD28 Superfamily*," Nature Rev. Immunol. 2:116-126; Dong, C. et al. (2003) "*Immune Regulation by Novel Costimulatory Molecules*," Immunolog. Res. 28(1):39-48; Lindley, P.S. et al. (2009) "*The Clinical Utility Of Inhibiting CD28-Mediated Costimulation*," Immunol. Rev. 229:307-321). Binding of B7.1 or of B7.2 to CD28 stimulates T cell activation; binding of B7.1 or B7.2 to CTLA4 inhibits such activation (Dong, C. *et al.* (2003) "*Immune Regulation by Novel Costimulatory Molecules*," Immunolog. Res. 28(1):39-48; Lindley, P.S. *et al.* (2009) "*The Clinical Utility Of Inhibiting CD28-Mediated Costimulation*," Immunol. Rev. 229:307-321; Greenwald, R.J. *et al.* (2005) "*The B7 Family Revisited*," Ann. Rev. Immunol. 23:515-548). CD28 is constitutively expressed on the surface of T cells (Gross, J., *et al.* (1992) "*Identification And Distribution*

Of The Costimulatory Receptor CD28 In The Mouse," J. Immunol. 149:380–388), whereas CTLA4 expression is rapidly up-regulated following T-cell activation (Linsley, P. *et al.* (1996) "*Intracellular Trafficking Of CTLA4 And Focal Localization Towards Sites Of TCR Engagement*," Immunity 4:535–543). Since CTLA4 is the higher affinity receptor (Sharpe, A.H. *et al.* (2002) "*The B7-CD28 Superfamily*," Nature Rev. Immunol. 2:116-126), binding first initiates T cell proliferation (via CD28) and then inhibits it (via nascent expression of CTLA4), thereby dampening the effect when proliferation is no longer needed.

[0008] Further investigations into the ligands of the CD28 receptor have led to the identification and characterization of a set of related B7 molecules (the "B7 Superfamily") (Coyle, A.J. *et al.* (2001) "*The Expanding B7 Superfamily: Increasing Complexity In Costimulatory Signals Regulating T Cell Function*," Nature Immunol. 2(3):203-209; Sharpe, A.H. *et al.* (2002) "*The B7-CD28 Superfamily*," Nature Rev. Immunol. 2:116-126; Greenwald, R.J. *et al.* (2005) "*The B7 Family Revisited*," Ann. Rev. Immunol. 23:515-548; Collins, M. *et al.* (2005) "*The B7 Family Of Immune-Regulatory Ligands*," Genome Biol. 6:223.1-223.7; Loke, P. *et al.* (2004) "*Emerging Mechanisms Of Immune Regulation: The Extended B7 Family And Regulatory T Cells*." Arthritis Res. Ther. 6:208-214; Korman, A.J. *et al.* (2007) "*Checkpoint Blockade in Cancer Immunotherapy*," Adv. Immunol. 90:297-339; Flies, D.B. *et al.* (2007) "*The New B7s: Playing a Pivotal Role in Tumor Immunity*," J. Immunother. 30(3):251-260; Agarwal, A. *et al.* (2008) "*The Role Of Positive Costimulatory Molecules In Transplantation And Tolerance*," Curr. Opin. Organ Transplant. 13:366-372; Lenschow, D.J. *et al.* (1996) "*CD28/B7 System of T Cell Costimulation*," Ann. Rev. Immunol. 14:233-258; Wang, S. *et al.* (2004) "*Co-Signaling Molecules Of The B7-CD28 Family In Positive And Negative Regulation Of T Lymphocyte Responses*," Microbes Infect. 6:759-766). There are currently eight known members of the family: B7.1 (CD80), B7.2 (CD86), the inducible co-stimulator ligand (ICOS-L), the programmed death-1 ligand (PD-L1; B7-H1), the programmed death-2 ligand (PD-L2; B7-DC), B7-H3, B7-H4 (also referred to as B7x and B7S1; Sica, G.L. *et al.* (2003) "*B7-4, A Molecule Of The B7 Family, Negatively Regulates T Cell Immunity*," Immunity18:849-861; Zang, X. *et al.* (2003) *B7x: A Widely Expressed B7 Family Member That Inhibits T Cell Activation*," Proc. Natl. Acad. Sci. (USA) 100:10388-10392; Prasad, D.V. *et al.* (2003) *B7S1, A Novel B7 Family Member That Negatively Regulates T Cell Activation*," Immunity 18:863-873), B7-H6 (Collins, M. *et al.* (2005) "*The B7 Family Of Immune-Regulatory Ligands*," Genome Biol. 6:223.1-223.7) and B7-H7 (Flajnik, M.F. *et al.* (2012) "*Evolution Of The B7 Family: Co-Evolution Of B7H6 And Nkp30, Identification Of A New B7 Family Member, B7H7, And Of B7's Historical*

Relationship With The MHC," Immunogenetics 64:571–590). The B7 family of genes is essential in the regulation of the adaptive immune system. Most B7 family members contain both variable (V)- and constant (C)-type domains of the immunoglobulin superfamily (IgSF).

[0009] B7 ligands are expressed on the cell surface of many different cell types including antigen presenting cells (APCs) and their interaction with receptor molecules on T cells provide activating and/or inhibitory signals that regulate T cell activation and tolerance (Collins, M. et al. (2005) "The B7 Family Of Immune-Regulatory Ligands," Genome Biol. 6:223.1-223.7). Some inhibitory B7 ligands are also expressed on tumor cells, resulting in suppression of immune responses (Keir, M.E. et al. (2008) "PD-1 And Its Ligands In Tolerance And Immunity," Annu. Rev. Immunol. 26:677-704; Zou, W. et al. (2008) "Inhibitory B7-Family Molecules In The Tumour Microenvironment," Nat. Rev. Immunol. 8:467-477). Therefore, stimulating or attenuating the interactions of B7 ligands and their receptors holds therapeutic potential for autoimmune diseases and cancer (WO 2011/020024; Flajnik, M.F. et al. (2012) "Evolution Of The B7 Family: Co-Evolution Of B7H6 And Nkp30, Identification Of A New B7 Family Member, B7H7, And Of B7*'s Historical* Relationship With The MHC," Immunogenetics 64:571–590).

[0010] Despite all prior advances in the treatment of inflammation and cancer, a need remains for compositions capable of providing enhanced immunotherapy for the treatment of such conditions.

[0011] It is an object of the invention to provide compositions capable of providing enhanced immunotherapy for the treatment of cancer, infectious disease, inflammation and other diseases and conditions.

SUMMARY OF THE INVENTION

[0012A] Antibodies and their antigen-binding fragments and other molecules that are capable of immunospecifically binding to the B7-H7 counter-receptor, H7CR, are provided. The B7-H7 counter-receptor is also known as B7-H7CR and CD28H (Yhu, et al., Nature Communications, 4:1-12 (2013)). Methods of their use in the treatment and diagnosis of cancer, infectious disease, inflammation and other diseases and conditions are also provided. The H7CR binding molecules can be a monoclonal antibody, a human antibody, a chimeric antibody or a humanized antibody.

[0012B] In one embodiment of the present invention there is provided an antibody or an antigen-binding fragment thereof that specifically binds to a human B7-H7CR, wherein the antibody or an antigen binding fragment thereof is genetically engineered and comprises:

(1) a light chain variable region comprising amino acid sequence **SEQ ID NO:17** and a heavy chain variable region comprising amino acid sequence **SEQ ID NO:23**;

(2) a light chain variable region comprising amino acid sequence **SEQ ID NO:17** and a heavy chain variable region comprising amino acid sequence **SEQ ID NO:24**;

(3) a light chain variable region comprising amino acid sequence **SEQ ID NO:17** and a heavy chain variable region comprising amino acid sequence **SEQ ID NO:25**;

(4) a light chain variable region comprising amino acid sequence **SEQ ID NO:17** and a heavy chain variable region comprising amino acid sequence **SEQ ID NO:26**;

(5) a light chain variable region comprising amino acid sequence **SEQ ID NO:17** and a heavy chain variable region comprising amino acid sequence **SEQ ID NO:27**;

(6) a light chain variable region comprising amino acid sequence **SEQ ID NO:17** and a heavy chain variable region comprising amino acid sequence **SEQ ID NO:28**;

(7) a light chain variable region comprising amino acid sequence **SEQ ID NO:18** and a heavy chain variable region comprising amino acid sequence **SEQ ID NO:24**;

(8) a light chain variable region comprising amino acid sequence **SEQ ID NO:18** and a heavy chain variable region comprising amino acid sequence **SEQ ID NO:25**;

(9) a light chain variable region comprising amino acid sequence **SEQ ID NO:18** and a heavy chain variable region comprising amino acid sequence **SEQ ID NO:27**;

(10) a light chain variable region comprising amino acid sequence **SEQ ID NO:18** and a heavy chain variable region comprising amino acid sequence **SEQ ID NO:28**;

(11) a light chain variable region comprising amino acid sequence **SEQ ID NO:19** and a heavy chain variable region comprising amino acid sequence **SEQ ID NO:24**;

(12) a light chain variable region comprising amino acid sequence **SEQ ID NO:19** and a heavy chain variable region comprising amino acid sequence **SEQ ID NO:25**;

(13) a light chain variable region comprising amino acid sequence **SEQ ID NO:19** and a heavy chain variable region comprising amino acid sequence **SEQ ID NO:27**; or

(14) a light chain variable region comprising amino acid sequence **SEQ ID NO:19** and a heavy chain variable region comprising amino acid sequence **SEQ ID NO:28.**

[0013] One embodiment provides H7CR binding molecules wherein the antigen-binding fragment includes six CDRs, wherein the CDRs include at least one CDR of the CDRs of

anti-H7CR antibodies: 1.3, 4.5 and 7.8, or a consensus CDR thereof, with all remaining CDRs selected from:

(A) the three light chain and the three heavy chain CDRs of anti-H7CR antibody 1.3;

(B) the three light chain and the three heavy chain CDRs of anti-H7CR antibody 4.5; or

(C) the three light chain and the three heavy chain CDRs of anti-H7CR antibody 7.8.

[0014] Another embodiment provides H7CR binding molecules wherein the six CDRs are:

(A) the three light chain and the three heavy chain CDRs of anti-H7CR antibody 1.3;

(B) the three light chain and the three heavy chain CDRs of anti-H7CR antibody 4.5; or

(C) the three light chain and the three heavy chain CDRs of anti-H7CR antibody 7.8.

[0015] Still another embodiment provides H7CR binding molecules having an antigen-binding fragment of a humanized variant of anti-human H7CR antibody 1.3 or 4.5, wherein the molecule immunospecifically binds to human H7CR, and wherein the antigen-binding fragment include:

(A) (1) a light chain variable region of a humanized variant of anti-human H7CR antibody 1.3, wherein said light chain variable region has the amino acid sequence of any of **SEQ ID NO:17-22**; and

(2) a heavy chain variable region of a humanized variant of anti-human H7CR antibody 1.3, wherein said heavy chain variable region has the amino acid sequence of any of **SEQ ID NO:23-28**;

or

(B) (1) a light chain variable region of a humanized variant of anti-human H7CR antibody 4.5, wherein said light chain variable region has the amino acid sequence of any of **SEQ ID NO:33-38**; and

(2) a heavy chain variable region of a humanized variant of anti-human H7CR antibody 4.5, wherein said heavy chain variable region has the amino acid sequence of any of **SEQ ID NO:39-44**.

[0016] A preferred embodiment concerns the embodiment wherein said H7CR binding molecule immunospecifically binds to H7CR that is:

(A) arrayed on the surface of a live cell; or

(B) expressed at an endogenous concentration.

[0017] In one embodiment the live cell is a T cell, an NK cell, or a plasmacytoid dendritic cell.

[0018] In still another embodiment the molecule is substantially incapable of blocking H7CR's interaction with B7-H7.

[0019] In another embodiment the molecule is capable of binding H7CR and agonizing H7CR activity.

[0020] Any of the antibodies can be a bispecific, trispecific or multispecific antibody. The molecule can be detectably labeled or includes a conjugated toxin, drug, receptor, enzyme, receptor ligand, or a combination thereof.

[0021] Another embodiment provides a pharmaceutical composition containing a therapeutically effective amount of any of the above-referenced molecules, and a physiologically acceptable carrier or excipient.

[0022] The disclosed compositions can be used to treat a disease in a subject exhibiting a symptom of the disease by administering to the subject, a therapeutically effective amount of any of the above-referenced pharmaceutical compositions to activate the B7-H7 pathway and stimulate an immune response. Specific indications to be treated include, but are not limited cancer, an infectious disease, a chronic viral disease, an inflammatory condition, or an autoimmune disease.

[0023] A method for treating a disease wherein the pharmaceutical composition agonizes an H7CR function is also provided.

[0024] Methods for prophylactically treating a disease include administering to a subject in advance of exhibiting a symptom of the disease a prophylactically effective amount of any of the above-referenced pharmaceutical compositions.

[0025] Methods for diagnosing a disease (especially cancer or a disease affecting T cell number and health) in a subject include assaying cells of the subject for their ability to bind to any of the above-referenced H7CR binding molecule, wherein the method provides a cytologic assay for diagnosing the immune responsiveness or the presence of the disease in the subject.

BRIEF DESCRIPTION OF THE DRAWINGS

[0026] **Figure 1** is a diagram of the structure, the expression pattern and the interaction between H7CR and B7-H7 on separate cells.

[0027] **Figure 2** is a line graph of Median Fluorescence Intensity versus log [Ab] (nM) showing the respective binding affinities of anti-H7CR antibodies 1.3 (Kd = 5.9 nM) and 4.5 (Kd = 3.5 nM) to H7CR CHO transfectants.

[0028] **Figures 3A** and **3B** are line graphs of Median Fluorescence Intensity versus log [Ab] (nM) showing H7CR mAb binding curves to human naïve (CD45RA+) CD4 and CD8 T cells from PBMC (Figure 3B).

[0029] **Figures 4(A)-4(C)** are histograms of flow cytometry data showing the ability of the antibodies 1.3, 4.5 and 7.8 to bind to human H7CR expressed on the surface of CHO transfectants. The data are presented as cell Count versus log fluorescence of Comp PE-A. The left peak in each panel presents isotype control antibody; the right peak represents H7CR antibody.

[0030] **Figures 5A-5D** are histograms of flow cytometry data showing that B7-H7Ig fusion protein binds to H7CR CHO transfectant. The data are presented as cell Count versus log fluorescence of Comp APC-A. Pre-incubation of antibodies 1.3 (Figure 5B), 4.5 (Figure 5C) and 7.8 (Figure 5D) with H7CR transfectants were each found to be substantially incapable of blocking H7CR's interaction with B7-H7.

[0031] **Figure 6** is photomicrograph showing the ability of anti-human H7CR antibody (H7CR 4.5) to bind to H7CR as endogenously expressed on the surface of human tonsil tissue.

[0032] **Figure 7 (Panels A-C)** are scatter plots of flow cytometery data showing that H7CR expression was associated with a naïve T cell phenotype in T and NK cells. **Panel A** shows scatter plots from four donors showing expression of H7CR on CD3+ T cells relative to their expression of CD45RO. The scatter plots are fluorescence of anti-H7-CR antibody versus fluorescence from anti-CD45RO. **Panel B** is a scatter plot showing gating of T cells and NK cells based on the expression of CD3 and CD16 markers. The scatter plot is fluorescence of anti-CD3 antibody versus fluorescence from anti-CD16 antibody. **Panel C** shows scatter plots from four donors showing expression of H7CR on CD16+ NK cells relative to their expression of CD45RO. The scatter plots are fluorescence of anti-H7-CR versus fluorescence from anti-CD45RO.

[0033] **Figures 8A-8H** are flow cytometery scatter plots of the expression profiles of H7CR and B7-H7 of four healthy PMBC donors (Donor 1, **Figures 8A and 8B**; Donor 2, **Figures 8C and 8D**; Donor 3 (**Figures 8E and Figure 8F**) and Donor 4 (**Figure 8G and Figure**

8H)). **Figures 8A, 8C, 8E, and 8G** are scatter plots of log fluorescence using antibody 1.3 versus log fluorescence using anti-CD3 antibody. Figures 8B, 8D, 8F, and 8H are scatter plots of log fluorescence using anti-B7H7 antibody 2D3 versus anti-CD14 antibody. All donors show expression of H7CR on CD3 T cell with minimal expression of B7-H7 in PBMC.

[0034] **Figures 9A-9H** are flow cytometery scatter plots showing the expression profiles of H7CR and B7-H7 of four healthy PMBC donors (Donor 1, **Figures 9A and 9B**; Donor 2, **Figures 9C and 9D**; Donor 3, **Figures 9E and 9F**; and Donor 4, **Figures 9G and 9H**). Figures 9A, 9C, 9E, and 9G are scatter plots of fluorescence using antibody 1.3 versus anti-CD3 antibody. Figures 9B, 9D, 9F, and 9H are scatter plots of fluorescence using anti-B7H7 antibody 2D3 versus anti-CD14 antibody. Donors 2, 3, 4 show expression of H7CR on CD3 T cell with minimal expression of B7-H7 in PBMC. Donor 1 shows high expression level of B7-H7 on CD14+ monocyte and low H7CR expression level on CD3 T cells.

[0035] **Figures 10A-10D** are flow cytometry histograms showing the expression of H7CR and B7-H7 by human monocytes (10A, 10F, 10K, 10P. 10U, and 10Z) CD8+ CD3+ lymphocytes (10B, 10 G, 10L, 10Q, 10V, 10AA), CD8– CD3+ lymphocytes (10C, 10H, 10M, 10R, 10W, and 10AB), CD16+ NK cells (10D, 10I, 10N, 10S, 10X, and 10AC), and CD3– CD8– cells. (10E, 10J, 10O, 10T, 10Y, and 10AD) Antibody 18C3 (10A-10E) and 2D3 (10F-10J) are anti-B7-H7 monoclonal antibodies. Figures 10K-10O use anti PD-1 antibody. Figures 10P-T use antibody 1.3. Figures 10U-Y use antibody 4.5. Figures 10Z-AD use antibody 7.8.

[0036] **Figures 11A-11D** are flow cytometry histograms showing the expression of H7CR and B7-H7 by cynomolgus monkey monocytes(11A, 11F, 11K, 11P. 11U, and 11Z), CD8+ CD3+ lymphocytes (11B, 11 G, 11L, 11Q, 11V, 11AA), CD8– CD3+ lymphocytes (11C, 11H, 11M, 11R, 11W, and 11AB), CD16+ NK cells (11D, 11I, 11N, 11S, 11X, and 11AC) and CD3– CD8–cells (11E, 11J, 11O, 11T, 11Y, and 11AD). Antibody 18C3 (Figures 10A-10E) and 2D3 (Figures 10F-10J) are anti-B7-H7 monoclonal antibodies. Figures 10K-10O use anti PD-1 antibody. Figures 10P-T use antibody 1.3. Figures 10U-Y use antibody 4.5. Figures 10Z-AD use antibody 7.8.

[0037] **Figures 12A-12K** are flow cytometry histograms of *in vitro* analysis of the expression of B7-H7 and other activation markers by matured monocyte-derived dendritic cells. Figure 12A is a histogram of Counts versus log Comp-FITC-A using anti-HLA-ABC

antibody. Figure 12B is a histogram of Counts versus log Comp-PE-A using anti-B7-H1 antibody. Figure 12C is a histogram of Counts versus log Comp-PerCP-Cy5-5-A using anti-HLA-DR antibody. Figure 12D is a histogram of Counts versus log Comp-PE-Cy7-A using anti-CD40 antibody. Figure 12E is a histogram of Counts versus log Comp-APC-A using anti-CD86 antibody. Figure 12F is a histogram of Counts versus log Comp-PacificBlue-A using anti-CD83 antibody. Figure 12G is a histogram of Counts versus log Comp-FITC-A using anti-CD80 antibody. Figure 12H is a histogram of Counts versus log Comp-PE-A using anti-B7-DC antibody. Figure 12I is a histogram of Counts versus log Comp-PacificBlue-A using anti-CD54 antibody. Figure 12J is a histogram of Counts versus log Comp-PerCP-Cy5-5A using anti-B7-H7 antibody. Figure 12K is a histogram of Counts versus log Comp-APC-A using anti-CCR7 antibody. Solid grey line represents isotype control. Dashed line represents immature dendritic cells. Dotted line represents cells treated with TNFα and PGE2 for one day. Solid black line represents cells treated with 1ng/ml TNFa and 1μg/ml PGE2 for two days.

[0038] **Figure 13** is a line graph of Percentage of divided cell (CFSE low) versus Days for Ctl Ig (■), H7CR1.3 (●), H7CR4.5 (▲), H7CR7.8 (♦) and T cell only (—) and shows that the anti-H7CR antibodies promote model antigen, Tetanus Toxoid, specific T cell responses.

[0039] **Figures 14A-14L** bar graphs that show the nature and levels of cytokines expressed by the cells subjected to a tetanus toxoid protein stimulation and H7CR antibody or control antibody treatment. Figure 14A is a bar graph of IFN-γ (pg/nl) cells treated with CtlIg, H7CR1.3, H7CR4.5, H7CR7.8 or T cell only. Figure 14B is a bar graph of IL-5 (pg/nl) cells treated with CtlIg, H7CR1.3, H7CR4.5, H7CR7.8 or T cell only. Figure 14D is a bar graph of IL-13 (pg/nl) cells treated with CtlIg, H7CR1.3, H7CR4.5, H7CR7.8 or T cell only. Figure 14E is a bar graph of GM-CSF (pg/nl) cells treated with CtlIg, H7CR1.3, H7CR4.5, H7CR7.8 or T cell only. Figure 14F is a bar graph of IL-10 (pg/nl) cells treated with CtlIg, H7CR1.3, H7CR4.5, H7CR7.8 or T cell only. Figure 14G is a bar graph of IL-6 (pg/nl) cells treated with CtlIg, H7CR1.3, H7CR4.5, H7CR7.8 or T cell only. Figure 14H is a bar graph of IL-12p70 (pg/nl) cells treated with CtlIg, H7CR1.3, H7CR4.5, H7CR7.8 or T cell only. Figure 14I is a bar graph of MCP-1 (pg/nl) cells treated with CtlIg, H7CR1.3, H7CR4.5, H7CR7.8 or T cell only. Figure 14J is a bar graph of IL-17 (pg/nl) cells treated with CtlIg, H7CR1.3, H7CR4.5, H7CR7.8 or T cell only. Figure 14AKis a bar graph of MIP-1β (pg/nl) cells treated with CtlIg, H7CR1.3, H7CR4.5, H7CR7.8 or T cell only. Figure 14L is a bar graph of IL-8 (pg/nl) cells treated with CtlIg, H7CR1.3, H7CR4.5, H7CR7.8 or T cell only.

[0040] **Figures 15A and 15B** are flow cytometry scatter plots that show that treatment with anti-H7CR antibodies enhanced proliferation and intracellular IFNγ expression in antigen-specific T cells. Figure 15A is a scatter plot of log Comp-PerCP-Cy5-5-A::IFNg versus Comp-FITC::CFSE using CtlIg. Figure 15B is a scatter plot of log Comp-PerCP-Cy5-5-A::IFNg versus Comp-FITC::CFSE.

[0041] **Figures 16A-16B** are bar graphs that show the effects of anti-H7CR antibodies on human T cell responses. **Figure 16A** is a bar graph of Divided CD4+ T Cells (%) that shows anti-CD28H antibodies (solid box) mediate a strongly augmented T cell proliferation in the absence of CTLA4-Ig. **Figure 16B** shows that anti-CD28H antibodies (solid box) mediate an increase in cytokine expression. **Figure 16B** includes panel A which is a bar graph of pg/ml of IFN-γ from T cells treated with control (open box) or anti-CD28H (solid box). Panel B is a bar graph of pg/ml the following cytokines (solid box) from left to right: IL-5, IL-10, TNF-α, IL-17. Control (open box).

[0042] **Figures 17A-17B** show Collier Perles 2D representations of the variable domains of the light chain (**Figure 17A**) and heavy chain (**Figure 17B**) of antibody 1.3. The three CDR loops of the chains are shown at the top of the diagrams. The hatched circles are missing residues for this mAb. The squared amino acids are the conserved amino acids at that position.

[0043] **Figures 18A-18B** show Collier Perles 2D representations of the variable domains of the light chain (**Figure 18A**) and heavy chain (**Figure 18B**) of antibody 4.5. The three CDR loops of the chains are shown at the top of the diagrams. The hatched circles are missing residues for this mAb. The squared amino acids are the conserved amino acids at that position.

[0044] **Figures 19A-D** are flow cytometry histograms of Cell Number versus CFSE showing that antibody 1.3 expands human CD4+ and CD8+ cells in vivo. Figures 19A and 19C are controls showing Cell number versus log fluorescence of a control antibody. Figure 19B shows CD4+ Cell number versus log fluorescence using anti-H7CR antibody 1.3. Figure 19D shows CD8+ Cell number versus log fluorescence using anti-H7CR antibody 1.3. Hamster IgG isotype control(Biolegend) was used as control antibody.

[0045] **Figures 20A-H** are flow cytometry scatter plots showing an increase in cells expressing of CD40L, IFNγ and CD107a in an NGS mouse injected with antibody 1.3. Figure 20A shows log anti-CD40L antibody fluorescence versus log anti-CD3 antibody fluorescence

of untreated CD4+ cells. Figure 20B shows log fluorescence of anti-CD40L antibody fluorescence versus log anti-CD3 antibody fluorescence of CD4+ cells treated with anti-H7CR antibody 1.3. Figure 20C shows log fluorescence of anti-IFNγ antibody versus log fluorescence of anti-CD3 antibody in untreated CD4+ cells. Figure 20D show log fluorescence of IFNγ antibody versus log fluorescence of H in CD4+ cells treated with anti-H7CR antibody. Figure 20E shows log anti-CD107a antibody fluorescence versus log anti-CD3 antibody fluorescence of untreated CD8+ cells. Figure 20F shows log fluorescence of anti-CD107a antibody fluorescence versus log anti-CD3 antibody fluorescence of CD8+ cells treated with anti-H7CR antibody 1.3. Figure 20G shows log fluorescence of anti-IFNγ antibody versus log fluorescence of anti-CD3 antibody in untreated CD8+ cells. Figure 20H show log fluorescence of IFNγ antibody versus log fluorescence of H in CD8+ cells treated with anti-H7CR antibody.

[0046] **Figure 21A** is a dot plot of IFN-γ (pg/mL) in resting human PMBCs stimulated with (from left to right) chimeric murine antiH7CR antibody (1.3), negative control (Ctl Ig), OKT3, OKT3 +CD28, chimeric murine antiH7CR antibody (1.3)-immobilized, negative control immobilized, and OKT3 – immobilized. Figure 22B is a dot plot of IFN-γ in activated PMBCs stimulated with (from left to right) chimeric murine antiH7CR antibody (1.3), negative control (Ctl Ig), OKT3, OKT3 +CD28, chimeric murine antiH7CR antibody (1.3) - immobilized, negative control immobilized, and OKT3 – immobilized. **Figure 21B** is a dot plot of IFN-γ in activated PMBCs stimulated with (from left to right) chimeric murine antiH7CR antibody (1.3),, negative control (Ctl Ig), OKT3, OKT3 +CD28, chimeric murine antiH7CR antibody (1.3) -immobilized, negative control (Ctl-Ig) immobilized, and OKT3 – immobilized at 10μg/ml concentration overnight.

[0047] **Figure 22** is a bar graph of Percentage of CFSE diluted T Cell for monocyte-derived dendritic cells matured by 1ng/ml TNFα and 1μg/ml PGE2 for two days. The dendritic cells were incubated with CFSE-labeled autologous T cells for two weeks with 100 ng/ml tetanus toxoid. Cells were treated with (from left to right) 10μg/ml soluble Control IgG4, chimeric murine antiH7CR antibody (1.3), and variants V1-V14 (see Table 10).

[0048] **Figure 23** provides a series of flow cytometry scatter plots of thirty-six humanized H7CR4.5 with the indicated heavy and light chains. Thirty-six variants were incubated with H7CR-GFP fusion protein transfected CHO cells and stained with anti-human Ig secondary

antibody. X axis shows H7CR-GFP expression and Y axis shows variant binding to the transfectants.

DETAILED DESCRIPTION OF THE INVENTION

[0049] Antibodies, humanized variants of antibodies and their antigen-binding fragments thereof and to other molecules that are capable of immunospecifically binding to the B7-H7 counter-receptor, H7CR (also known as B7-H7CR and CD28H) and their uses in the treatment and diagnosis of cancer and other diseases are provided.

[0050] B7-H7 is expressed on antigen presenting cells; it is constitutively expressed on macrophages and inducible on dendritic cells. B7-H7 interacts with a counter-receptor (H7CR) to stimulate the immune system and immune responses (**Figure 1**). H7CR is particularly expressed on naïve T cells, NK cells, and plasmacytoid dendritic cells (especially in the spleen, lymph node and thymus), and its expression is down-regulated on matured or activated cells. Such down-regulation of H7CR impairs activated/memory T cell survival *in vivo*, and leads to a return to immune system quiescence in normal individuals. Thus, the interaction between B7-H7 and H7CR is important for native T cell priming and activated/memory T cell survival *in vivo*. However, H7CR is also seen to be down-regulated in chronically antigen-exposed / exhausted T cells. Molecules, such as B7-H7 Ig and anti-H7CR antibodies, that are capable of binding to H7CR are capable of serving as agonists of T cell proliferation and cytokine production. Such molecules have utility in the treatment of cancer, infectious disease and diseases characterized by an inadequate T cell response. Conversely, molecules, such as anti-B7-H7 antibodies and H7CR Ig, that are capable of blocking the interaction between B7-H7 and H7CR serve as antagonists of T cell proliferation and cytokine production. Such molecules have utility in the treatment of inflammation and in particular, autoimmune disease.

A. B7-H7

[0051] B7-H7 was discovered through a search of *Xenopus* databases as a gene that exhibited significant homology to *Xenopus* B7-H4. The B7-H4 protein possesses 282 amino acid residues, which have been categorized as having an amino terminal extracellular domain, a large hydrophobic transmembrane domain and a very short intracellular domain (consisting of only 2 amino acid residues). Like other B7 family members, B7-H4 possesses a pair of Ig-like regions in its extracellular domain. The B7-H4 protein has an overall structure of a type I transmembrane protein.

[0052] The B7-H7 amino acid sequence was found to be similar to a previously discovered human gene, HHLA2 (human endogenous retrovirus-H long terminal repeat-associating

protein 2 (HHLA2); Mager, D.L. *et al.* (1999) "*Endogenous Retroviruses Provide The Primary Polyadenylation Signal For Two New Human Genes (HHLA2 And HHLA3*," Genomics 59:255-263), that had no known function (Flajnik, M.F. *et al.* (2012) "*Evolution Of The B7 Family: Co-Evolution Of B7H6 And Nkp30, Identification Of A New B7 Family Member, B7H7, And Of B7's Historical Relationship With The MHC*," Immunogenetics 64:571–590).

[0053] The human B7-H7 sequence has been found to have homologs in chicken, opossum, hoofed mammals (*e.g.*, horse, pig), salmon, and shark. However, only pseudogenes have been thus far identified in rodents (mouse and rat). The amino acid sequences of such genes reveal a similar domain structures in all species, with conservation of the canonical residues for Ig superfamily domains.

[0054] Human B7-H7 polypeptide is 414 amino acids in length and has been reported to contain the following: a signal sequence, an extracellular domain, 3 immunoglobulin-like (Ig-like) domains, a transmembrane domain, and a cytoplasmic domain. In particular, the human B7-H7 polypeptide has been reported to contain an Ig-like V-type 1 domain, an Ig-like C-1 type domain, and an Ig-like V-type 2 domain. Multiple naturally occurring variants of B7-H7 exist (*e.g.*, Accession No. Q9UM44-1 (*homo sapiens*), NP_009003 (GI:5901964, *homo sapiens*), and AAD48396 (GI:15726285, *homo sapiens*); see WO 2011/020024).

[0055] The term "native-B7-H7" refers to any naturally occurring B7-H7 amino acid sequence, including immature or precursor and mature forms. Mature forms of B7-H7 include B7-H7 proteins that have been post-translationally modified, for example B7-H7 polypeptides that have had a signal or leader amino acid sequence cleaved. The amino acid sequence of a representative human B7-H7, Accession No. Q9UM44-1, is (**SEQ ID NO:1**):

```
MKAQTALSFF LILITSLSGS QGIFPLAFFI YVPMNEQIVI GRLDEDIILP
SSFERGSEVV IHWKYQDSYK VHSYYKGSDH LESQDPRYAN RTSLFYNEIQ
NGNASLFFRR VSLLDEGIYT CYVGTAIQVI TNKVVLKVGV FLTPVMKYEK
RNTNSFLICS VLSVYPRPII TWKMDNTPIS ENNMEETGSL DSFSINSPLN
ITGSNSSYEC TIENSLLKQT WTGRWTMKDG LHKMQSEHVS LSCQPVNDYF
SPNQDFKVTW SRMKSGTFSV LAYYLSSSQN TIINESRFSW NKELINQSDF
SMNLMDLNLS DSGEYLCNIS SDEYTLLTIH TVHVEPSQET ASHNKGLWIL
VPSAILAAFL LIWSVKCCRA QLEARRSRHP ADGAQQERCC VPPGERCPSA
PDNGEENVPL SGKV
```

[0056] The human B7-H7 has been reported to contain the following predicted domains based on *in silico* analysis: a signal sequence at amino acid residues 1 to 22 of **SEQ ID NO:1**, an Ig-like V-type 1 domain at amino acid residues 61 to 131 of **SEQ ID NO:1**, an Ig-like C-1 type domain at amino acid residues 138 to 222 of **SEQ ID NO:1**, an Ig-like V-type 2 domain at amino acid residues 235 to 328 of **SEQ ID NO:1**, and a transmembrane domain at amino acid residues 345 to 365 of **SEQ ID NO:1**. The predicted dimer interface for human

B7-H7 polypeptide is amino acid residues 141-144, 156, 158, 160, 162, 193-196, 198, 200, 201, 224, and 225 of **SEQ ID NO:1**. The predicted N-linked glycosylation sites for human B7-H7 polypeptide are at amino acid residues 90, 103, and 318 of **SEQ ID NO:1**. Natural variations of human B7-H7 polypeptide include BOT, N344K, and S346R (UniProt Q9UM44) (see, WO 2011/020024, which reference is herein incorporated by reference in its entirety for its teaching of the structure and sequence of human B7-H7).

[0057] A DNA sequence encoding human B7-H7 (**SEQ ID NO:1**) is (**SEQ ID NO:2**):

```
atgaaggcac agacagcact gtctttcttc ctcattctca taacatctct
gagtggatct caaggcatat tccctttggc tttcttcatt tatgttccta
tgaatgaaca aatcgtcatt ggaagacttg atgaagatat aattctccct
tcttcatttg agaggggatc cgaagtcgta atacactgga agtatcaaga
tagctataag gttcatagtt actacaaagg cagtgaccat ttggaaagcc
aagatcccag atatgcaaac aggacatccc ttttctataa tgagattcaa
aatgggaatg cgtcactatt tttcagaaga gtaagccttc tggacgaagg
aatttacacc tgctatgtag gaacagcaat tcaagtgatt acaaacaaag
tggtgctaaa ggtgggagtt tttctcacac ccgtgatgaa gtatgaaaag
aggaacacaa acagcttctt aatatgcagc gtgttaagtg tttatcctcg
tccaattatc acgtggaaaa tggacaacac acctatctct gaaaacaaca
tggaagaaac agggtctttg gattcttttt ctattaacag cccactgaat
attacaggat caaattcatc ttatgaatgt acaattgaaa attcactgct
gaagcaaaca tggacagggc gctggacgat gaaagatggc cttcataaaa
tgcaaagtga acacgtttca ctctcatgtc aacctgtaaa tgattatttt
tcaccaaacc aagacttcaa agttacttgg tccagaatga aaagtgggac
tttctctgtc ctggcttact atctgagctc ctcacaaaat acaattatca
atgaatcccg attctcatgg aacaaagagc tgataaacca gagtgacttc
tctatgaatt tgatggatct taatctttca gacagtgggg aatatttatg
caatatttct tcggatgaat atactttact taccatccac acagtgcatg
tagaaccgag ccaagaaaca gcttcccata acaaaggctt atggattttg
gtgccctctg cgattttggc agcttttctg ctgatttgga gcgtaaaatg
ttgcagagcc cagctagaag ccaggaggag cagacaccct gctgatggag
cccaacaaga aagatgttgt gtccctcctg gtgagcgctg tcccagtgca
cccgataatg gcgaagaaaa tgtgcctctt tcaggaaaag ta
```

[0058] In contrast to human B7-H4, which is widely expressed, human B7-H7 is found to exhibit more limited expression (*e.g.*, expressed in the gut, kidney, lung, epithelial cells and lymphocytes). Human HHLA2 is found on chromosome 3q13.33 near B7.1 and B7.2. B7-H7 is constitutively expressed on macrophages and inducible on dendritic cells (DC).

B. H7CR

[0059] As used herein, the term "native H7CR" refers to any naturally occurring counter-receptor of B7-H7. H7CR is also referred to as B7-H7CR and CD28H. H7CR is expressed by T cells, NK cells, and plasmacytoid dendritic cells. The human H7CR polypeptide is otherwise referred to as transmembrane and immunoglobulin domain containing 2 (TMIGD2) in the literature/databases (Rahimi, N. *et al.* (Epub 2012 Mar 14) "*Identification Of IGPR-1 As A Novel Adhesion Molecule Involved In Angiogenesis*," Molec. Biol. Cell. 23(9):1646-1656) but the function of B7-H7CR was not previously elucidated. Non-limiting examples of Accession Nos. for the amino acid sequence of such native H7CR molecules include:

Q96BF3-1 (homo sapiens), Q96BF3-2 (homo sapiens), NP_653216.1 (GI:21389429; homo sapiens) and NP_653216.2 (GI:281306838; homo sapiens). A representative amino acid sequence (Q96BF3-2) of a native H7CR molecule is provided below as **SEQ ID NO:3**:

```
MGSPGMVLGL LVQIWALQEA SSLSVQQGPN LLQVRQGSQA TLVCQVDQAT
AWERLRVKWT KDGAILCQPY ITNGSLSLGV CGPQGRLSWQ APSHLTLQLD
PVSLNHSGAY VCWAAVEIPE LEEAEGNITR LFVDPDDPTQ NRNRIASFPG
FLFVLLGVGS MGVAAIVWGA WFWGRRSCQQ RDSGNSPGNA FYSNVLYRPR
GAPKKSEDCS GEGKDQRGQS IYSTSFPQPA PRQPHLASRP CPSPRPCPSP
RPGHPVSMVR VSPRPSPTQQ PRPKGFPKVG EE
```

[0060] A DNA sequence encoding human H7CR (**SEQ ID NO:3**) is (**SEQ ID NO:4**):

```
atggggtccc cgggcatggt gctgggcctc ctggtgcaga tctgggccct
gcaagaagcc tcaagcctga gcgtgcagca ggggcccaac ttgctgcagg
tgaggcaggg cagtcaggcg accctggtct gccaggtgga ccaggccaca
gcctgggaac ggctccgtgt taagtggaca aaggatgggg ccatcctgtg
tcaaccgtac atcaccaacg gcagcctcag cctgggggtc tgcgggcccc
agggacggct ctcctggcag gcacccagcc atctcaccct gcagctggac
cctgtgagcc tcaaccacag cggggcgtac gtgtgctggg cggccgtaga
gattcctgag ttggaggagg ctgagggcaa cataacaagg ctctttgtgg
acccagatga ccccacacag aacagaaacc ggatcgcaag cttcccagga
ttcctcttcg tgctgctggg ggtgggaagc atgggtgtgg ctgcgatcgt
gtggggtgcc tggttctggg gccgccgcag ctgccagcaa agggactcag
gtaacagccc aggaaatgca ttctacagca acgtcctata ccggccccgg
ggggccccaa agaagagtga ggactgctct ggagagggga aggaccagag
gggccagagc atttattcaa cctccttccc gcaaccggcc ccccgccagc
cgcacctggc gtcaagaccc tgccccagcc cgagaccctg ccccagcccc
aggcccggcc accccgtctc tatggtcagg gtctctccta gaccaagccc
cacccagcag ccgaggccaa aagggttccc caaagtggga gaggag
```

C. Definitions

[0061] As used herein, a molecule is said to be able to "**immunospecifically bind**" a second molecule if such binding exhibits the specificity and affinity of an antibody to its cognate antigen. Antibodies are said to be capable of "**immunospecifically binding**" to a target region or conformation ("epitope") of an antigen (and in particular, the antigen H7CR) if such binding involves the antigen recognition site of the immunoglobulin molecule. An antibody that immunospecifically binds to a particular antigen may bind to other antigens with lower affinity if the other antigen has some sequence or conformational similarity that is recognized by the antigen recognition site as determined by, *e.g.*, immunoassays, BIACORE® assays, or other assays known in the art, but would not bind to a totally unrelated antigen. Preferably, however, antibodies (and their antigen binding fragments) will not cross-react with other antigens. Antibodies may also bind to other molecules in a way that is not immunospecific, such as to Fc receptors (FcR), by virtue of binding domains in other regions/domains of the molecule that do not involve the antigen recognition site, such as the Fc region.

[0062] The term "**substantially**," as used in the context of binding or exhibited effect, is intended to denote that the observed effect is physiologically or therapeutically relevant.

Thus, for example, a molecule is able to substantially block an activity of H7CR if the extent of blockage is physiologically or therapeutically relevant (for example if such extent is greater than 60% complete, greater than 70% complete, greater than 75% complete, greater than 80% complete, greater than 85% complete, greater than 90% complete, greater than 95% complete, or greater than 97% complete). Similarly, a molecule is said to have substantially the same immunospecificity and/or characteristic as another molecule, if such immunospecificities and characteristics are greater than 60% identical, greater than 70% identical, greater than 75% identical, greater than 80% identical, greater than 85% identical, greater than 90% identical, greater than 95% identical, or greater than 97% identical).

[0063] As used herein, the term "**subject**" is intended to denote a mammal such as a non-primate (*e.g.*, cows, pigs, horses, cats, dogs, rats etc.) and a primate (*e.g.*, monkey and human), most preferably a human. The term "**patient**" is intended to denote a subject receiving a disclosed composition for a diagnostic, therapeutic or prophylactic purpose.

[0064] As used herein, the term "**antibody**" is intended to denote an immunoglobulin molecule that possesses a "variable region" antigen recognition site. The term "variable region" is intended to distinguish such domain of the immunoglobulin from domains that are broadly shared by antibodies (such as an antibody Fc domain). The variable region includes a "hypervariable region" whose residues are responsible for antigen binding. The hypervariable region includes amino acid residues from a "Complementarity Determining Region" or "**CDR**" (*i.e.*, typically at approximately residues 24-34 (L1), 50-56 (L2) and 89-97 (L3) in the light chain variable domain and at approximately residues 27-35 (H1), 50-65 (H2) and 95-102 (H3) in the heavy chain variable domain; Kabat *et al., Sequences of Proteins of Immunological Interest,* 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD. (1991)) and/or those residues from a "hypervariable loop" (*i.e.*, residues 26-32 (L1), 50-52 (L2) and 91-96 (L3) in the light chain variable domain and 26-32 (H1), 53-55 (H2) and 96-101 (H3) in the heavy chain variable domain; Chothia and Lesk, 1987, *J. Mol. Biol.* 196:901-917). "Framework Region" or "FR" residues are those variable domain residues other than the hypervariable region residues as herein defined. The term antibody includes monoclonal antibodies, multi-specific antibodies, human antibodies, humanized antibodies, synthetic antibodies, chimeric antibodies, camelized antibodies (*See e.g.*, Muyldermans *et al.*, 2001, *Trends Biochem. Sci.* 26:230; Nuttall *et al.*, 2000, *Cur. Pharm. Biotech.* 1:253; Reichmann and Muyldermans, 1999, *J. Immunol. Meth.* 231:25; International Publication Nos. WO 94/04678 and WO 94/25591; U.S. Patent No. 6,005,079), single-chain Fvs (scFv) (see, *e.g.*, *see* Pluckthun in *The Pharmacology of Monoclonal Antibodies*, vol.

113, Rosenburg and Moore eds. Springer-Verlag, New York, pp. 269-315 (1994)), single chain antibodies, disulfide-linked Fvs (sdFv), intrabodies, and anti-idiotypic (anti-Id) antibodies (including, *e.g.*, anti-Id and anti-anti-Id antibodies to antibodies disclosed herein). In particular, such antibodies include immunoglobulin molecules of any type (*e.g.*, IgG, IgE, IgM, IgD, IgA and IgY), class (*e.g.*, IgG_1, IgG_2, IgG_3, IgG_4, IgA_1 and IgA_2) or subclass.

[0065] As used herein, the term "**antigen binding fragment**" of an antibody refers to one or more portions of an antibody that contain the antibody's Complementarity Determining Regions ("CDRs") and optionally the framework residues that include the antibody's "variable region" antigen recognition site, and exhibit an ability to immunospecifically bind antigen. Such fragments include Fab', $F(ab')_2$, Fv, single chain (ScFv),and mutants thereof, naturally occurring variants, and fusion proteins including the antibody's "variable region" antigen recognition site and a heterologous protein (*e.g.*, a toxin, an antigen recognition site for a different antigen, an enzyme, a receptor or receptor ligand, *etc.*). As used herein, the term "**fragment**" refers to a peptide or polypeptide including an amino acid sequence of at least 5 contiguous amino acid residues, at least 10 contiguous amino acid residues, at least 15 contiguous amino acid residues, at least 20 contiguous amino acid residues, at least 25 contiguous amino acid residues, at least 40 contiguous amino acid residues, at least 50 contiguous amino acid residues, at least 60 contiguous amino residues, at least 70 contiguous amino acid residues, at least 80 contiguous amino acid residues, at least 90 contiguous amino acid residues, at least 100 contiguous amino acid residues, at least 125 contiguous amino acid residues, at least 150 contiguous amino acid residues, at least 175 contiguous amino acid residues, at least 200 contiguous amino acid residues, or at least 250 contiguous amino acid residues.

[0066] Human, chimeric or humanized antibodies are particularly preferred for *in vivo* use in humans, however, murine antibodies or antibodies of other species may be advantageously employed for many uses (for example, *in vitro* or *in situ* detection assays, acute *in vivo* use, *etc.*). Completely human antibodies are particularly desirable for therapeutic treatment of human subjects.

[0067] Human antibodies can be made by a variety of methods known in the art including phage display methods described above using antibody libraries derived from human immunoglobulin sequences (*see* U.S. Patent Nos. 4,444,887 and 4,716,111; and International Publication Nos. WO 98/46645, WO 98/50433, WO 98/24893, WO 98/16654, WO 96/34096, WO 96/33735, and WO 91/10741). Human antibodies can be produced using transgenic mice which are incapable of expressing functional endogenous immunoglobulins,

but which can express human immunoglobulin genes. For example, the human heavy and light chain immunoglobulin gene complexes may be introduced randomly or by homologous recombination into mouse embryonic stem cells. Alternatively, the human variable region, constant region, and diversity region may be introduced into mouse embryonic stem cells in addition to the human heavy and light chain genes. The mouse heavy and light chain immunoglobulin genes may be rendered non-functional separately or simultaneously with the introduction of human immunoglobulin loci by homologous recombination. In particular, homozygous deletion of the J_H region prevents endogenous antibody production. The modified embryonic stem cells are expanded and microinjected into blastocysts to produce chimeric mice. The chimeric mice are then bred to produce homozygous offspring which express human antibodies. The transgenic mice are immunized using conventional methodologies with a selected antigen, *e.g.*, all or a portion of a polypeptide. Monoclonal antibodies directed against the antigen can be obtained from the immunized, transgenic mice using conventional hybridoma technology (see, *e.g.*, U.S. Patent No. 5,916,771). The human immunoglobulin transgenes harbored by the transgenic mice rearrange during B cell differentiation, and subsequently undergo class switching and somatic mutation. Thus, using such a technique, it is possible to produce therapeutically useful IgG, IgA, IgM and IgE antibodies. For an overview of this technology for producing human antibodies, *see* Lonberg and Huszar (1995, *Int. Rev. Immunol.* 13:65-93, which is incorporated herein by reference in its entirety). For a detailed discussion of this technology for producing human antibodies and human monoclonal antibodies and protocols for producing such antibodies, *see, e.g.*, International Publication Nos. WO 98/24893, WO 96/34096, and WO 96/33735; and U.S. Patent Nos. 5,413,923, 5,625,126, 5,633,425, 5,569,825, 5,661,016, 5,545,806, 5,814,318, and 5,939,598, which are incorporated by reference herein in their entirety. In addition, companies such as Abgenix, Inc. (Freemont, CA) and Medarex (Princeton, NJ) can be engaged to provide human antibodies directed against a selected antigen using technology similar to that described above.

[0068] A "**chimeric antibody**" is a molecule in which different portions of the antibody are derived from different immunoglobulin molecules such as antibodies having a variable region derived from a non-human antibody and a human immunoglobulin constant region. Methods for producing chimeric antibodies are known in the art. *See e.g.*, Morrison, 1985, *Science* 229:1202; Oi *et al.*, 1986, *BioTechniques* 4:214; Gillies *et al.*, 1989, *J. Immunol. Methods* 125:191-202; and U.S. Patent Nos. 6,311,415, 5,807,715, 4,816,567, and 4,816,397. Chimeric antibodies containing one or more CDRs from a non-human species and framework

regions from a human immunoglobulin molecule can be produced using a variety of techniques known in the art including, for example, CDR-grafting (EP 239,400; International Publication No. WO 91/09967; and U.S. Patent Nos. 5,225,539, 5,530,101, and 5,585,089), veneering or resurfacing (EP 592,106; EP 519,596; Padlan, 1991, *Molecular Immunology* 28(4/5):489-498; Studnicka *et al.*, 1994, *Protein Engineering* 7:805; and Roguska *et al.*, 1994, *Proc. Natl. Acad. Sci. USA* 91:969), and chain shuffling (U.S. Patent No. 5,565,332).

[0069] "**Humanized antibodies**" are known in the art (see, *e.g.*, European Patent Nos. EP 239,400, EP 592,106, and EP 519,596; International Publication Nos. WO 91/09967 and WO 93/17105; U.S. Patent Nos. 5,225,539, 5,530,101, 5,565,332, 5,585,089, 5,766,886, and 6,407,213; and Padlan, 1991, *Molecular Immunology* 28(4/5):489-498; Studnicka *et al.*, 1994, *Protein Engineering* 7(6):805-814; Roguska *et al.*, 1994, *PNAS* 91:969-973; Tan *et al.*, 2002, *J. Immunol.* 169:1119-1125; Caldas *et al.*, 2000, *Protein Eng.* 13:353-360; Morea *et al.*, 2000, *Methods* 20:267-79; Baca *et al.*, 1997, *J. Biol. Chem.* 272:10678-10684; Roguska *et al.*, 1996, *Protein Eng.* 9:895-904; Couto *et al.*, 1995, *Cancer Res.* 55 (23 Supp):5973s-5977s; Couto *et al.*, 1995, *Cancer Res.* 55:1717-22; Sandhu, 1994, *Gene* 150:409-10; Pedersen *et al.*, 1994, *J. Mol. Biol.* 235:959-973; Jones *et al.*, 1986, *Nature* 321:522-525; Reichmann *et al.*, 1988, *Nature* 332:323-329; and Presta, 1992, *Curr. Op. Struct. Biol.* 2:593-596). As used herein, the term "humanized antibody" refers to an immunoglobulin including a human framework region and one or more CDR's from a non-human (usually a mouse or rat) immunoglobulin. The non-human immunoglobulin providing the CDR's is called the "donor" and the human immunoglobulin providing the framework is called the "acceptor." Constant regions need not be present, but if they are, they must be substantially identical to human immunoglobulin constant regions, *i.e.*, at least about 85-90%, preferably about 95% or more identical. Hence, all parts of a humanized immunoglobulin, except possibly the CDR's, are substantially identical to corresponding parts of natural human immunoglobulin sequences. A humanized antibody is an antibody containing a humanized light chain and a humanized heavy chain immunoglobulin. For example, a humanized antibody would not encompass a typical chimeric antibody, because, *e.g.*, the entire variable region of a chimeric antibody is non-human. A donor antibody has been "humanized," by the process of "humanization," because the resultant humanized antibody is expected to bind to the same antigen as the donor antibody that provides the CDR's. For the most part, humanized antibodies are human immunoglobulins (recipient antibody) in which hypervariable region residues of the recipient are replaced by hypervariable region residues from a non-human species (donor antibody) such as mouse, rat, rabbit or a non-human

primate having the desired specificity, affinity, and capacity. In some instances, Framework Region (FR) residues of the human immunoglobulin are replaced by corresponding non-human residues. Furthermore, humanized antibodies may include residues which are not found in the recipient antibody or in the donor antibody. These modifications are made to further refine antibody performance. In general, the humanized antibody will include substantially all of at least one, and typically two, variable domains, in which all or substantially all of the hypervariable regions correspond to those of a non-human immunoglobulin and all or substantially all of the FRs are those of a human immunoglobulin sequence. The humanized antibody optionally also will include at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin that immunospecifically binds to an FcγRIIB polypeptide, that has been altered by the introduction of amino acid residue substitutions, deletions or additions (*i.e.,* mutations).

[0070] Human, chimeric or humanized derivatives of anti-human H7CR antibodies are particularly preferred for *in vivo* use in humans, however, murine antibodies or antibodies of other species may be advantageously employed for many uses (for example, *in vitro* or *in situ* detection assays, acute *in vivo* use, *etc.*). Such a human or humanized antibody include amino acid residue substitutions, deletions or additions in one or more non-human CDRs. The humanized antibody derivative may have substantially the same binding, stronger binding or weaker binding when compared to a non-derivative humanized antibody. In specific embodiments, one, two, three, four, or five amino acid residues of the CDR have been substituted, deleted or added (*i.e.,* mutated). Completely human antibodies are particularly desirable for therapeutic treatment of human subjects.

[0071] Such human antibodies can be made by a variety of methods known in the art including phage display methods using antibody libraries derived from human immunoglobulin sequences (*see* U.S. Patent Nos. 4,444,887 and 4,716,111; and International Publication Nos. WO 98/46645, WO 98/50433, WO 98/24893, WO 98/16654, WO 96/34096, WO 96/33735, and WO 91/10741). Such human antibodies can be produced using transgenic mice which are incapable of expressing functional endogenous immunoglobulins, but which can express human immunoglobulin genes. For example, the human heavy and light chain immunoglobulin gene complexes may be introduced randomly or by homologous recombination into mouse embryonic stem cells. Alternatively, the human variable region, constant region, and diversity region may be introduced into mouse embryonic stem cells in addition to the human heavy and light chain genes. The mouse heavy and light chain

immunoglobulin genes may be rendered non-functional separately or simultaneously with the introduction of human immunoglobulin loci by homologous recombination. In particular, homozygous deletion of the J_H region prevents endogenous antibody production. The modified embryonic stem cells are expanded and microinjected into blastocysts to produce chimeric mice. The chimeric mice are then bred to produce homozygous offspring which express human antibodies. The transgenic mice are immunized using conventional methodologies with a selected antigen, *e.g.*, all or a portion of a polypeptide. Monoclonal antibodies directed against the antigen can be obtained from the immunized, transgenic mice using conventional hybridoma technology (see, *e.g.*, U.S. Patent No. 5,916,771). The human immunoglobulin transgenes harbored by the transgenic mice rearrange during B cell differentiation, and subsequently undergo class switching and somatic mutation. Thus, using such a technique, it is possible to produce therapeutically useful IgG, IgA, IgM and IgE antibodies. For an overview of this technology for producing human antibodies, *see* Lonberg and Huszar (1995, *Int. Rev. Immunol.* 13:65-93, which is incorporated herein by reference in its entirety). For a detailed discussion of this technology for producing human antibodies and human monoclonal antibodies and protocols for producing such antibodies, *see, e.g.*, International Publication Nos. WO 98/24893, WO 96/34096, and WO 96/33735; and U.S. Patent Nos. 5,413,923, 5,625,126, 5,633,425, 5,569,825, 5,661,016, 5,545,806, 5,814,318, and 5,939,598, which are incorporated by reference herein in their entirety. In addition, companies such as Abgenix, Inc. (Freemont, CA) and Medarex (Princeton, NJ) can be engaged to provide human antibodies directed against a selected antigen using technology similar to that described above.

[0072] The antibodies used in the disclosed methods may be monospecific. Also of interest are bispecific antibodies, trispecific antibodies or antibodies of greater multispecificity that exhibit specificity to different targets in addition to H7CR, such as other molecules of the immune system. For example, such antibodies may bind to both H7CR and to an antigen that is important for targeting the antibody to a particular cell type or tissue (for example, to an antigen associated with a cancer antigen of a tumor being treated). In another embodiment, such multispecific antibody binds to both B7-H7 and to H7CR, and thus serves to promote association of cells possessing such molecules to thereby agonize T cell responses. Such molecules have particular utility in the treatment of cancer and infectious disease. In another embodiment, such multispecific antibody binds to molecules (receptors or ligands) involved in alternative or supplemental immunomodulatory pathways, such as CTLA4, TIM3, TIM4, OX40, CD40, GITR, 4-1-BB, B7-H4, LIGHT or LAG3, in order to enhance the

immunomodulatory effects. Furthermore, the multispecific antibody may bind to effecter molecules such as cytokines (*e.g.*, IL-7, IL-15, IL-12, IL-4 TGF-beta, IL-10, IL-17, IFNg, Flt3, BLys) and chemokines (*e.g.*, CCL21), which may be particularly relevant for modulating both acute and chronic immune responses.

[0073] DNA sequences coding for preferred human acceptor framework sequences include but are not limited to FR segments from the human germline VH segment VH1-18 and JH6 and the human germline VL segment VK-A26 and JK4. In a specific embodiment, one or more of the CDRs are inserted within framework regions using routine recombinant DNA techniques. The framework regions may be naturally occurring or consensus framework regions, and preferably human framework regions (*see*, *e.g.*, Chothia *et al.*, 1998, "*Structural Determinants In The Sequences Of Immunoglobulin Variable Domain*," *J. Mol. Biol.* 278: 457-479 for a listing of human framework regions).

[0074] The disclosed humanized or chimeric antibody may contain substantially all of at least one, and typically two, variable domains in which all or substantially all of the CDR regions correspond to those of a non-human immunoglobulin (*i.e.*, donor antibody) and all or substantially all of the framework regions are those of a human immunoglobulin consensus sequence. Preferably, the antibody also includes at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin. The constant domains of the antibodies may be selected with respect to the proposed function of the antibody, in particular the effector function which may be required. In some embodiments, the constant domains of the antibodies are (or include) human IgA, IgD, IgE, IgG or IgM domains. In a specific embodiment, human IgG constant domains, especially of the IgG1 and IgG3 isotypes are used, when the humanized antibodies are intended for therapeutic uses and antibody effector functions such as antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) activity are needed. In alternative embodiments, IgG2 and IgG4 isotypes are used when the antibody is intended for therapeutic purposes and antibody effector function is not required. The Fc constant domains of the antibodies can include one or more amino acid modifications which alter antibody effector functions such as those disclosed in U.S. Patent Application Publication Nos. 2005/0037000 and 2005/0064514.

[0075] In some embodiments, the antibody contains both the light chain as well as at least the variable domain of a heavy chain. In other embodiments, the antibody may further include one or more of the CH1, hinge, CH2, CH3, and CH4 regions of the heavy chain. The antibody can be selected from any class of immunoglobulins, including IgM, IgG, IgD, IgA and IgE, and any isotype, including IgG_1, IgG_2, IgG_3 and IgG_4. In some embodiments, the

constant domain is a complement fixing constant domain where it is desired that the antibody exhibit cytotoxic activity, and the class is typically IgG_1. In other embodiments, where such cytotoxic activity is not desirable, the constant domain may be of the IgG_2 class. The antibody may include sequences from more than one class or isotype, and selecting particular constant domains to optimize desired effector functions is within the ordinary skill in the art.

[0076] In a specific aspect, the present disclosure provides an Fc variant, wherein the Fc region includes at least one modification (e.g., amino acid substitutions, amino acid insertions, amino acid deletions) at one or more positions selected from the group consisting of 228, 234, 235 and 331 as numbered by the EU index as set forth in Kabat et al. (1991, NIH Publication 91-3242, National Technical Information Service, Springfield, Va.). In one aspect, the modification is at least one substitution selected from the group consisting of 228P, 234F, 235E, 235F, 235Y, and 331S as numbered by the EU index as set forth in Kabat.

[0077] In another specific aspect, the present disclosure provides an Fc variant, wherein the Fc region is an IgG4 Fc region and includes at least one modification at one or more positions selected from the group consisting of 228 and 235 as numbered by the EU index as set forth in Kabat. In still another specific aspect, the Fc region is an IgG4 Fc region and the non-naturally occurring amino acids are selected from the group consisting of 228P, 235E and 235Y as numbered by the EU index as set forth in Kabat.

[0078] In another specific aspect, the present disclosure provides an Fc variant, wherein the Fc region includes at least one non-naturally occurring amino acid at one or more positions selected from the group consisting of 239, 330 and 332 as numbered by the EU index as set forth in Kabat. In one aspect, the modification is at least one substitution selected from the group consisting of 239D, 330L, 330Y, and 332E as numbered by the EU index as set forth in Kabat. See, U.S. Patent Number 7,317,091, incorporated herein by referenced in its entirety.

[0079] In a specific aspect, the present disclosure provides an Fc variant 1, wherein the Fc region includes at least one non-naturally occurring amino acid at one or more positions selected from the group consisting of 252, 254, and 256 as numbered by the EU index as set forth in Kabat. In one aspect, the modification is at least one substitution selected from the group consisting of 252Y, 254T and 256E as numbered by the EU index as set forth in Kabat. See, U.S. Patent Number 7,083,784, incorporated herein by reference in its entirety.

[0080] In certain aspects, the present disclosure provides an Fc variant, wherein the Fc region includes a non-naturally occurring amino acid at position 428 as numbered by the EU index as set forth in Kabat. In one aspect, the modification at position 428 is selected from the group consisting of 428T, 428L, 428F, and 428S as numbered by the EU index as set

forth in Kabat. See, U.S. Patent Number 7,670,600, incorporated herein by reference in its entirety. In another aspect, an Fc variant may further includes a non-naturally occurring amino acid at position 434 as numbered by the EU index as set forth in Kabat. In one aspect, the modification at position 434 is selected from the group consisting of 434A, 434S, and 434F as numbered by the EU index as set forth in Kabat. In other aspects, the present disclosure provides an Fc variant, wherein the Fc region includes a non-naturally occurring amino acid at positions 428 and 434 as numbered by the EU index as set forth in Kabat. In a specific aspect, the Fc region includes 428L, 434S. See, U.S. Patent Number 8,088,376.

[0081] The framework and CDR regions of a humanized antibody need not correspond precisely to the parental sequences, *e.g.*, the donor CDR or the consensus framework may be mutagenized by substitution, insertion or deletion of at least one residue so that the CDR or framework residue at that site does not correspond to either the consensus or the donor antibody. Such mutations, however, are preferably not extensive. Usually, at least 75% of the humanized antibody residues will correspond to those of the parental framework region (FR) and CDR sequences, more often 90%, and most preferably greater than 95%. Humanized antibodies can be produced using variety of techniques known in the art, including, but not limited to, CDR-grafting (European Patent No. EP 239,400; International Publication No. WO 91/09967; and U.S. Patent Nos. 5,225,539, 5,530,101, and 5,585,089), veneering or resurfacing (European Patent Nos. EP 592,106 and EP 519,596; Padlan, 1991, *Molecular Immunology* 28(4/5):489-498; Studnicka *et al.*, 1994, *Protein Engineering* 7(6):805-814; and Roguska *et al.*, 1994, *Proc. Natl. Acad. Sci.* 91:969-973), chain shuffling (U.S. Patent No. 5,565,332), and techniques disclosed in, *e.g.*, U.S. Patent Nos. 6,407,213, 5,766,886, 5,585,089, International Publication No. WO 9317105, Tan *et al.*, 2002, *J. Immunol.* 169:1119-25, Caldas *et al.*, 2000, *Protein Eng.* 13:353-60, Morea *et al.*, 2000, *Methods* 20:267-79, Baca *et al.*, 1997, *J. Biol. Chem.* 272:10678-84, Roguska *et al.*, 1996, *Protein Eng.* 9:895-904, Couto *et al.*, 1995, *Cancer Res.* 55 (23 Supp):5973s-5977s, Couto *et al.*, 1995, *Cancer Res.* 55:1717-22, Sandhu, 1994, *Gene* 150:409-10, Pedersen *et al.*, 1994, J. *Mol. Biol.* 235:959-73, Jones *et al.*, 1986, *Nature* 321:522-525, Riechmann *et al.*, 1988, *Nature* 332:323, and Presta, 1992, *Curr. Op. Struct. Biol.* 2:593-596. Often, framework residues in the framework regions will be substituted with the corresponding residue from the CDR donor antibody to alter, preferably improve, antigen binding. These framework substitutions are identified by methods well known in the art, *e.g.*, by modeling of the interactions of the CDR and framework residues to identify framework residues important for antigen binding and sequence comparison to identify unusual framework residues at

particular positions. (*See, e.g.*, Queen *et al.*, U.S. Patent No. 5,585,089; U.S. Publication Nos. 2004/0049014 and 2003/0229208; U.S. Patent Nos. 6,350,861; 6,180,370; 5,693,762; 5,693,761; 5,585,089; and 5,530,101 and Riechmann *et al.*, 1988, *Nature* 332:323).

[0082] The antibodies may be produced by any method known in the art useful for the production of polypeptides, *e.g.*, *in vitro* synthesis, recombinant DNA production, and the like. Preferably, the humanized antibodies are produced by recombinant DNA technology. The antibodies may be produced using recombinant immunoglobulin expression technology. The recombinant production of immunoglobulin molecules, including humanized antibodies are described in U.S. Patent No. 4,816,397 (Boss *et al.*), U.S. Patent Nos. 6,331,415 and 4,816,567 (both to Cabilly *et al.*), U.K. patent GB 2,188,638 (Winter *et al.*), and U.K. patent GB 2,209,757. Techniques for the recombinant expression of immunoglobulins, including humanized immunoglobulins, can also be found, in Goeddel *et al.*, Gene Expression Technology Methods in Enzymology Vol. 185 Academic Press (1991), and Borreback, Antibody Engineering, W. H. Freeman (1992). Additional information concerning the generation, design and expression of recombinant antibodies can be found in Mayforth, Designing Antibodies, Academic Press, San Diego (1993).

[0083] An exemplary process for the production of the recombinant chimeric antibodies may include the following: a) constructing, by conventional molecular biology methods, an expression vector that encodes and expresses an antibody heavy chain in which the CDRs and variable region of a murine anti-human H7CR monoclonal antibody are fused to an Fc region derived from a human immunoglobulin, thereby producing a vector for the expression of a chimeric antibody heavy chain; b) constructing, by conventional molecular biology methods, an expression vector that encodes and expresses an antibody light chain of the murine anti-human H7CR monoclonal antibody, thereby producing a vector for the expression of chimeric antibody light chain; c) transferring the expression vectors to a host cell by conventional molecular biology methods to produce a transfected host cell for the expression of chimeric antibodies; and d) culturing the transfected cell by conventional cell culture techniques so as to produce chimeric antibodies.

[0084] An exemplary process for the production of the recombinant humanized antibodies may include the following: a) constructing, by conventional molecular biology methods, an expression vector that encodes and expresses an anti-human H7CR heavy chain in which the CDRs and a minimal portion of the variable region framework that are required to retain donor antibody binding specificity are derived from a non-human immunoglobulin, such as a murine anti-human H7CR monoclonal antibody, and the remainder of the antibody is derived

from a human immunoglobulin, thereby producing a vector for the expression of a humanized antibody heavy chain; b) constructing, by conventional molecular biology methods, an expression vector that encodes and expresses an antibody light chain in which the CDRs and a minimal portion of the variable region framework that are required to retain donor antibody binding specificity are derived from a non-human immunoglobulin, such as a murine anti-human H7CR monoclonal antibody, and the remainder of the antibody is derived from a human immunoglobulin, thereby producing a vector for the expression of humanized antibody light chain; c) transferring the expression vectors to a host cell by conventional molecular biology methods to produce a transfected host cell for the expression of humanized antibodies; and d) culturing the transfected cell by conventional cell culture techniques so as to produce humanized antibodies.

[0085] With respect to either exemplary method, host cells may be co-transfected with such expression vectors, which may contain different selectable markers but, with the exception of the heavy and light chain coding sequences, are preferably identical. This procedure provides for equal expression of heavy and light chain polypeptides. Alternatively, a single vector may be used which encodes both heavy and light chain polypeptides. The coding sequences for the heavy and light chains may include cDNA or genomic DNA or both. The host cell used to express the recombinant antibody may be either a bacterial cell such as *Escherichia coli*, or more preferably a eukaryotic cell (*e.g.*, a Chinese hamster ovary (CHO) cell or a HEK-293 cell). The choice of expression vector is dependent upon the choice of host cell, and may be selected so as to have the desired expression and regulatory characteristics in the selected host cell. Other cell lines that may be used include, but are not limited to, CHO-K1, NSO, and PER.C6 (Crucell, Leiden, Netherlands).

[0086] Any of the disclosed antibodies can be used to generate anti-idiotype antibodies using techniques well known to those skilled in the art (see, *e.g.*, Greenspan, N.S. *et al.* (1989) "*Idiotypes: Structure And Immunogenicity*," FASEB J. 7:437-444; and Nisinoff, A. (1991) "*Idiotypes: Concepts And Applications*," J. Immunol. 147(8):2429-2438).

[0087] The binding properties of the disclosed antibodies can, if desired, be further improved by screening for variants that exhibit such desired characteristics. For example, such antibodies can be generated using various phage display methods known in the art. In phage display methods, functional antibody domains are displayed on the surface of phage particles which carry the polynucleotide sequences encoding them. In a particular embodiment, such phage can be utilized to display antigen binding domains, such as Fab and Fv or disulfide-bond stabilized Fv, expressed from a repertoire or combinatorial antibody

library (*e.g.*, human or murine). Phage expressing an antigen binding domain that binds the antigen of interest can be selected or identified with antigen, *e.g.*, using labeled antigen or antigen bound or captured to a solid surface or bead. Phage used in these methods are typically filamentous phage, including fd and M13. The antigen binding domains are expressed as a recombinantly fused protein to either the phage gene III or gene VIII protein. Examples of phage display methods that can be used to make the immunoglobulins, or fragments thereof, include those disclosed in Brinkman, U. *et al.* (1995) "*Phage Display Of Disulfide-Stabilized Fv Fragments*," *J. Immunol. Methods*, 182:41-50, 1995; Ames, R.S. *et al.* (1995) "*Conversion Of Murine Fabs Isolated From A Combinatorial Phage Display Library To Full Length Immunoglobulins*," *J. Immunol. Methods*, 184:177-186; Kettleborough, C.A. *et al.* (1994) "*Isolation Of Tumor Cell-Specific Single-Chain Fv From Immunized Mice Using Phage-Antibody Libraries And The Re-Construction Of Whole Antibodies From These Antibody Fragments*," Eur. J. Immunol., 24:952-958, 1994; Persic, L. *et al.* (1997) "*An Integrated Vector System For The Eukaryotic Expression Of Antibodies Or Their Fragments After Selection From Phage Display Libraries*," *Gene*, 187:9-18; Burton, D.R. *et al.* (1994) "*Human Antibodies From Combinatorial Libraries*," Adv. Immunol. 57:191-280; PCT Publications WO 92/001047; WO 90/02809; WO 91/10737; WO 92/01047; WO 92/18619; WO 93/11236; WO 95/15982; WO 95/20401; and U.S. Patents Nos. 5,698,426; 5,223,409; 5,403,484; 5,580,717; 5,427,908; 5,750,753; 5,821,047; 5,571,698; 5,427,908; 5,516,637; 5,780,225; 5,658,727; 5,733,743 and 5,969,108.

[0088] As described in the above references, after phage selection, the antibody coding regions from the phage can be isolated and used to generate whole antibodies, including humanized antibodies, or any other desired fragments, and expressed in any desired host, including mammalian cells, insect cells, plant cells, yeast, and bacteria, *e.g.*, as described in detail below. For example, techniques to recombinantly produce Fab, Fab' and $F(ab')_2$ fragments can also be employed using methods known in the art (such as those disclosed in PCT Publication WO 92/22324; Mullinax, R.L. *et al.* (1992) "*Expression Of A Heterodimeric Fab Antibody Protein In One Cloning Step*," *BioTechniques*, 12(6):864-869; and Sawai *et al.* (1995) "*Direct Production Of The Fab Fragment Derived From The Sperm Immobilizing Antibody Using Polymerase Chain Reaction And cDNA Expression Vectors*," Am. J. Reprod. Immunol. 34:26-34; and Better, M. *et al.* (1988) "*Escherichia coli Secretion Of An Active Chimeric Antibody Fragment*," Science 240:1041-1043). Examples of techniques which can be used to produce single-chain Fvs and antibodies include those described in U.S. Patent Nos. 4,946,778 and 5,258,498; Huston, J.S. *et al.* (1991) "*Protein Engineering Of Single-*

Chain Fv Analogs And Fusion Proteins," Methods in Enzymology 203:46-88; Shu, L. *et al.*, "*Secretion Of A Single-Gene-Encoded Immunoglobulin From Myeloma Cells*," Proc. Natl. Acad. Sci. (USA) 90:7995-7999; and Skerra. A. *et al.* (1988) "*Assembly Of A Functional Immunoglobulin Fv Fragment In Escherichia coli*," Science 240:1038-1040.

[0089] Phage display technology can be used to increase the affinity of the disclosed antibodies for H7CR. This technique would be useful in obtaining high affinity antibodies that could be used in the combinatorial methods. This technology, referred to as affinity maturation, employs mutagenesis or CDR walking and re-selection using such receptors or ligands (or their extracellular domains) or an antigenic fragment thereof to identify antibodies that bind with higher affinity to the antigen when compared with the initial or parental antibody (*See, e.g.,* Glaser, S.M. *et al.* (1992) "*Antibody Engineering By Codon-Based Mutagenesis In A Filamentous Phage Vector System*," J. Immunol. 149:3903-3913). Mutagenizing entire codons rather than single nucleotides results in a semi-randomized repertoire of amino acid mutations. Libraries can be constructed consisting of a pool of variant clones each of which differs by a single amino acid alteration in a single CDR and which contain variants representing each possible amino acid substitution for each CDR residue. Mutants with increased binding affinity for the antigen can be screened by contacting the immobilized mutants with labeled antigen. Any screening method known in the art can be used to identify mutant antibodies with increased avidity to the antigen (*e.g.*, ELISA) (see, *e.g.*, Wu, H. *et al.* (1998) "*Stepwise In Vitro Affinity Maturation Of Vitaxin, An Alphav Beta3-Specific Humanized Mab*," Proc. Natl. Acad. Sci. (USA) 95(11):6037-6042; Yelton, D.E. *et al.* (1995) "*Affinity Maturation Of The BR96 Anti-Carcinoma Antibody By Codon-Based Mutagenesis*," J. Immunol. 155:1994-2004). CDR walking which randomizes the light chain may be used possible (see, Schier *et al.* (1996) "*Isolation Of Picomolar Affinity Anti-C-Erbb-2 Single-Chain Fv By Molecular Evolution Of The Complementarity Determining Regions In The Center Of The Antibody Binding Site*," J. Mol. Biol. 263:551-567).

[0090] Random mutagenesis can also be used to identify improved CDRs. Phage display technology can alternatively be used to increase (or decrease) CDR affinity. This technology, referred to as affinity maturation, employs mutagenesis or "CDR walking" and re-selection uses the target antigen or an antigenic fragment thereof to identify antibodies having CDRs that bind with higher (or lower) affinity to the antigen when compared with the initial or parental antibody (see, *e.g.*, Glaser, S.M. *et al.* (1992) "*Antibody Engineering By Codon-Based Mutagenesis In A Filamentous Phage Vector System*," J. Immunol. 149:3903-3913).

Mutagenizing entire codons rather than single nucleotides results in a semi-randomized repertoire of amino acid mutations. Libraries can be constructed consisting of a pool of variant clones each of which differs by a single amino acid alteration in a single CDR and which contain variants representing each possible amino acid substitution for each CDR residue. Mutants with increased (or decreased) binding affinity for the antigen can be screened by contacting the immobilized mutants with labeled antigen. Any screening method known in the art can be used to identify mutant antibodies with increased (or decreased) avidity to the antigen (e.g., ELISA) (see, Wu, H. *et al.* (1998) "*Stepwise In Vitro Affinity Maturation Of Vitaxin, An Alphav Beta3-Specific Humanized Mab*," Proc. Natl. Acad. Sci. (USA) 95(11):6037-6042; Yelton, D.E. *et al.* (1995) "*Affinity Maturation Of The BR96 Anti-Carcinoma Antibody By Codon-Based Mutagenesis*," J. Immunol. 155:1994-2004). CDR walking which randomizes the light chain may be used possible (see, Schier *et al.* (1996) "*Isolation Of Picomolar Affinity Anti-C-Erbb-2 Single-Chain Fv By Molecular Evolution Of The Complementarity Determining Regions In The Center Of The Antibody Binding Site*," J. Mol. Biol. 263:551-567).

[0091] Methods for accomplishing such affinity maturation are described for example in: Krause, J.C. *et al.* (2011) "*An Insertion Mutation That Distorts Antibody Binding Site Architecture Enhances Function Of A Human Antibody*," MBio. 2(1) pii: e00345-10. doi: 10.1128/mBio.00345-10; Kuan, C.T. *et al.* (2010) "*Affinity-Matured Anti-Glycoprotein NMB Recombinant Immunotoxins Targeting Malignant Gliomas And Melanomas*," Int. J. Cancer 10.1002/ijc.25645; Hackel, B.J. *et al.* (2010) "*Stability And CDR Composition Biases Enrich Binder Functionality Landscapes*," J. Mol. Biol. 401(1):84-96; Montgomery, D.L. *et al.* (2009) "*Affinity Maturation And Characterization Of A Human Monoclonal Antibody Against HIV-1 gp41*," MAbs 1(5):462-474; Gustchina, E. *et al.* (2009) "*Affinity Maturation By Targeted Diversification Of The CDR-H2 Loop Of A Monoclonal Fab Derived From A Synthetic Naïve Human Antibody Library And Directed Against The Internal Trimeric Coiled-Coil Of Gp41 Yields A Set Of Fabs With Improved HIV-1 Neutralization Potency And Breadth*," Virology 393(1):112-119; Finlay, W.J. *et al.* (2009) "*Affinity Maturation Of A Humanized Rat Antibody For Anti-RAGE Therapy: Comprehensive Mutagenesis Reveals A High Level Of Mutational Plasticity Both Inside And Outside The Complementarity-Determining Regions*," J. Mol. Biol. 388(3):541-558; Bostrom, J. *et al.* (2009) "*Improving Antibody Binding Affinity And Specificity For Therapeutic Development*," Methods Mol. Biol. 525:353-376; Steidl, S. *et al.* (2008) "*In Vitro Affinity Maturation Of Human GM-CSF Antibodies By Targeted CDR-Diversification*," Mol. Immunol. 46(1):135-144; and Barderas,

R. *et al.* (2008) "Affinity maturation of antibodies assisted by *in silico* modeling," Proc. Natl. Acad. Sci. (USA) 105(26):9029-9034.

[0092] The production and use of "**derivatives**" of any of the above-described antibodies and their antigen-binding fragments are also provided.

[0093] The term "**derivative**" refers to an antibody or antigen-binding fragment thereof that immunospecifically binds to an antigen but which includes, one, two, three, four, five or more amino acid substitutions, additions, deletions or modifications relative to a "parental" (or wild-type) molecule. Such amino acid substitutions or additions may introduce naturally occurring (*i.e.*, DNA-encoded) or non-naturally occurring amino acid residues. The term "derivative" encompasses, for example, chimeric or humanized variants of any of antibodies 1.3, 4.5 or 7.8, as well as variants having altered CH1, hinge, CH2, CH3 or CH4 regions, so as to form, for example antibodies, *etc.*, having variant Fc regions that exhibit enhanced or impaired effector or binding characteristics. The term "derivative" additionally encompasses non amino acid modifications, for example, amino acids that may be glycosylated (*e.g.*, have altered mannose, 2-N-acetylglucosamine, galactose, fuctose, glucose, sialic acid, 5-N-acetylneuraminic acid, 5-glycolneuraminic acid, *etc.* content), acetylated, pegylated, phosphorylated, amidated, derivatized by known protecting/blocking groups, proteolytic cleavage, linked to a cellular ligand or other protein, *etc.* In some embodiments, the altered carbohydrate modifications modulate one or more of the following: solubilization of the antibody, facilitation of subcellular transport and secretion of the antibody, promotion of antibody assembly, conformational integrity, and antibody-mediated effector function. In a specific embodiment the altered carbohydrate modifications enhance antibody mediated effector function relative to the antibody lacking the carbohydrate modification. Carbohydrate modifications that lead to altered antibody mediated effector function are well known in the art (for example, *see* Shields, R.L. *et al.* (2002) "*Lack Of Fucose On Human IgG N-Linked Oligosaccharide Improves Binding To Human Fcgamma RIII And Antibody-Dependent Cellular Toxicity.*," J. Biol. Chem. 277(30): 26733-26740; Davies J. *et al.* (2001) "*Expression Of GnTIII In A Recombinant Anti-CD20 CHO Production Cell Line: Expression Of Antibodies With Altered Glycoforms Leads To An Increase In ADCC Through Higher Affinity For FC Gamma RIII*," Biotechnology & Bioengineering 74(4): 288-294). Methods of altering carbohydrate contents are known to those skilled in the art, *see, e.g.*, Wallick, S.C. *et al.* (1988) "*Glycosylation Of A VH Residue Of A Monoclonal Antibody Against Alpha (1---6) Dextran Increases Its Affinity For Antigen*," J. Exp. Med. 168(3): 1099-1109; Tao, M.H. *et al.* (1989) "*Studies Of Aglycosylated Chimeric Mouse-Human IgG. Role Of Carbohydrate*

In The Structure And Effector Functions Mediated By The Human IgG Constant Region," J. Immunol. 143(8): 2595-2601; Routledge, E.G. *et al.* (1995) "*The Effect Of Aglycosylation On The Immunogenicity Of A Humanized Therapeutic CD3 Monoclonal Antibody*," Transplantation 60(8):847-53; Elliott, S. *et al.* (2003) "*Enhancement Of Therapeutic Protein In Vivo Activities Through Glycoengineering*," Nature Biotechnol. 21:414-21; Shields, R.L. *et al.* (2002) "*Lack Of Fucose On Human IgG N-Linked Oligosaccharide Improves Binding To Human Fcgamma RIII And Antibody-Dependent Cellular Toxicity.*," J. Biol. Chem. 277(30): 26733-26740).

[0094] In some embodiments, a humanized antibody is a derivative. Such a humanized antibody includes amino acid residue substitutions, deletions or additions in one or more non-human CDRs. The humanized antibody derivative may have substantially the same binding, better binding, or worse binding when compared to a non-derivative humanized antibody. In specific embodiments, one, two, three, four, or five amino acid residues of the CDR have been substituted, deleted or added (*i.e.,* mutated).

[0095] A derivative antibody or antibody fragment may be modified by chemical modifications using techniques known to those of skill in the art, including, but not limited to, specific chemical cleavage, acetylation, formulation, metabolic synthesis of tunicamycin, *etc.* In one embodiment, an antibody derivative will possess a similar or identical function as the parental antibody. In another embodiment, an antibody derivative will exhibit an altered activity relative to the parental antibody. For example, a derivative antibody (or fragment thereof) can bind to its epitope more tightly or be more resistant to proteolysis than the parental antibody.

[0096] Substitutions, additions or deletions in the derivatized antibodies may be in the Fc region of the antibody and may thereby serve to modify the binding affinity of the antibody to one or more FcγR. Methods for modifying antibodies with modified binding to one or more FcγR are known in the art, *see, e.g.*, PCT Publication Nos. WO 04/029207, WO 04/029092, WO 04/028564, WO 99/58572, WO 99/51642, WO 98/23289, WO 89/07142, WO 88/07089, and U.S. Patent Nos. 5,843,597 and 5,642,821. Some embodiments encompass antibodies whose Fc region will have been deleted (for example, an Fab or F(ab)2, *etc.*) or modified so that the molecule will exhibit diminished or no Fc receptor (FcR) binding activity, or will exhibit enhanced antibody-dependent cell-mediated cytotoxicity (ADCC) or complement dependent cytotoxicity (CDC) activities. Some embodiments, encompasses antibodies that have altered affinity for an activating FcγR, *e.g.*, FcγRIIIA. Preferably such modifications

also have an altered Fc-mediated effector function. Modifications that affect Fc-mediated effector function are well known in the art (*see* U.S. Patent No. 6,194,551, and WO 00/42072). In one particular embodiment, the modification of the Fc region results in an antibody with an altered antibody-mediated effector function, an altered binding to other Fc receptors (*e.g.*, Fc activation receptors), an altered antibody-dependent cell-mediated cytotoxicity (ADCC) activity, an altered C1q binding activity, an altered complement-dependent cytotoxicity activity (CDC), a phagocytic activity, or any combination thereof.

[0097] Derivatized antibodies may be used to alter the half-lives (*e.g.*, serum half-lives) of parental antibodies in a mammal, preferably a human. Preferably such alteration will result in a half-life of greater than 15 days, preferably greater than 20 days, greater than 25 days, greater than 30 days, greater than 35 days, greater than 40 days, greater than 45 days, greater than 2 months, greater than 3 months, greater than 4 months, or greater than 5 months. The increased half-lives of the humanized antibodies or fragments thereof in a mammal, preferably a human, results in a higher serum titer of said antibodies or antibody fragments in the mammal, and thus, reduces the frequency of the administration of said antibodies or antibody fragments and/or reduces the concentration of said antibodies or antibody fragments to be administered. Antibodies or fragments thereof having increased *in vivo* half-lives can be generated by techniques known to those of skill in the art. For example, antibodies or fragments thereof with increased *in vivo* half-lives can be generated by modifying (*e.g.*, substituting, deleting or adding) amino acid residues identified as involved in the interaction between the Fc domain and the FcRn receptor. The humanized antibodies may be engineered to increase biological half-lives (*see, e.g.* U.S. Patent No. 6,277,375). For example, humanized antibodies may be engineered in the Fc-hinge domain to have increased *in vivo* or serum half-lives.

[0098] Antibodies or fragments thereof with increased *in vivo* half-lives can be generated by attaching to said antibodies or antibody fragments polymer molecules such as high molecular weight polyethyleneglycol (PEG). PEG can be attached to said antibodies or antibody fragments with or without a multifunctional linker either through site-specific conjugation of the PEG to the N– or C- terminus of said antibodies or antibody fragments or via epsilon-amino groups present on lysine residues. Linear or branched polymer derivatization that results in minimal loss of biological activity will be used. The degree of conjugation will be closely monitored by SDS-PAGE and mass spectrometry to ensure proper conjugation of PEG molecules to the antibodies. Unreacted PEG can be separated from antibody-PEG conjugates by, *e.g.*, size exclusion or ion-exchange chromatography.

[0099] The antibodies may also be modified by the methods and coupling agents described by Davis *et al.* (*See* U.S. Patent No. 4,179,337) in order to provide compositions that can be injected into the mammalian circulatory system with substantially no immunogenic response.

[00100] The framework residues of the humanized antibodies can be modified. Framework residues in the framework regions may be substituted with the corresponding residue from the CDR donor antibody to alter, preferably improve, antigen binding. These framework substitutions are identified by methods well known in the art, *e.g.*, by modeling of the interactions of the CDR and framework residues to identify framework residues important for antigen binding and sequence comparison to identify unusual framework residues at particular positions. (*See*, *e.g.*, U.S. Patent No. 5,585,089; and Riechmann, L. *et al.* (1988) "*Reshaping Human Antibodies For Therapy*," Nature 332:323-327).

[00101] Anti-human H7CR antibodies (and more preferably, humanized antibodies) and antigen-binding fragments thereof that are recombinantly fused or chemically conjugated (including both covalently and non-covalently conjugations) to a heterologous molecule (*i.e.*, an unrelated molecule) are also provided. The fusion does not necessarily need to be direct, but may occur through linker sequences.

[00102] In one embodiment such heterologous molecules are polypeptides having at least 10, at least 20, at least 30, at least 40, at least 50, at least 60, at least 70, at least 80, at least 90 or at least 100 amino acids. Such heterologous molecules may alternatively be enzymes, hormones, cell surface receptors, drug moieties, such as: **toxins** (such as abrin, ricin A, pseudomonas exotoxin (*i.e.*, PE-40), diphtheria toxin, ricin, gelonin, or pokeweed antiviral protein), **proteins** (such as tumor necrosis factor, interferon (*e.g.*, α-interferon, β-interferon), nerve growth factor, platelet derived growth factor, tissue plasminogen activator, or an apoptotic agent (*e.g.*, tumor necrosis factor-α, tumor necrosis factor-β)), **biological response modifiers** (such as, for example, a lymphokine (*e.g.*, 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 macrophage colony stimulating factor, ("M-CSF")), or growth factors (*e.g.*, growth hormone ("GH"))), **cytotoxins** (*e.g.*, a cytostatic or cytocidal agent, such as paclitaxol, 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), **antimetabolites** (*e.g.*, methotrexate, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil decarbazine),

alkylating agents (*e.g.*, mechlorethamine, thioepa chlorambucil, melphalan, BiCNU® (carmustine; BSNU) and lomustine (CCNU), cyclothosphamide, busulfan, dibromomannitol, streptozotocin, mitomycin C, and cisdichlorodiamine platinum (II) (DDP) cisplatin), anthracyclines (*e.g.*, daunorubicin (formerly daunomycin) and doxorubicin), **antibiotics** (*e.g.*, dactinomycin (formerly actinomycin), bleomycin, mithramycin, and anthramycin (AMC)), or **anti-mitotic** agents (*e.g.*, vincristine and vinblastine).

[00103] Techniques for conjugating such therapeutic moieties 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.), 1985, pp. 243-56, Alan R. Liss, Inc.); Hellstrom *et al.*, "*Antibodies For Drug Delivery*", in CONTROLLED DRUG DELIVERY *(2nd Ed.)*, Robinson *et al.* (eds.), 1987, pp. 623-53, Marcel Dekker, Inc.); Thorpe, "*Antibody Carriers Of Cytotoxic Agents In Cancer Therapy: A Review*", in MONOCLONAL ANTIBODIES '84: BIOLOGICAL AND CLINICAL APPLICATIONS, Pinchera *et al.* (eds.), 1985, pp. 475-506); "*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.), 1985, pp. 303-16, Academic Press; and Thorpe *et al.* (1982) "*The Preparation And Cytotoxic Properties Of Antibody-Toxin Conjugates*," Immunol. Rev. 62:119-158.

[00104] In one embodiment, the antibodies or fusion molecules include an Fc portion. The Fc portion of such molecules may be varied by isotype or subclass, may be a chimeric or hybrid, and/or may be modified, for example to improve effector functions, control of half-life, tissue accessibility, augment biophysical characteristics such as stability, and improve efficiency of production (and less costly). Many modifications useful in construction of disclosed fusion proteins and methods for making them are known in the art, see for example Mueller, J.P. *et al.* (1997) "*Humanized Porcine VCAM-Specific Monoclonal Antibodies With Chimeric IgG2/G4 Constant Regions Block Human Leukocyte Binding To Porcine Endothelial Cells*," Mol. Immun. 34(6):441-452, Swann, P.G. (2008) "*Considerations For The Development Of Therapeutic Monoclonal Antibodies*," Curr. Opin. Immun. 20:493-499 (2008), and Presta, L.G. (2008) "*Molecular Engineering And Design Of Therapeutic Antibodies*," Curr. Opin. Immun. 20:460-470. In some embodiments the Fc region is the native IgG1, IgG2, or IgG4 Fc region. In some embodiments the Fc region is a hybrid, for example a chimeric consisting of IgG2/IgG4 Fc constant regions. Modifications to the Fc region include, but are not limited to, IgG4 modified to prevent binding to Fc gamma receptors and complement, IgG1 modified to improve binding to one or more Fc gamma

receptors, IgG1 modified to minimize effector function (amino acid changes), IgG1 with altered/no glycan (typically by changing expression host), and IgG1 with altered pH-dependent binding to FcRn, and IgG4 with serine at amino acid resident #228 in the hinge region changed to proline (S228P) to enhance stability. The Fc region may include the entire hinge region, or less than the entire hinge region.

[00105] The therapeutic outcome in patients treated with rituximab (a chimeric mouse/human IgG1 monoclonal antibody against CD20) for non-Hodgkin's lymphoma or Waldenstrom's macroglobulinemia correlated with the individual's expression of allelic variants of Fcγ receptors with distinct intrinsic affinities for the Fc domain of human IgG1. In particular, patients with high affinity alleles of the low affinity activating Fc receptor CD16A (FcγRIIIA) showed higher response rates and, in the cases of non-Hodgkin's lymphoma, improved progression-free survival. In another embodiment, the Fc domain may contain one or more amino acid insertions, deletions or substitutions that reduce binding to the low affinity inhibitory Fc receptor CD32B (FcγRIIB) and retain wild-type levels of binding to or enhance binding to the low affinity activating Fc receptor CD16A (FcγRIIIA).

[00106] Another embodiment includes IgG2-4 hybrids and IgG4 mutants that have reduce binding to FcR which increase their half-life. Representative IG2-4 hybrids and IgG4 mutants are described in Angal, S. *et al.* (1993) "*A Single Amino Acid Substitution Abolishes The Heterogeneity Of Chimeric Mouse/Human (Igg4) Antibody*," Molec. Immunol. 30(1):105-108; Mueller, J.P. *et al.* (1997) "*Humanized Porcine VCAM-Specific Monoclonal Antibodies With Chimeric Igg2/G4 Constant Regions Block Human Leukocyte Binding To Porcine Endothelial Cells*," Mol. Immun. 34(6):441-452; and U.S. Patent No. 6,982,323. In some embodiments the IgG1 and/or IgG2 domain is deleted for example, Angal, s. *et al.* describe IgG1 and IgG2 having serine 241 replaced with a proline.

[00107] In a preferred embodiment, the Fc domain contains amino acid insertions, deletions or substitutions that enhance binding to CD16A. A large number of substitutions in the Fc domain of human IgG1 that increase binding to CD16A and reduce binding to CD32B are known in the art and are described in Stavenhagen, J.B. *et al.* (2007) "*Fc Optimization Of Therapeutic Antibodies Enhances Their Ability To Kill Tumor Cells In Vitro And Controls Tumor Expansion In Vivo Via Low-Affinity Activating Fcgamma Receptors*," Cancer Res. 57(18):8882-8890. Exemplary variants of human IgG1 Fc domains with reduced binding to CD32B and/or increased binding to CD16A contain F243L, R929P, Y300L, V305I or P296L substitutions. These amino acid substitutions may be present in a human IgG1 Fc domain in

any combination. In one embodiment, the human IgG1 Fc domain variant contains a F243L, R929P and Y300L substitution. In another embodiment, the human IgG1 Fc domain variant contains a F243L, R929P, Y300L, V305I and P296L substitution. In another embodiment, the human IgG1 Fc domain variant contains an N297Q substitution, as this mutation abolishes FcR binding.

[00108] Any of the described molecules can be fused to marker sequences, such as a peptide, to facilitate purification. In preferred embodiments, the marker amino acid sequence is a hexa-histidine peptide, the hemagglutinin "HA" tag, which corresponds to an epitope derived from the influenza hemagglutinin protein (Wilson, I.A. *et al.* (1984) "*The Structure Of An Antigenic Determinant In A Protein*," Cell, 37:767-778) and the "flag" tag (Knappik, A. *et al.* (1994) "*An Improved Affinity Tag Based On The FLAG Peptide For The Detection And Purification Of Recombinant Antibody Fragments*," Biotechniques 17(4):754-761).

[00109] The antibodies or their antigen-binding fragments can be conjugated to a diagnostic or therapeutic agent or any other molecule for which serum half-life is desired to be increased. The antibodies can be used diagnostically (*in vivo*, *in situ* or *in vitro*) to, for example, monitor the development or progression of a disease, disorder or infection as part of a clinical testing procedure to, *e.g.*, determine the efficacy of a given treatment regimen. Detection can be facilitated by coupling the antibody to a detectable substance. Examples of detectable substances include various enzymes, prosthetic groups, fluorescent materials, luminescent materials, bioluminescent materials, radioactive materials, positron emitting metals, and nonradioactive paramagnetic metal ions. The detectable substance may be coupled or conjugated either directly to the antibody or indirectly, through an intermediate (such as, for example, a linker known in the art) using techniques known in the art. *See*, for example, U.S. Patent No. 4,741,900 for metal ions which can be conjugated to antibodies for use as diagnostics. Such diagnosis and detection can be accomplished by coupling the antibody to detectable substances including, but not limited to, various enzymes, enzymes including, but not limited to, horseradish peroxidase, alkaline phosphatase, beta-galactosidase, or acetylcholinesterase; prosthetic group complexes such as, but not limited to, streptavidin/biotin and avidin/biotin; fluorescent materials such as, but not limited to, umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; luminescent material such as, but not limited to, luminol; bioluminescent materials such as, but not limited to, luciferase, luciferin, and aequorin; radioactive material such as, but not limited to, bismuth (^{213}Bi), carbon (^{14}C), chromium (^{51}Cr), cobalt (^{57}Co), fluorine (^{18}F), gadolinium (^{153}Gd, ^{159}Gd), gallium (^{68}Ga,

^{67}Ga), germanium (^{68}Ge), holmium (^{166}Ho), indium (^{115}In, ^{113}In, ^{112}In, ^{111}In), iodine (^{131}I, ^{125}I, ^{123}I, ^{121}I), lanthanium (^{140}La), lutetium (^{177}Lu), manganese (^{54}Mn), molybdenum (^{99}Mo), palladium (^{103}Pd), phosphorous (^{32}P), praseodymium (^{142}Pr), promethium (^{149}Pm), rhenium (^{186}Re, ^{188}Re), rhodium (^{105}Rh), ruthemium (^{97}Ru), samarium (^{153}Sm), scandium (^{47}Sc), selenium (^{75}Se), strontium (^{85}Sr), sulfur (^{35}S), technetium (^{99}Tc), thallium (^{201}Ti), tin (^{113}Sn, ^{117}Sn), tritium (^{3}H), xenon (^{133}Xe), ytterbium (^{169}Yb, ^{175}Yb), yttrium (^{90}Y), zinc (^{65}Zn); positron emitting metals using various positron emission tomographies, and nonradioactive paramagnetic metal ions.

[00110] The molecules can be conjugated to a second antibody to form an antibody heteroconjugate as described by Segal in U.S. Patent No. 4,676,980. Such heteroconjugate antibodies may additionally bind to haptens (such as fluorescein, *etc.*), or to cellular markers (*e.g.*, 4-1-BB, B7-H4, B7-H7, CD4, CD8, CD14, CD25, CD27, CD40, CD68, CD163, CTLA4, GITR, LAG-3, OX40, TIM3, TIM4, TLR2, LIGHT, *etc.*) or to cytokines (*e.g.*, IL-7, IL-15, IL-12, IL-4 TGF-beta, IL-10, IL-17, IFNg, Flt3, BLys) or chemokines (*e.g.*, CCL21), *etc.*

[00111] The molecules may be attached to solid supports, which are particularly useful for immunoassays or purification of the target antigen or of other molecules that are capable of binding to target antigen that has been immobilized to the support via binding to an antibody or antigen-binding fragment. Such solid supports include, but are not limited to, glass, cellulose, polyacrylamide, nylon, polystyrene, polyvinyl chloride or polypropylene.

[00112] Nucleic acid molecules (DNA or RNA) that encode any such antibodies, fusion proteins or fragments, as well as vector molecules (such as plasmids) that are capable of transmitting or of replication such nucleic acid molecules and expressing such antibodies, fusion proteins or fragments in a cell line are also provided. The nucleic acids can be single-stranded, double-stranded, may contain both single-stranded and double-stranded portions.

D. Preferred Modulator Compositions

[00113] As used herein the term "**modulate**" relates to a capacity to alter an effect or result. In particular, a humanized variant of an anti-human H7CR antibody or any of its antigen-binding fragments that immunospecifically binds human H7CR or molecules that physiospecifically bind H7CR are capable of modulating the binding between H7CR and its cognate ligands and/or of modulating the signal transduction that occurs as a consequence of H7CR – cognate ligand binding.

[00114] The antibody can be an agonist antibody that agonizes H7CR. Agonizing antibodies can bind H7CR and stimulate signal transduction through H7CR.

[00115] In one embodiment, the antibodies, or fragments thereof, or fusion molecules immunospecifically bind to H7CR but are substantially incapable of blocking H7CR's interaction with B7-H7 *in vitro*, or in a recipient subject or patient. As used herein, a molecule that is "**substantially incapable of blocking H7CR's interaction with B7-H7**" denotes that the presence of such molecule attenuates H7CR - B7-H7 interactions by less than 50%, more preferably less than 40%, still more preferably less than 30%, still more preferably less than 20%, still more preferably less than 10%, still more preferably less than 5%, still more preferably less than 1%, and most preferably completely fails to attenuate such interaction, as measured by any of the assays disclosed herein. Such antibodies, fragments and fusion molecules have particular utility as therapeutic agents or in diagnostic, cytological and histological assays for H7CR (or B7-H7) expression. Additionally, multi-specific anti-H7CR antibodies, anti-H7CR antigen-binding fragments and their respective fusion products that have the added ability to bind B7-H7 or other cellular ligands or receptors have particular utility in facilitating the co-localization of cells expressing such ligands or receptors to cells that express H7CR.

[00116] In a second embodiment, the antibodies, or fragments thereof, or fusion molecules immunospecifically bind to H7CR and are capable of substantially blocking H7CR's interaction with B7-H7 *in vitro*, or in a recipient subject or patient. As used herein, a molecule that is "**capable of substantially blocking H7CR's interaction with B7-H7**" denotes that the provision of such molecule attenuates H7CR - B7-H7 interactions by more than 50%, more preferably by more than 60%, more than 70%, more than 80%, more than 90%, more than 95%, more than 99% or most preferably completely attenuates such interaction, as measured by any of the assays disclosed herein. Such antibodies, fragments and fusion molecules have particular utility in attenuating the biological effects of B7-H7 – H7CR interactions.

[00117] A preferred embodiment provides humanized antibodies and fragments or human antibodies and fragments.

[00118] Most preferably, such molecules will possess sufficient affinity and avidity to be able to bind to H7CR when expressed at an endogenous concentration and arrayed on the surface of a subject's cells. The term "**endogenous concentration**" refers to the level at which a molecule is natively expressed (*i.e.*, in the absence of expression vectors or recombinant promoters) in a normal, cancer or pathogen-infected cell.

(1) Preferred Rodent Anti-Human H7CR Antibodies and Their CDRs

[00119] Such molecules can be produced by screening hybridoma lines for those that produce antibody that are immunospecific for human H7CR, and then optionally screening amongst such lines for those exhibiting modulating activity (*e.g.*, neutralizing activity, agonizing activity, altered signal transducing activity, *etc.*). In one embodiment the antibodies are hamster anti-human H7CR clones: 1.3, 4.5 and 7.8. These antibodies are capable of binding to human H7CR and are substantially incapable of blocking H7CR's interaction with B7-H7. The antibodies expressed by the anti-human H7CR clones were sequenced to reveal their variable domains. CDR sequences of the variable domains are shown in bold and underlined:

Anti-Human H7CR Clone 1.3

Light Chain Variable Region:

DIVMTQSPSS LAVSAGEKVT ISCLSS**QSLF** **SSNTNRNY**LN WYLQKPGQSP
KLLIY**HAS**TR LTGVPDRFIG SGSGTDFTLT ISSVQAEDLG DYYC**QHHYET**
PLTFGDGTKL EIK **(SEQ ID NO:5)**

Heavy Chain Variable Region:

QIQLQESGPG LVKPSQSLSL TCSVT**GFSIS** **TSG**YYWTWIR QFPGKRLEWM
GY**INYGGGT**S YNPSLKSRIS ITRDTSKNQF LLHLNSVTTE DTATYCC**ATM**
ADRFAFFDVW GQGIQVTVSS **(SEQ ID NO:6)**

Anti-Human H7CR Clone 4.5

Light Chain Variable Region:

DIVMTQSPSS LAVSAGEKVT ISCLSS**QSLF** **SSNTKRNY**LN WYLQKPGQSP
KLLIY**HAS**TR LTGVPGRFIG SGSGTDFTLT VSTVQAEDLG DYFC**QQHYET**
PLTFGDGTRL EIK **(SEQ ID NO:7)**

Heavy Chain Variable Region:

QIQLQESGPG LVKPSQSLSL TCSVT**GFSIT** **TGGYY**WNWIR QFPGKKLEWM
GY**IYTSGRT**S YNPSLKSRIS ITRDTSKNQF FLQLNSMTTE DTATYYC**ADM**
ADKGGWFAYW GQGTLVTVSS **(SEQ ID NO:8)**

Anti-Human H7CR Clone 7.8

Light Chain Variable Region:

DIVMTQSPSS LTVSAGEKVT ISC**LSSQSLF** **SSNTNRNYLS** WYLQRPGQSP
KLLIY**HASTR** **LT**GVPGRFIG SGSGTDFTLT VSTVQAGDLG DYFC**QQHYVT**
PLTFGDGTRL EIK **(SEQ ID NO:9)**

Heavy Chain Variable Region:

QIQLQESGPG LVKPSQSLSL TCSVT**GFSIT** **TGG**YYWNWIR QFPGKKLEWM
GY**IYSSGRT**S YNPSLKSRIS ITRDTSKNQF FLQLNSVTTE DTATYYC**ADM**
ADKGGWFDYW GQGTLVTVSS **(SEQ ID NO:10)**

(2) Consensus CDRs of the Anti-Human H7CR Antibodies

[00120] Analyses of the CDRs of the identified antibodies were conducted in order to identify consensus CDR sequences and likely variant CDR sequences that would provide similar binding attributes. Such variant CDRs were computed using Blosum62.iij analysis according to **Table 1**. **Table 1** presents the Blosum62.iij substitution scores. The higher the score the more conservative the substitution and thus the more likely the substitution will not affect function.

Table 1

	A	R	N	D	C	Q	E	G	H	I	L	K	M	F	P	S	T	W	Y	V
A	+4	-1	-2	-2	0	-1	-1	0	-2	-1	-1	-1	-1	-2	-1	+1	0	-3	-2	0
R	-1	+5	0	-2	-3	+1	0	-2	0	-3	-2	+2	-1	-3	-2	-1	-1	-3	-2	-3
N	-2	0	+6	+1	-3	0	0	0	+1	-3	-3	0	-2	-3	-2	+1	0	-4	-2	-3
D	-2	-2	+1	+6	-3	0	+2	-1	-1	-3	-4	-1	-3	-3	-1	0	-1	-4	-3	-3
C	0	-3	-3	-3	+9	-3	-4	-3	-3	-1	-1	-3	-1	-2	-3	-1	-1	-2	-2	-1
Q	-1	+1	0	0	-3	+5	+2	-2	0	-3	-2	+1	0	-3	-1	0	-1	-2	-1	-2
E	-1	0	0	+2	-4	+2	+5	-2	0	-3	-3	+1	-2	-3	-1	0	-1	-3	-2	-2
G	0	-2	0	-1	-3	-2	-2	+6	-2	-4	-4	-2	-3	-3	-2	0	-2	-2	-3	-3
H	-2	0	+1	-1	-3	0	0	-2	+8	-3	-3	-1	-2	-1	-2	-1	-2	-2	+2	-3
I	-1	-3	-3	-3	-1	-3	-3	-4	-3	+4	+2	-3	+1	0	-3	-2	-1	-3	-1	+3
L	-1	-2	-3	-4	-1	-2	-3	-4	-3	+2	+4	-2	+2	0	-3	-2	-1	-2	-1	+1
K	-1	+2	0	-1	-3	+1	+1	-2	-1	-3	-2	+5	-1	-3	-1	0	-1	-3	-2	-2
M	-1	-1	-2	-3	-1	0	-2	-3	-2	+1	+2	-1	+5	0	-2	-1	-1	-1	-1	+1
F	-2	-3	-3	-3	-2	-3	-3	-3	-1	0	0	-3	0	+6	-4	-2	-2	+1	+3	-1
P	-1	-2	-2	-1	-3	-1	-1	-2	-2	-3	-3	-1	-2	-4	+7	-1	-1	-4	-3	-2
S	+1	-1	+1	0	-1	0	0	0	-1	-2	-2	0	-1	-2	-1	+4	+1	-3	-2	-2
T	0	-1	0	-1	-1	-1	-1	-2	-2	-1	-1	-1	-1	-2	-1	+1	+5	-2	-2	0
W	-3	-3	-4	-4	-2	-2	-3	-2	-2	-3	-2	-3	-1	+1	-4	-3	-2	+11	+2	-3
Y	-2	-2	-2	-3	-2	-1	-2	-3	+2	-1	-1	-2	-1	+3	-3	-2	-2	+2	+7	-1
V	0	-3	-3	-3	-1	-2	-2	-3	-3	+3	+1	-2	+1	-1	-2	-2	0	-3	-1	+4

[00121] Antibodies and antigen-binding fragments having 1, 2, 3, 4, 5 or 6 variant CDRs are disclosed. A substantial number of distinct CDRs were identified permitting the recognition of CDR residues that are likely to be required in any variant of a particular identified CDR. Such residues are shown in boldface in **Table 2** and **Table 3.** For those residues that are found to vary among the compared CDRs, the substitution scores of **Table 1** provide a method for determining the identities of permitted substitutions. For example, if a particular residue of a particular CDR is found to vary as R or S, then since R and S have a substitution score of -1, any substitution of R or S having a substitution score of -1 or greater are as likely as the observed variants (R or S) (or are more likely than R or S) to create a variant CDR

having binding attributes that are sufficiently similar to those of the particular CDR to permit the variant CDR to be employed in lieu thereof so as to form a functional anti-H7CR antibody or antigen-binding fragment. For each position, the selection of a residue having a higher substitution score is preferred over the selection of a residue having a lower substitution score.

[00122] **Table 2** presents an analysis of the light chain CDRs of the anti-H7CR antibodies and provides the consensus sequence of the observed and preferred variant light chain ("LC") anti-H7CR CDRs.

Table 2: Anti-H7CR Light Chain CDRs

Light Chain CDR1																					
Antibody	**Sequence**																				**SEQ ID NO**
1.3	Q	S	L	F	S	S	N	T	N	R	N	Y									**29**
4.5	Q	S	L	F	S	S	N	T	K	R	N	Y									**30**
7.8	Q	S	L	F	S	S	N	T	N	R	N	Y									**29**
LC CDR1 Consensus Sequence:	Q	S	L	F	S	S	N	T	**X_1**	R	N	Y									**31**
X_1 is	N or K or a substitution having an equal or greater substitution score (*i.e.*, ≥ 0): R, N, Q, E, K, or S																				
Light Chain CDR2																					
Antibody	**Sequence**																				**SEQ ID NO**
1.3	H	A	S																		**32**
4.5	H	A	S																		**32**
7.8	H	A	S																		**32**
LC CDR2 Consensus Sequence:	H	A	S																		**32**
Light Chain CDR3																					
Antibody	**Sequence**																				**SEQ ID NO**
1.3	Q	H	H	Y	E	T	P	L	T												**45**
4.5	Q	Q	H	Y	E	T	P	L	T												**46**
7.8	Q	Q	H	Y	V	T	P	L	T												**47**
LC CDR3 Consensus Sequence:	Q	**X_1**	H	Y	**X_2**	T	P	L	T												**48**
X_1 is	H or Q or a substitution having an equal or greater substitution score (*i.e.*, ≥ 0): R, N, Q, E, or H																				
X_2 is	E or V or a substitution having an equal or greater substitution score (*i.e.*, ≥ -2): A, Q, E, K, M, P, S, T, Y, or V																				

[00123] **Table 3** presents an analysis of the heavy chain CDRs of the anti-H7CR antibodies and provides the consensus sequence of the observed and preferred variant anti-H7CR heavy chain ("HC") CDRs.

Table 3: Anti-H7CR Heavy Chain CDRs

Heavy Chain CDR1									
Antibody	**Sequence**								**SEQ ID NO**
1.3	G	F	S	I	S	T	S	G	**49**
4.5	G	F	S	I	T	T	G	G	**50**

Table 3: Anti-H7CR Heavy Chain CDRs										
7.8	G	F	S	I	T	T	G	G		**50**
HC CDR1 Consensus Sequence:	G	F	D	I	**X_1**	T	**X_2**	G		**51**
X_1 is	S or T or a substitution having an equal or greater substitution score (*i.e.*, ≥ +1): S or T									
X_2 is	S or G or a substitution having an equal or greater substitution score (*i.e.*, ≥ 0): A, N, G, or S									
Heavy Chain CDR2										
Antibody	**Sequence**									**SEQ ID NO**
1.3	I	N	Y	G	G	G	T			**52**
4.5	I	Y	T	S	G	R	T			**53**
7.8	I	Y	S	S	G	R	T			**54**
HC CDR2 Consensus Sequence:	I	**X_1**	**X_2**	**X_3**	G	**X_4**	T			**55**
X_1 is	N or Y or a substitution having an equal or greater substitution score (*i.e.*, ≥ -2): A, R, N, Q, E, H, K, M, S, T, Y									
X_2 is	Y, T or S or a substitution having an equal or greater substitution score (*i.e.*, ≥ -2): A, R, N, C, Q, E, H, I, L, K, M, F, S, T, Y, or V									
X_3 is	S or G or a substitution having an equal or greater substitution score (*i.e.*, ≥ 0): A, N, G, or S									
X_4 is	G or R or a substitution having an equal or greater substitution score (*i.e.*, ≥ -2): A, R, N, D, Q, E, G, H, K, P, S, or T									
Heavy Chain CDR3										
Antibody	**Sequence**									**SEQ ID NO**
1.3	A	T	M	A	D	R	F	A	F	**56**
4.5	A	D	M	A	D	K	G	G	W	**57**
7.8	A	D	M	A	D	K	G	G	W	**58**
HC CDR3 Consensus Sequence:	A	**X_1**	M	A	D	**X_2**	**X_3**	**X_4**	**X_5**	**59**
X_1 is	T or D or a substitution having an equal or greater substitution score (*i.e.*, ≥ -1): N, D, Q, E, K, P, S, or T									
X_2 is	R or K or a substitution having an equal or greater substitution score (*i.e.*, ≥ +2): R, or K									
X_3 is	F or G or a substitution having an equal or greater substitution score (*i.e.*, ≥ -3): A, R, N, D, C, Q, E, G, H, K, M, F, S, T, W, Y, or V									
X_4 is	A or G or a substitution having an equal or greater substitution score (*i.e.*, ≥ 0): A, G, or S									
X_5 is	F or W or a substitution having an equal or greater substitution score (*i.e.*, ≥ +1): F, W, or Y									
X_6 is	A or D or a substitution having an equal or greater substitution score (*i.e.*, ≥ -4): A, R, N, D, C, Q, E, G, H, I, L, K, M, F, P, S, T, W, Y, or V									
X_7 is	V or Y or a substitution having an equal or greater substitution score (*i.e.*, ≥ -2): A, R, N, D, Q, E, G, H, K, P, S, or T									

[00124] Thus, in addition to antibodies and antigen-binding fragments thereof that possess the CDRs of the anti-H7CR antibodies: 1.3, 4.5 and 7.8, antibodies and antigen-binding fragments thereof that possess CDRs having the above-described light and/or heavy chain consensus sequences are also provided.

[00125] The antibodies or fragments thereof include an amino acid sequence of a variable heavy chain and/or variable light chain that is at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical to the amino acid sequence of the variable heavy chain and/or light chain of the hamster monoclonal antibody produced by any of the above clones, and

which exhibit immunospecific binding to H7CR. Additionally, the antibodies or fragments thereof can include a CDR that is at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical to the amino acid sequence of a CDR of the above-listed clones and which exhibit immunospecific binding to H7CR. The determination of percent identity of two amino acid sequences can be determined by BLAST protein comparison.

[00126] In a specific embodiment, an antibody or an antigen-binding fragment thereof contains one, two, three, four, five, or more preferably, all 6 CDRs of the above-described preferred antibodies and will exhibit the ability to bind to human H7CR.

(3) Preferred Humanized Anti-Human H7CR Antibodies and Their CDRs

[00127] Multiple preferred light and heavy chain humanized derivatives of anti-human H7CR antibodies 1.3 and 4.5 were prepared.

(a) Humanized Variants Of Anti-Human H7CR Antibody 1.3

[00128] The amino acid sequences of the Light Chain Variable Region of preferred humanized variants of anti-human H7CR antibody 1.3, derived from the **IGKV4-1*01** acceptor framework, are shown below (CDRs are shown underlined):

1. VL1A IGKV4-1*01 (Humanized 1):

   DIVMTQSPDS LAVSLGERAT INCKSS**QSLF** **SSNTNRNY**LA WYQQKPGQPP KLLIY**HAS**TR ESGVPDRFSG SGSGTDFTLT ISSLQAEDVA VYYC**QHHYET** **PLT**FGQGTKL EIK **(SEQ ID NO:17)**

2. VL1B IGKV4-1*01 (Humanized 2):

   DIVMTQSPDS LAVSLGERAT INCKSS**QSLF** **SSNTNRNY**LN WYQQKPGQSP KLLIY**HAS**TR LSGVPDRFSG SGSGTDFTLT ISSLQAEDVA DYYC**QHHYET** **PLT**FGDGTKL EIK **(SEQ ID NO:18)**

3. VL1C IGKV4-1*01 (Humanized 3):

   DIVMTQSPDS LAVSLGERAT INCLSS**QSLF** **SSNTNRNY**LN WYLQKPGQSP KLLIY**HAS**TR LSGVPDRFIG SGSGTDFTLT ISSLQAEDVG DYYC**QHHYET** **PLT**FGDGTKL EIK **(SEQ ID NO:19)**

[00129] The amino acid sequences of the **Light Chain Variable Region** of preferred humanized variants of anti-human H7CR antibody 1.3 derived from the **IGKV2D-28*01** acceptor framework, are shown below (CDRs are shown underlined):

1. VL2A IGKV2D-28*01 (Humanized 1):

   DIVMTQSPLS LPVTPGEPAS ISCRSS**QSLF** **SSNTNRNY**LD WYLQKPGQSP QLLIY**HAS**NR ASGVPDRFSG SGSGTDFTLK ISRVEAEDVG VYYC**QHHYET** **PLT**FGDGTKL EIK **(SEQ ID NO:20)**

2. VL2B IGKV2D-28*01 (Humanized 2):

DIVMTQSPLS LPVTPGEPAS ISCRSS**QSLF** **SSNTNRNY**LN WYLQKPGQSP KLLIY**HAS**TR ASGVPDRFSG SGSGTDFTLK ISRVEAEDVG VYYC**QHHYET** **PLT**FGDGTKL EIK **(SEQ ID NO:21)**

3. VL2C IGKV2D-28*01 (Humanized 3):

DIVMTQSPLS LPVTPGEPAS ISCLSS**QSLF** **SSNTNRNY**LN WYLQKPGQSP KLLIY**HAS**TR LSGVPDRFSG SGSGTDFTLK ISRVEAEDVG DYYC**QHHYET** **PLT**FGDGTKL EIK **(SEQ ID NO:22)**

[00130] The amino acid sequences of the **Heavy Chain Variable Region** of preferred humanized variants of anti-human H7CR antibody 1.3 derived from the **IGHV4-31*02** acceptor framework, are shown below (CDRs are shown underlined):

1. VH1A IGHV4-31*02 (Humanized 1):

QVQLQESGPG LVKPSQTLSL TCTVS**GFSIS** **TSG**YYWSWIR QHPGKGLEWI GY**INYGGGT**Y YNPSLKSRVT ISVDTSKNQF SLKLSSVTAA DTAVYYC**ATM** **ADRFAFFDV**W GQGTMVTVSS **(SEQ ID NO:23)**

2. VH1B IGHV4-31*02 (Humanized 2):

QVQLQESGPG LVKPSQTLSL TCTVS**GFSIS** **TSG**YYWSWIR QHPGKRLEWI GY**INYGGGT**S YNPSLKSRVT ISRDTSKNQF SLKLSSVTAA DTAVYCC**ATM** **ADRFAFFDV**W GQGTMVTVSS **(SEQ ID NO:24)**

3. VH1C IGHV4-31*02 (Humanized 3):

QVQLQESGPG LVKPSQTLSL TCTVS**GFSIS** **TSG**YYWSWIR QFPGKRLEWM GY**INYGGGT**S YNPSLKSRVT ISRDTSKNQF SLKLSSVTAA DTATYCC**ATM** **ADRFAFFDV**W GQGTMVTVSS **(SEQ ID NO:25)**

[00131] The amino acid sequences of the **Heavy Chain Variable Region** of preferred humanized variants of anti-human H7CR antibody 1.3, derived from the **AAY33199.1** acceptor framework, are shown below (CDRs are shown underlined):

1. VH2A AAY33199.1 (Humanized 1):

QVQLQESGPG LVKPAQTLSL TCTVS**GFSIS** **TSG**YYWSWIR QYPGKGLEWI GY**INYGGGT**Y YNPSLKSRVT ISVDTSKNQF SLKLTSVTAA DTAVYHC**ATM** **ADRFAFFDV**W GQGTMVTVSS **(SEQ ID NO:26)**

2. VH2B AAY33199.1 (Humanized 2):

QVQLQESGPG LVKPAQTLSL TCTVS**GFSIS** **TSG**YYWSWIR QYPGKRLEWI GY**INYGGGT**S YNPSLKSRVT ISRDTSKNQF SLKLTSVTAA DTATYCC**ATM** **ADRFAFFDV**W GQGTMVTVSS **(SEQ ID NO:27)**

3. VH2C AAY33199.1 (Humanized 3):

QVQLQESGPG LVKPAQTLSL TCTVS**GFSIS** **TSG**YYWSWIR QFPGKRLEWM GY**INYGGGT**S YNPSLKSRVT ISRDTSKNQF SLKLTSVTAA DTATYCC**ATM** **ADRFAFFDV**W GQGTMVTVSS **(SEQ ID NO:28)**

[00132] The antibodies, and their antigen-binding fragments can include any of the 36 combinations of the above-described humanized variants of anti-human H7CR antibody 1.3. Specifically, such antibodies include the combinations shown in **Table 4**:

Table 4

Humanized Variants of anti-human H7CR Antibody 1.3

Humanized Variant No.	Light Chain	SEQ ID NO.	Heavy Chain	SEQ ID NO.
1	VL1A IGKV4-1*01 **(Humanized 1)**	**17**	VH1A IGHV4-31*02 **(Humanized 1)**	**23**
2	VL1A IGKV4-1*01 **(Humanized 1)**	**17**	VH1B IGHV4-31*02 **(Humanized 2)**:	**24**
3	VL1A IGKV4-1*01 **(Humanized 1)**	**17**	VH1C IGHV4-31*02 **(Humanized 3)**	**25**
4	VL1A IGKV4-1*01 **(Humanized 1)**	**17**	VH2A AAY33199.1 **(Humanized 1)**	**26**
5	VL1A IGKV4-1*01 **(Humanized 1)**	**17**	VH2B AAY33199.1 **(Humanized 2)**	**27**
6	VL1A IGKV4-1*01 **(Humanized 1)**	**17**	VH2C AAY33199.1 **(Humanized 3)**	**28**
7	VL1B IGKV4-1*01 **(Humanized 2)**	**18**	VH1A IGHV4-31*02 **(Humanized 1)**	**23**
8	VL1B IGKV4-1*01 **(Humanized 2)**	**18**	VH1B IGHV4-31*02 **(Humanized 2)**:	**24**
9	VL1B IGKV4-1*01 **(Humanized 2)**	**18**	VH1C IGHV4-31*02 **(Humanized 3)**	**25**
10	VL1B IGKV4-1*01 **(Humanized 2)**	**18**	VH2A AAY33199.1 **(Humanized 1)**	**26**
11	VL1B IGKV4-1*01 **(Humanized 2)**	**18**	VH2B AAY33199.1 **(Humanized 2)**	**27**
12	VL1B IGKV4-1*01 **(Humanized 2)**	**18**	VH2C AAY33199.1 **(Humanized 3)**	**28**
13	VL1C IGKV4-1*01 **(Humanized 3)**	**19**	VH1A IGHV4-31*02 **(Humanized 1)**	**23**
14	VL1C IGKV4-1*01 **(Humanized 3)**	**19**	VH1B IGHV4-31*02 **(Humanized 2)**:	**24**
15	VL1C IGKV4-1*01 **(Humanized 3)**	**19**	VH1C IGHV4-31*02 **(Humanized 3)**	**25**
16	VL1C IGKV4-1*01 **(Humanized 3)**	**19**	VH2A AAY33199.1 **(Humanized 1)**	**26**
17	VL1C IGKV4-1*01 **(Humanized 3)**	**19**	VH2B AAY33199.1 **(Humanized 2)**	**27**
18	VL1C IGKV4-1*01 **(Humanized 3)**	**19**	VH2C AAY33199.1 **(Humanized 3)**	**28**
19	VL2A IGKV2D-28*01 **(Humanized 1)**	**20**	VH1A IGHV4-31*02 **(Humanized 1)**	**23**
20	VL2A IGKV2D-28*01 **(Humanized 1)**	**20**	VH1B IGHV4-31*02 **(Humanized 2)**:	**24**
21	VL2A IGKV2D-28*01 **(Humanized 1)**	**20**	VH1C IGHV4-31*02 **(Humanized 3)**	**25**
22	VL2A IGKV2D-28*01 **(Humanized 1)**	**20**	VH2A AAY33199.1 **(Humanized 1)**	**26**
23	VL2A IGKV2D-28*01 **(Humanized 1)**	**20**	VH2B AAY33199.1 **(Humanized 2)**	**27**
24	VL2A IGKV2D-28*01	**20**	VH2C AAY33199.1	**28**

Table 4				
Humanized Variants of anti-human H7CR Antibody 1.3				
Humanized Variant No.	**Light Chain**	**SEQ ID NO.**	**Heavy Chain**	**SEQ ID NO.**
	(Humanized 1)		**(Humanized 3)**	
25	VL2B IGKV2D-28*01 **(Humanized 2)**	**21**	VH1A IGHV4-31*02 **(Humanized 1)**	**23**
26	VL2B IGKV2D-28*01 **(Humanized 2)**	**21**	VH1B IGHV4-31*02 **(Humanized 2)**:	**24**
27	VL2B IGKV2D-28*01 **(Humanized 2)**	**21**	VH1C IGHV4-31*02 **(Humanized 3)**	**25**
28	VL2B IGKV2D-28*01 **(Humanized 2)**	**21**	VH2A AAY33199.1 **(Humanized 1)**	**26**
29	VL2B IGKV2D-28*01 **(Humanized 2)**	**21**	VH2B AAY33199.1 **(Humanized 2)**	**27**
30	VL2B IGKV2D-28*01 **(Humanized 2)**	**21**	VH2C AAY33199.1 **(Humanized 3)**	**28**
31	VL2C IGKV2D-28*01 **(Humanized 3)**	**22**	VH1A IGHV4-31*02 **(Humanized 1)**	**23**
32	VL2C IGKV2D-28*01 **(Humanized 3)**	**22**	VH1B IGHV4-31*02 **(Humanized 2)**:	**24**
33	VL2C IGKV2D-28*01 **(Humanized 3)**	**22**	VH1C IGHV4-31*02 **(Humanized 3)**	**25**
34	VL2C IGKV2D-28*01 **(Humanized 3)**	**22**	VH2A AAY33199.1 **(Humanized 1)**	**26**
35	VL2C IGKV2D-28*01 **(Humanized 3)**	**22**	VH2B AAY33199.1 **(Humanized 2)**	**27**
36	VL2C IGKV2D-28*01 **(Humanized 3)**	**22**	VH2C AAY33199.1 **(Humanized 3)**	**28**

(b) Humanized Variants Of Anti-Human H7CR Antibody 4.5

[00133] The amino acid sequences of the Light Chain Variable Region of preferred humanized variants of anti-human H7CR antibody 4.5, derived from the **IGKV4-1*01** acceptor framework, are shown below (CDRs are shown underlined):

1. VL1A IGKV4-1*01 (Humanized 1):

DIVMTQSPDS LAVSLGERAT INCKSS**QSLF** **SSNTKRNY**LA WYQQKPGQPP KLLIY**HAS**TR ESGVPDRFSG SGSGTDFTLT ISSLQAEDVA VYYC**QQHYET** **PLT**FGQGTRLEIK **(SEQ ID NO:33)**

2. VL1B IGKV4-1*01 (Humanized 2):

DIVMTQSPDS LAVSLGERAT INCKSS**QSLF** **SSNTKRNY**LN WYQQKPGQPP KLLIY**HAS**TR LSGVPDRFSG SGSGTDFTLT ISSLQAEDVA DYFC**QQHYET** **PLT**FGDGTRL EIK **(SEQ ID NO:34)**

3. VL1C IGKV4-1*01 (Humanized 3):

DIVMTQSPDS LAVSLGERAT INCLSS**QSLF** **SSNTKRNY**LN WYQQKPGQSP KLLIY**HAS**TR LSGVPDRFSG SGSGTDFTLT ISSLQAEDVA DYFC**QQHYET** **PLT**FGDGTRL EIK **(SEQ ID NO:35)**

[00134] The amino acid sequences of the Light Chain Variable Region of preferred humanized variants of anti-human H7CR antibody 4.5, derived from the **IGKV2D-40*01** acceptor framework, are shown below (CDRs are shown underlined):

1. VL2A IGKV2D-40*01 (Humanized 1):

DIVMTQTPLS LPVTPGEPAS ISCRSS**QSLF** **SSNTKRNY**LD WYLQKPGQSP QLLIY**HAS**YR ASGVPDRFSG SGSGTDFTLK ISRVEAEDVG VYYC**QQHYET** **PLT**FGQGTRL EIK **(SEQ ID NO:36)**

2. VL2B IGKV2D-40*01 (Humanized 2):

DIVMTQTPLS LPVTPGEPAS ISCRSS**QSLF** **SSNTKRNY**LN WYLQKPGQSP KLLIY**HAS**TR LSGVPDRFSG SGSGTDFTLK ISRVEAEDVG DYFC**QQHYET** **PLT**FGDGTRL EIK **(SEQ ID NO:37)**

3. VL2C IGKV2D-40*01 (Humanized 3):

DIVMTQTPSS LPVTPGEPAS ISCLSS**QSLF** **SSNTKRNY**LN WYLQKPGQSP KLLIY**HAS**TR LSGVPDRFSG SGSGTDFTLK ISRVEAEDVG DYFC**QQHYET** **PLT**FGDGTRL EIK **(SEQ ID NO:38)**

[00135] The amino acid sequences of the Heavy Chain Variable Region of preferred humanized variants of anti-human H7CR antibody 1.3, derived from the **IGHV4-31*02** acceptor framework, are shown below (CDRs are shown underlined):

1. VH1A IGHV4-31*02 (Humanized 1):

QVQLQESGPG LVKPSQTLSL TCTVS**GFSIT** **TGGYY**WSWIR QHPGKGLEWI GY**IYTSGRT**Y YNPSLKSRVT ISVDTSKNQF SLKLSSVTAA DTAVYYC**ADM** **ADKGGWFAY**W GQGTLVTVSS **(SEQ ID NO:39)**

2. VH1B IGHV4-31*02 (Humanized 2):

QVQLQESGPG LVKPSQTLSL TCTVS**GFSIT** **TGGYY**WNWIR QHPGKKLEWI GY**IYTSGRT**S YNPSLKSRVT ISRDTSKNQF SLKLSSVTAA DTAVYYC**ADM** **ADKGGWFAY**W GQGTLVTVSS **(SEQ ID NO:40)**

3. VH1C IGHV4-31*02 (Humanized 3):

QVQLQESGPG LVKPSQTLSL TCTVS**GFSIT** **TGGYY**WNWIR QFPGKKLEWM GY**IYTSGRT**S YNPSLKSRVT ISRDTSKNQF SLKLSSVTAA DTAVYYC**ADM** **ADKGGWFAY**W GQGTLVTVSS **(SEQ ID NO:41)**

[00136] The amino acid sequences of the Heavy Chain Variable Region of preferred humanized variants of anti-human H7CR antibody 1.3, derived from the **IGHV2-5*01** acceptor framework, are shown below (CDRs are shown underlined):

1. VH2A IGHV2-5*01 (Humanized 1):

QITLKESGPT LVKPTQTLTL TCTFS**GFSIT** **TGGYY**VGWIR QPPGKALEWL AL**IYTSGRT**R YSPSLKSRLT ITKDTSKNQV VLTMTNMDPV DTATYYC**ADM** **ADKGGWFAY**W GQGTLVTVSS **(SEQ ID NO:42)**

2. VH2B IGHV2-5*01 (Humanized 2):

QITLKESGPT LVKPTQTLTL TCTVS**GFSIT** **TGGYY**WNWIR QPPGKKLEWL
AL**IYTSGRT**S YNPSLKSRLT ITKDTSKNQV VLTMTNMDPV DTATYYC**ADM**
ADKGGWFAYW GQGTLVTVSS **(SEQ ID NO:43)**

3. VH2C IGHV2-5*01 (Humanized 3):

QIQLKESGPT LVKPTQTLTL TCTVS**GFSIT** **TGGYY**WNWIR QPPGKKLEWM
AL**IYTSGRT**S YNPSLKSRLT ITKDTSKNQV VLTMTNMDPV DTATYYC**ADM**
ADKGGWFAYW GQGTLVTVSS **(SEQ ID NO:44)**

[00137] The antibodies, and their antigen-binding fragments can include any of the 36 combinations of the above-described humanized variants of anti-human H7CR antibody 4.5. Specifically, such antibodies include the combinations shown in **Table 5**:

Table 5

Humanized Variants of anti-human H7CR Antibody 4.5

Humanized Variant No.	Light Chain	SEQ ID NO.	Heavy Chain	SEQ ID NO.
1	VL1A IGKV4-1*01 **(Humanized 1)**	**33**	VH1A IGHV4-31*02 **(Humanized 1)**	**39**
2	VL1A IGKV4-1*01 **(Humanized 1)**	**33**	VH1B IGHV4-31*02 **(Humanized 2)**:	**40**
3	VL1A IGKV4-1*01 **(Humanized 1)**	**33**	VH1C IGHV4-31*02 **(Humanized 3)**	**41**
4	VL1A IGKV4-1*01 **(Humanized 1)**	**33**	VH2A IGHV2-5*01 **(Humanized 1)**	**42**
5	VL1A IGKV4-1*01 **(Humanized 1)**	**33**	VH2B IGHV2-5*01 **(Humanized 2)**	**43**
6	VL1A IGKV4-1*01 **(Humanized 1)**	**33**	VH2C IGHV2-5*01 **(Humanized 3)**	**44**
7	VL1B IGKV4-1*01 **(Humanized 2)**	**34**	VH1A IGHV4-31*02 **(Humanized 1)**	**39**
8	VL1B IGKV4-1*01 **(Humanized 2)**	**34**	VH1B IGHV4-31*02 **(Humanized 2)**:	**40**
9	VL1B IGKV4-1*01 **(Humanized 2)**	**34**	VH1C IGHV4-31*02 **(Humanized 3)**	**41**
10	VL1B IGKV4-1*01 **(Humanized 2)**	**34**	VH2A IGHV2-5*01 **(Humanized 1)**	**42**
11	VL1B IGKV4-1*01 **(Humanized 2)**	**34**	VH2B IGHV2-5*01 **(Humanized 2)**	**43**
12	VL1B IGKV4-1*01 **(Humanized 2)**	**34**	VH2C IGHV2-5*01 **(Humanized 3)**	**44**
13	VL1C IGKV4-1*01 **(Humanized 3)**	**35**	VH1A IGHV4-31*02 **(Humanized 1)**	**39**
14	VL1C IGKV4-1*01 **(Humanized 3)**	**35**	VH1B IGHV4-31*02 **(Humanized 2)**:	**40**
15	VL1C IGKV4-1*01 **(Humanized 3)**	**35**	VH1C IGHV4-31*02 **(Humanized 3)**	**41**
16	VL1C IGKV4-1*01 **(Humanized 3)**	**35**	VH2A IGHV2-5*01 **(Humanized 1)**	**42**
17	VL1C IGKV4-1*01 **(Humanized 3)**	**35**	VH2B IGHV2-5*01 **(Humanized 2)**	**43**
18	VL1C IGKV4-1*01	**35**	VH2C IGHV2-5*01	**44**

Table 5

Humanized Variants of anti-human H7CR Antibody 4.5

Humanized Variant No.	Light Chain	SEQ ID NO.	Heavy Chain	SEQ ID NO.
	(Humanized 3)		**(Humanized 3)**	
19	VL2A IGKV2D-40*01 **(Humanized 1)**	**36**	VH1A IGHV4-31*02 **(Humanized 1)**	**39**
20	VL2A IGKV2D-40*01 **(Humanized 1)**	**36**	VH1B IGHV4-31*02 **(Humanized 2)**:	**40**
21	VL2A IGKV2D-40*01 **(Humanized 1)**	**36**	VH1C IGHV4-31*02 **(Humanized 3)**	**41**
22	VL2A IGKV2D-40*01 **(Humanized 1)**	**36**	VH2A IGHV2-5*01 **(Humanized 1)**	**42**
23	VL2A IGKV2D-40*01 **(Humanized 1)**	**36**	VH2B IGHV2-5*01 **(Humanized 2)**	**43**
24	VL2A IGKV2D-40*01 **(Humanized 1)**	**36**	VH2C IGHV2-5*01 **(Humanized 3)**	**44**
25	VL2B IGKV2D-40*01 **(Humanized 2)**	**37**	VH1A IGHV4-31*02 **(Humanized 1)**	**39**
26	VL2B IGKV2D-40*01 **(Humanized 2)**	**37**	VH1B IGHV4-31*02 **(Humanized 2)**:	**40**
27	VL2B IGKV2D-40*01 **(Humanized 2)**	**37**	VH1C IGHV4-31*02 **(Humanized 3)**	**41**
28	VL2B IGKV2D-40*01 **(Humanized 2)**	**37**	VH2A IGHV2-5*01 **(Humanized 1)**	**42**
29	VL2B IGKV2D-40*01 **(Humanized 2)**	**37**	VH2B IGHV2-5*01 **(Humanized 2)**	**43**
30	VL2B IGKV2D-40*01 **(Humanized 2)**	**37**	VH2C IGHV2-5*01 **(Humanized 3)**	**44**
31	VL2C IGKV2D-40*01 **(Humanized 3)**	**38**	VH1A IGHV4-31*02 **(Humanized 1)**	**39**
32	VL2C IGKV2D-40*01 **(Humanized 3)**	**38**	VH1B IGHV4-31*02 **(Humanized 2)**:	**40**
33	VL2C IGKV2D-40*01 **(Humanized 3)**	**38**	VH1C IGHV4-31*02 **(Humanized 3)**	**41**
34	VL2C IGKV2D-40*01 **(Humanized 3)**	**38**	VH2A IGHV2-5*01 **(Humanized 1)**	**42**
35	VL2C IGKV2D-40*01 **(Humanized 3)**	**38**	VH2B IGHV2-5*01 **(Humanized 2)**	**43**
36	VL2C IGKV2D-40*01 **(Humanized 3)**	**38**	VH2C IGHV2-5*01 **(Humanized 3)**	**44**

[00138] The disclosed antibodies or fragments thereof include an amino acid sequence of a variable heavy chain and/or variable light chain that is at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical to the amino acid sequence of the variable heavy chain and/or light chain of the mouse monoclonal antibody produced by any of the above clones, and which exhibit immunospecific binding to human H7CR. Other antibodies or fragments thereof include a CDR that is at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%,

or at least 99% identical to the amino acid sequence of a CDR of the above-listed clones and which exhibit immunospecific binding to H7CR. The determination of percent identity of two amino acid sequences can be determined by BLAST protein comparison.

[00139] In a preferred embodiment, the antibody is a humanized immunoglobulin molecule (*e.g.*, an antibody, diabody, fusion protein, *etc.*) that includes one, two or three light chain CDRs and one, two or three heavy chain CDRs (most preferably three light chain CDRs and three heavy chain CDRs), wherein the **light** chain CDRs include:

(1) the light chain CDR1 of a humanized variant of anti-human H7CR antibody 1.3;

(2) the light chain CDR2 of a humanized variant of anti-human H7CR antibody 4.5;

(3) the light chain CDR3 of a humanized variant of anti-human H7CR antibody 7.8;

(4) the light chain CDR1 and the light chain CDR2 of a humanized variant of anti-human H7CR antibody 1.3, 4.5 or 7.8;

(5) the light chain CDR1 and the light chain CDR3 of a humanized variant of anti-human H7CR antibody 1.3, 4.5 or 7.8;

(6) the light chain CDR2 and the light chain CDR3 of a humanized variant of anti-human H7CR antibody 1.3, 4.5 or 7.8;

or

(7) the light chain CDR1, the light chain CDR2 and the light chain CDR3 of a humanized variant of anti-human H7CR antibody 1.3, 4.5 or 7.8.

[00140] In an alternative preferred embodiment, the humanized immunoglobulin molecule includes one, two or three light chain CDRs and one, two or three heavy chain CDRs (most preferably three light chain CDRs and three heavy chain CDRs), wherein the **heavy** chain CDRs include:

(1) the heavy chain CDR1 of a humanized variant of anti-human H7CR antibody 1.3;

(2) the heavy chain CDR2 of a humanized variant of anti-human H7CR antibody 4.5;

(3) the heavy chain CDR3 of a humanized variant of anti-human H7CR antibody 7.8;

(4) the heavy chain CDR1 and the heavy chain CDR2 of a humanized variant of anti-human H7CR antibody 1.3, 4.5 or 7.8;

(5) the heavy chain CDR1 and the heavy chain CDR3 of a humanized variant of anti-human H7CR antibody 1.3, 4.5 or 7.8;

(6) the heavy chain CDR2 and the heavy chain CDR3 of a humanized variant of anti-human H7CR antibody 1.3, 4.5 or 7.8;

or

(7) the heavy chain CDR1, the heavy chain CDR2 and the heavy chain CDR3 of a humanized variant of anti-human H7CR antibody 1.3, 4.5 or 7.8.

[00141] In a particularly preferred embodiment, the antibody is a humanized immunoglobulin molecule that includes one, two or three light chain CDRs and one, two or three heavy chain CDRs (most preferably three light chain CDRs and three heavy chain CDRs), wherein the **light** chain CDRs include:

(1) the light chain CDR1 of a humanized variant of anti-human H7CR antibody 1.3;

(2) the light chain CDR2 of a humanized variant of anti-human H7CR antibody 4.5;

(3) the light chain CDR3 of a humanized variant of anti-human H7CR antibody 7.8;

(4) the light chain CDR1 and the light chain CDR2 of a humanized variant of anti-human H7CR antibody 1.3, 4.5 or 7.8;

(5) the light chain CDR1 and the light chain CDR3 of a humanized variant of anti-human H7CR antibody 1.3, 4.5 or 7.8;

(6) the light chain CDR2 and the light chain CDR3 of a humanized variant of anti-human H7CR antibody 1.3, 4.5 or 7.8;

or

(7) the light chain CDR1, the light chain CDR2 and the light chain CDR3 of a humanized variant of anti-human H7CR antibody 1.3, 4.5 or 7.8,

and wherein the **heavy** chain CDRs include:

(1) the heavy chain CDR1 of a humanized variant of anti-human H7CR antibody 1.3;

(2) the heavy chain CDR2 of a humanized variant of anti-human H7CR antibody 4.5;

(3) the heavy chain CDR3 of a humanized variant of anti-human H7CR antibody 7.8;

(4) the heavy chain CDR1 and the heavy chain CDR2 of a humanized variant of anti-human H7CR antibody 1.3, 4.5 or 7.8;

(5) the heavy chain CDR1 and the heavy chain CDR3 of a humanized variant of anti-human H7CR antibody 1.3, 4.5 or 7.8;

(6) the heavy chain CDR2 and the heavy chain CDR3 of a humanized variant of anti-human H7CR antibody 1.3, 4.5 or 7.8;

or

(7) the heavy chain CDR1, the heavy chain CDR2 and the heavy chain CDR3 of a humanized variant of anti-human H7CR antibody 1.3, 4.5 or 7.8.

[00142] Most preferably, such CDRs shall be of the same humanized variant of anti-human H7CR antibody 1.3, 4.5 or 7.8, respectively.

[00143] In a specific embodiment, an antibody or an antigen-binding fragment will include one, two, three, four, five, or more preferably, all 6 CDRs of the humanized variants of anti-human H7CR antibody 1.3, 4.5 or 7.8 and will exhibit the same ability to bind to human H7CR as the parental antibody.

E. Therapeutic and Prophylactic Uses of the Preferred Compositions

[00144] As used herein, the terms "**treat**," "**treating**," "**treatment**" and "**therapeutic use**" refer to the elimination, reduction or amelioration of one or more symptoms of a disease or disorder that would benefit from an increased or decreased immune response. As used herein, a "**therapeutically effective amount**" refers to that amount of a therapeutic agent sufficient to mediate an altered immune response, and more preferably, a clinically relevant altered immune response, sufficient to mediate a reduction or amelioration of a symptom of a disease or condition. An effect is clinically relevant if its magnitude is sufficient to impact the health or prognosis of a recipient subject. A therapeutically effective amount may refer to the amount of therapeutic agent sufficient to reduce or minimize disease progression, *e.g.*, delay or minimize the spread of cancer. A therapeutically effective amount may also refer to the amount of the therapeutic agent that provides a therapeutic benefit in the treatment or management of a disease. Further, a therapeutically effective amount with respect to a therapeutic agent means that amount of therapeutic agent alone, or in combination with other therapies, that provides a therapeutic benefit in the treatment or management of a disease, *e.g.*, sufficient to enhance the therapeutic efficacy of a therapeutic antibody sufficient to treat or manage a disease.

[00145] As used herein, the term "**prophylactic agent**" refers to an agent that can be used in the prevention of a disorder or disease prior to the detection of any symptoms of such disorder or disease. A "**prophylactically effective**" amount is the amount of prophylactic agent sufficient to mediate such protection. A prophylactically effective amount may also refer to the amount of the prophylactic agent that provides a prophylactic benefit in the prevention of disease. Further, a prophylactically effective amount with respect to a prophylactic agent means that amount of prophylactic agent alone, or in combination with other agents, that provides a prophylactic benefit in the prevention of disease.

[00146] The dosage amounts and frequencies of administration provided herein are encompassed by the terms therapeutically effective and prophylactically effective. The dosage and frequency further will typically vary according to factors specific for each patient depending on the specific therapeutic or prophylactic agents administered, the severity and type of cancer, the route of administration, as well as age, body weight, response, and the past medical history of the patient. Suitable regimens can be selected by one skilled in the art by considering such factors and by following, for example, dosages reported in the literature and recommended in the *Physician's Desk Reference* (56th Ed., 2002).

1. Uses of Up-Modulators of the Immune System

[00147] One embodiment concerns H7CR-binding molecules, such as anti-H7CR antibodies (and fragments of such antibodies that bind to H7CR) or B7-H7 Ig, that, by binding to H7CR agonize (*i.e.*, enhance) T cell proliferation and/or cytokine production. The administration of such molecules to a subject **up-modulates** the immune system of the subject. As H7CR expression is associated with a naïve T cell phenotype, administration of such molecules would be effective for increasing T cell priming and activation and thus would be good to combine with vaccines. Furthermore, agonistic anti-H7CR (and B7-H7 Ig) would be very good to combine with molecules that target immune-checkpoints and inhibit receptors that would normally dampen the immune response: anti-PD-1, anti-B7-H1, anti-CTLA4 etc. Such antibodies may be better administered in sequence, *i.e.*, anti-H7CR first to enhance T cell priming, followed by *e.g.*, anti-PD-1 to prevent T cell exhaustion. Bi-specific molecules targeting H7CR and immune-checkpoint blockade are also contemplated.

[00148] Up-modulation of the immune system is particularly desirable in the treatment of cancers and chronic infections (*e.g.*, HIV infection, AIDS, *etc.*) and thus the disclosed molecules have utility in the treatment of such disorders. Macrophages have been shown to contribute significantly to the initial steps of HIV infection (Carter, C. A. *et al.* (2008) "*Cell*

Biology Of HIV-1 Infection Of Macrophages," Ann. Rev. Microbiol. 62:425-443; Noursadeghi, M. *et al.* (2006) "*HIV-1 Infection Of Mononuclear Phagocytic Cells: The Case For Bacterial Innate Immune Deficiency In AIDS*," Lancet Infect. Dis. 6:794-804). Accordingly antibodies (particularly if conjugated to a toxin) that bind B7-H7 have utility in preventing or treating HIV infection.

[00149] As used herein, the term "**cancer**" refers to a neoplasm or tumor resulting from abnormal uncontrolled growth of cells. As used herein, cancer explicitly includes leukemias and lymphomas. The term refers to a disease involving cells that have the potential to metastasize to distal sites and exhibit phenotypic traits that differ from those of non-cancer cells, for example, formation of colonies in a three-dimensional substrate such as soft agar or the formation of tubular networks or weblike matrices in a three-dimensional basement membrane or extracellular matrix preparation. Non-cancer cells do not form colonies in soft agar and form distinct sphere-like structures in three-dimensional basement membrane or extracellular matrix preparations.

[00150] Cancers and related disorders that can be treated or prevented include, but are not limited to, the following: leukemias including, but not limited to, acute leukemia, acute lymphocytic leukemia, acute myelocytic leukemias such as myeloblastic, promyelocytic, myelomonocytic, monocytic, erythroleukemia leukemias and myelodysplastic syndrome, chronic leukemias such as but not limited to, chronic myelocytic (granulocytic) leukemia, chronic lymphocytic leukemia, hairy cell leukemia; polycythemia vera; lymphomas such as, but not limited to, Hodgkin's disease, non-Hodgkin's disease; multiple myelomas such as, but not limited to, smoldering multiple myeloma, nonsecretory myeloma, osteosclerotic myeloma, plasma cell leukemia, solitary plasmacytoma and extramedullary plasmacytoma; Waldenström's macroglobulinemia; monoclonal gammopathy of undetermined significance; benign monoclonal gammopathy; heavy chain disease; bone and connective tissue sarcomas such as, but not limited to, bone sarcoma, osteosarcoma, chondrosarcoma, Ewing's sarcoma, malignant giant cell tumor, fibrosarcoma of bone, chordoma, periosteal sarcoma, soft-tissue sarcomas, angiosarcoma (hemangiosarcoma), fibrosarcoma, Kaposi's sarcoma, leiomyosarcoma, liposarcoma, lymphangiosarcoma, neurilemmoma, rhabdomyosarcoma, synovial sarcoma; brain tumors including but not limited to, glioma, astrocytoma, brain stem glioma, ependymoma, oligodendroglioma, nonglial tumor, acoustic neurinoma, craniopharyngioma, medulloblastoma, meningioma, pineocytoma, pineoblastoma, primary brain lymphoma; breast cancer including, but not limited to, adenocarcinoma, lobular (small cell) carcinoma, intraductal carcinoma, medullary breast cancer, mucinous breast cancer,

tubular breast cancer, papillary breast cancer, Paget's disease, and inflammatory breast cancer; adrenal cancer, including but not limited to, pheochromocytom and adrenocortical carcinoma; thyroid cancer such as but not limited to papillary or follicular thyroid cancer, medullary thyroid cancer and anaplastic thyroid cancer; pancreatic cancer, including but not limited to, insulinoma, gastrinoma, glucagonoma, vipoma, somatostatin-secreting tumor, and carcinoid or islet cell tumor; pituitary cancers including but not limited to, Cushing's disease, prolactin-secreting tumor, acromegaly, and diabetes insipius; eye cancers including, but not limited to, ocular melanoma such as iris melanoma, choroidal melanoma, and cilliary body melanoma, and retinoblastoma; vaginal cancers, including, but not limited to, squamous cell carcinoma, adenocarcinoma, and melanoma; vulvar cancer, including but not limited to, squamous cell carcinoma, melanoma, adenocarcinoma, basal cell carcinoma, sarcoma, and Paget's disease; cervical cancers including, but not limited to, squamous cell carcinoma, and adenocarcinoma; uterine cancers including, but not limited to, endometrial carcinoma and uterine sarcoma; ovarian cancers including, but not limited to, ovarian epithelial carcinoma, borderline tumor, germ cell tumor, and stromal tumor; esophageal cancers including, but not limited to, squamous cancer, adenocarcinoma, adenoid cyctic carcinoma, mucoepidermoid carcinoma, adenosquamous carcinoma, sarcoma, melanoma, plasmacytoma, verrucous carcinoma, and oat cell (small cell) carcinoma; stomach cancers including, but not limited to, adenocarcinoma, fungating (polypoid), ulcerating, superficial spreading, diffusely spreading, malignant lymphoma, liposarcoma, fibrosarcoma, and carcinosarcoma; colon cancers; rectal cancers; liver cancers including, but not limited to, hepatocellular carcinoma and hepatoblastoma, gallbladder cancers including, but not limited to, adenocarcinoma; cholangiocarcinomas including, but not limited to, papillary, nodular, and diffuse; lung cancers including but not limited to, non-small cell lung cancer, squamous cell carcinoma (epidermoid carcinoma), adenocarcinoma, large-cell carcinoma and small-cell lung cancer; testicular cancers including, but not limited to, germinal tumor, seminoma, anaplastic, classic (typical), spermatocytic, nonseminoma, embryonal carcinoma, teratoma carcinoma, choriocarcinoma (yolk-sac tumor), prostate cancers including, but not limited to, adenocarcinoma, leiomyosarcoma, and rhabdomyosarcoma; penal cancers; oral cancers including, but not limited to, squamous cell carcinoma; basal cancers; salivary gland cancers including, but not limited to, adenocarcinoma, mucoepidermoid carcinoma, and adenoidcystic carcinoma; pharynx cancers including, but not limited to, squamous cell cancer, and verrucous; skin cancers including, but not limited to, basal cell carcinoma, squamous cell carcinoma and melanoma, superficial spreading melanoma, nodular

melanoma, lentigo malignant melanoma, acral lentiginous melanoma; kidney cancers including, but not limited to, renal cell cancer, adenocarcinoma, hypernephroma, fibrosarcoma, transitional cell cancer (renal pelvis and/ or uterer); Wilms' tumor; bladder cancers including, but not limited to, transitional cell carcinoma, squamous cell cancer, adenocarcinoma, carcinosarcoma. In addition, cancers include myxosarcoma, osteogenic sarcoma, endotheliosarcoma, lymphangioendotheliosarcoma, mesothelioma, synovioma, hemangioblastoma, epithelial carcinoma, cystadenocarcinoma, bronchogenic carcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma and papillary adenocarcinomas (for a review of such disorders, *see* Fishman *et al.*, 1985, *Medicine*, 2d Ed., J.B. Lippincott Co., Philadelphia and Murphy *et al.*, 1997, *Informed Decisions: The Complete Book of Cancer Diagnosis, Treatment, and Recovery*, Viking Penguin, Penguin Books U.S.A., Inc., United States of America).

[00151] Accordingly, the disclosed methods and compositions are also useful in the treatment, inhibition or prevention of a variety of cancers or other abnormal proliferative diseases, including (but not limited to) the following: carcinoma, including that of the bladder, breast, colon, kidney, liver, lung, ovary, pancreas, stomach, cervix, thyroid and skin; including squamous cell carcinoma; hematopoietic tumors of lymphoid lineage, including leukemia, acute lymphocytic leukemia, acute lymphoblastic leukemia, B-cell lymphoma, T-cell lymphoma, Berketts lymphoma; hematopoietic tumors of myeloid lineage, including acute and chronic myelogenous leukemias and promyelocytic leukemia; tumors of mesenchymal origin, including fibrosarcoma and rhabdomyoscarcoma; other tumors, including melanoma, seminoma, tetratocarcinoma, neuroblastoma and glioma; tumors of the central and peripheral nervous system, including astrocytoma, neuroblastoma, glioma, and schwannomas; tumors of mesenchymal origin, including fibrosafcoma, rhabdomyoscarama, and osteosarcoma; and other tumors, including melanoma, xenoderma pegmentosum, keratoactanthoma, seminoma, thyroid follicular cancer and teratocarcinoma. It is also contemplated that cancers caused by aberrations in apoptosis would also be treated by the disclosed methods and compositions. Such cancers may include, but are not be limited to, follicular lymphomas, carcinomas with p53 mutations, hormone dependent tumors of the breast, prostate and ovary, and precancerous lesions such as familial adenomatous polyposis, and myelodysplastic syndromes. In specific embodiments, malignancy or dysproliferative changes (such as metaplasias and dysplasias), or hyperproliferative disorders, are treated or prevented by the disclosed methods and compositions in the ovary, bladder, breast, colon,

lung, skin, pancreas, or uterus. In other specific embodiments, sarcoma, melanoma, or leukemia is treated or prevented by the disclosed methods and compositions.

[00152] Cancer cells acquire a characteristic set of functional capabilities during their development, albeit through various mechanisms. Such capabilities include evading apoptosis, self-sufficiency in growth signals, insensitivity to anti-growth signals, tissue invasion/metastasis, limitless explicative potential, and sustained angiogenesis. The term "cancer cell" is meant to encompass both pre-malignant and malignant cancer cells. In some embodiments, cancer refers to a benign tumor, which has remained localized. In other embodiments, cancer refers to a malignant tumor, which has invaded and destroyed neighboring body structures and spread to distant sites. In yet other embodiments, the cancer is associated with a specific cancer antigen (e.g., pan-carcinoma antigen (KS 1/4), ovarian carcinoma antigen (CA125), prostate specific antigen (PSA), carcinoembryonic antigen (CEA), CD19, CD20, HER2/neu, etc.).

[00153] Similar to its application to tumors as discussed above, the disclosed antibodies and antigen-binding fragments can be used alone, or as an adjuvant, in combination with vaccines or with antimibrobial agents, to stimulate the immune response against toxins or self-antigens or against pathogens (*e.g.*, viruses, such as HIV, HTLV, hepatitis virus, influenza virus, respiratory syncytial virus, vaccinia virus, rabies virus; bacteria, such as those of *Mycobacteria*, *Staphylococci*, *Streptococci*, *Pneumonococci*, *Meningococci*, *Conococci*, *Klebsiella, Proteus, Serratia, Pseudomonas, Legionella, Corynebacteria*, *Salmonella, Vibrio*, *Clostridia*, *Bacilli*, *Pasteurella*, *Leptospirosis*, *Bordatella*, and particularly such pathogens associated with cholera, tetanus, botulism, anthrax, plague, and Lyme disease; or fungal or parasitic pathogens, such as *Candida (albicans, krusei, glabrata, tropicalis,* etc.), *Cryptococcus*, *Aspergillus (jumigatus, niger,* etc.), Genus Mucorales *(mucor, absidia, rhizophus), Sporothrix (schenkii), Blastomyces (dermatitidis), Paracoccidioides (brasiliensis), Coccidioides (immitis)* and *Histoplasma (capsulatum), Entamoeba, histolytica, Balantidium coli, Naegleria fowleri, Acanthamoeba* sp., *Giardia lambia, Cryptosporidium* sp., *Pneumocystis carinii, Plasmodium vivax, Babesia microti, Trypanosoma brucei, Trypanosoma cruzi, Toxoplasma gondi, etc.)., Sporothrix, Blastomyces, Paracoccidioides, Coccidioides, Histoplasma, Entamoeba, Histolytica, Balantidium, Naegleria, Acanthamoeba, Giardia, Cryptosporidium*, *Pneumocystis, Plasmodium, Babesia,* or *Trypanosoma, etc.* Thus, the antibodies and antigen-binding fragments have utility in the treatment of infectious disease.

[00154] Another use of the antibodies and antigen-binding fragments is to block or deplete T cells in patients having T cell cancers. In one embodiment such blockage or depletion is accomplished using anti-H7CR antibodies that bind to a site proximal to the binding site of H7CR to its ligand, such that normal H7CR function is impaired or disrupted. As a consequence of such disruption the effective (functional) concentration of T cells is depleted. In a preferred embodiment, such depletion is accomplished using anti-H7CR antibodies that are conjugated to a toxin, such that their binding to a T cell leads to the death of the cell. Preferably, in either embodiment, the sequence of the Fc region of the antibody will have been deleted (for example, an Fab or $F(ab)_2$, *etc.*) or modified so that the molecule will exhibit diminished or no Fc receptor (FcR) binding activity, or will exhibit enhanced antibody-dependent cell-mediated cytotoxicity (ADCC) or complement dependent cytotoxicity (CDC) activities.

2. Uses of Down-Modulators of the Immune System

[00155] An alternative embodiment relates to molecules, such as anti-B7-H7 antibodies (and fragments of such antibodies that bind to B7-H7 or H7CR Ig, that, by binding to B7-H7 antagonize (*i.e.*, attenuate or impair) H7CR function and T cell proliferation and/or cytokine production. The administration of such molecules to a subject **down-modulates** the immune system of the subject, and is particularly useful for the treatment of inflammation or autoimmunity.

[00156] Another embodiment provides antibodies that bind to H7CR and block ligand interaction with H7CR and do not agonize H7CR.

[00157] Down-modulation of the immune system is desirable in the treatment of inflammatory and auto-immune diseases. Examples of autoimmune disorders that may be treated by administering the antibodies include, but are not limited to, alopecia areata, ankylosing spondylitis, antiphospholipid syndrome, autoimmune Addison's disease, autoimmune diseases of the adrenal gland, autoimmune hemolytic anemia, autoimmune hepatitis, autoimmune oophoritis and orchitis, autoimmune thrombocytopenia, Behcet's disease, bullous pemphigoid, cardiomyopathy, celiac sprue-dermatitis, chronic fatigue immune dysfunction syndrome (CFIDS), chronic inflammatory demyelinating polyneuropathy, Churg-Strauss syndrome, cicatrical pemphigoid, CREST syndrome, cold agglutinin disease, Crohn's disease, discoid lupus, essential mixed cryoglobulinemia, fibromyalgia-fibromyositis, glomerulonephritis, Graves' disease, Guillain-Barre, Hashimoto's thyroiditis, idiopathic pulmonary fibrosis, idiopathic thrombocytopenia purpura

(ITP), IgA neuropathy, juvenile arthritis, lichen planus, lupus erthematosus, Ménière's disease, mixed connective tissue disease, multiple sclerosis, Neuromyelitis optica (NMO), type 1 or immune-mediated diabetes mellitus, myasthenia gravis, pemphigus vulgaris, pernicious anemia, polyarteritis nodosa, polychrondritis, polyglandular syndromes, polymyalgia rheumatica, polymyositis and dermatomyositis, primary agammaglobulinemia, primary biliary cirrhosis, psoriasis, psoriatic arthritis, Raynauld's phenomenon, Reiter's syndrome, Rheumatoid arthritis, sarcoidosis, scleroderma, Sjögren's syndrome, stiff-man syndrome, systemic lupus erythematosus, lupus erythematosus, takayasu arteritis, temporal arteristis/ giant cell arteritis, ulcerative colitis, uveitis, vasculitides such as dermatitis herpetiformis vasculitis, vitiligo, and Wegener's granulomatosis.

[00158] Examples of inflammatory disorders which can be prevented, treated or managed include, but are not limited to, asthma, encephilitis, inflammatory bowel disease, chronic obstructive pulmonary disease (COPD), allergic disorders, septic shock, pulmonary fibrosis, undifferentiated spondyloarthropathy, undifferentiated arthropathy, arthritis, inflammatory osteolysis, and chronic inflammation resulting from chronic viral or bacterial infections.

[00159] The described anti-H7CR antibodies may be employed to produce anti-idiotypic peptides or antibodies (Wallmann, J. *et al.* (2010) "*Anti-Ids in Allergy: Timeliness of a Classic Concept*," World Allergy Organiz. J. 3(6):195–201; Nardi, M. *et al.* (2000) "*Antiidiotype Antibody Against Platelet Anti-GpIIIa Contributes To The Regulation Of Thrombocytopenia In HIV-1-ITP Patients*," J. Exp. Med. 191(12):2093-2100) or mimetics (Zang, Y.C. *et al.* (2003) "*Human Anti-Idiotypic T Cells Induced By TCR Peptides Corresponding To A Common CDR3 Sequence Motif In Myelin Basic Protein-Reactive T Cells*," Int. Immunol. 15(9):1073-1080; Loiarro, M. *et al.* (Epub 2010 Apr 8) "*Targeting TLR/IL-1R Signalling In Human Diseases*," Mediators Inflamm. 2010:674363) of H7CR. Such molecules serve as surrogates for H7CR, and thus their administration to a subject down-modulates the immune system of such subject by engaging the B7-H7 ligand and preventing it from binding the endogenous H7CR receptor. Such molecules have utility in the treatment of graft vs. host disease. Similarly, agonist antibodies that enhance binding between such antibodies and such receptor/ligand have utility as agonists of H7CR signaling and thus have utility in the treatment of inflammation and autoimmune disease.

[00160] Thus, the antibodies and antigen-binding fragments have utility in the treatment of inflammatory and auto-immune diseases.

F. Methods of Administration

[00161] Various delivery systems are known and can be used to administer the therapeutic or prophylactic compositions described herein, *e.g.*, encapsulation in liposomes, microparticles, microcapsules, recombinant cells capable of expressing the antibody or fusion protein, receptor-mediated endocytosis (*see*, *e.g.*, Wu and Wu, 1987, *J. Biol. Chem.* 262:4429-4432), construction of a nucleic acid as part of a retroviral or other vector, *etc.*

[00162] Methods of administering a humanized antibody include, but are not limited to, parenteral administration (*e.g.*, intradermal, intramuscular, intraperitoneal, intravenous and subcutaneous), epidural, and mucosal (*e.g.*, intranasal and oral routes). In a specific embodiment, the disclosed antibodies are administered intramuscularly, intravenously, or subcutaneously. The compositions may be administered by any convenient route, for example, by infusion or bolus injection, by absorption through epithelial or mucocutaneous linings (*e.g.*, oral mucosa, rectal and intestinal mucosa, *etc.*) and may be administered together with other biologically active agents. Administration can be systemic or local. In addition, pulmonary administration can also be employed, *e.g.*, by use of an inhaler or nebulizer, and formulation with an aerosolizing agent. *See*, *e.g.*, U.S. Patent Nos. 6,019,968; 5,985, 20; 5,985,309; 5,934,272; 5,874,064; 5,855,913; 5,290,540; and 4,880,078; and PCT Publication Nos. WO 92/19244; WO 97/32572; WO 97/44013; WO 98/31346; and WO 99/66903. In a specific embodiment, it may be desirable to administer the pharmaceutical compositions locally to the area in need of treatment; this may be achieved by, for example, and not by way of limitation, local infusion, by injection, or by means of an implant, said implant being of a porous, non-porous, or gelatinous material, including membranes, such as sialastic membranes, or fibers. Preferably, when administering one or more of the disclosed antibodies, care must be taken to use materials to which the antibody or the fusion protein does not absorb.

[00163] In some embodiments, the humanized or chimeric antibodies are formulated in liposomes for targeted delivery of the disclosed antibodies. Liposomes are vesicles composed of concentrically ordered phopsholipid bilayers which encapsulate an aqueous phase. Liposomes typically include various types of lipids, phospholipids, and/or surfactants. The components of liposomes are arranged in a bilayer configuration, similar to the lipid arrangement of biological membranes. Liposomes are particularly preferred delivery vehicles due, in part, to their biocompatibility, low immunogenicity, and low toxicity. Methods for preparation of liposomes are known in the art, *see*, *e.g.*, Epstein *et al.*, 1985,

Proc. Natl. Acad. Sci. USA, 82: 3688; Hwang *et al.*, 1980 *Proc. Natl. Acad. Sci. USA*, 77: 4030-4; U.S. Patent Nos. 4,485,045 and 4,544,545.

[00164] Methods of preparing liposomes with a prolonged serum half-life, *i.e.*, enhanced circulation time, such as those disclosed in U.S. Patent No. 5,013,556 can be used to produce antibody formulations. Preferred liposomes used in the disclosed methods are not rapidly cleared from circulation, *i.e.*, are not taken up into the mononuclear phagocyte system (MPS). The liposomes include sterically stabilized liposomes which are prepared using common methods known to one skilled in the art. Although not intending to be bound by a particular mechanism of action, sterically stabilized liposomes contain lipid components with bulky and highly flexible hydrophilic moieties, which reduces the unwanted reaction of liposomes with serum proteins, reduces oposonization with serum components and reduces recognition by MPS. Sterically stabilized liposomes are preferably prepared using polyethylene glycol. For preparation of liposomes and sterically stabilized liposome, *see, e.g.,* Bendas *et al.*, 2001 *BioDrugs*, 15(4): 215-224; Allen *et al.*, 1987 *FEBS Lett.* 223: 42-6; Klibanov *et al.*, 1990 *FEBS Lett.*, 268: 235-7; Blum *et al.*, 1990, *Biochim. Biophys. Acta.*, 1029: 91-7; Torchilin *et al.*, 1996, *J. Liposome Res.* 6: 99-116; Litzinger *et al.*, 1994, *Biochim. Biophys. Acta*, 1190: 99-107; Maruyama *et al.*, 1991, *Chem. Pharm. Bull.*, 39: 1620-2; Klibanov *et al.*, 1991, *Biochim Biophys Acta*, 1062; 142-8; Allen *et al.*, 1994, *Adv. Drug Deliv. Rev*, 13: 285-309. Liposomes that are adapted for specific organ targeting, *see, e.g.*, U.S. Patent No. 4,544,545, or specific cell targeting, see, e.g., U.S. Patent Application Publication No. 2005/0074403 can also be used. Particularly useful liposomes for use in the compositions and methods can be generated by reverse phase evaporation method with a lipid composition including phosphatidylcholine, cholesterol, and PEG derivatized phosphatidylethanolamine (PEG-PE). Liposomes are extruded through filters of defined pore size to yield liposomes with the desired diameter. In some embodiments, a fragment of an antibody, *e.g.*, F(ab'), may be conjugated to the liposomes using previously described methods, *see, e.g.*, Martin *et al.*, 1982, *J. Biol. Chem.* 257: 286-288.

[00165] The humanized or chimeric antibodies may also be formulated as immunoliposomes. Immunoliposomes refer to a liposomal composition, wherein an antibody or a fragment thereof is linked, covalently or non-covalently to the liposomal surface. The chemistry of linking an antibody to the liposomal surface is known in the art, *see, e.g.*, U.S. Patent No. 6,787,153; Allen *et al.*, 1995, Stealth Liposomes, Boca Rotan: CRC Press, 233-44; Hansen *et al.*, 1995, *Biochim. Biophys. Acta*, 1239: 133-144.

[00166] The humanized or chimeric antibodies can be packaged in a hermetically sealed container, such as an ampoule or sachette, indicating the quantity of antibody. In one embodiment, the antibodies are supplied as a dry sterilized lyophilized powder or water free concentrate in a hermetically sealed container and can be reconstituted, *e.g.*, with water or saline to the appropriate concentration for administration to a subject. Preferably, the antibodies are supplied as a dry sterile lyophilized powder in a hermetically sealed container at a unit dosage of at least 5 mg, more preferably at least 10 mg, at least 15 mg, at least 25 mg, at least 35 mg, at least 45 mg, at least 50 mg, or at least 75 mg. The lyophilized antibodies should be stored at between 2 and 8°C in their original container and the antibodies should be administered within 12 hours, preferably within 6 hours, within 5 hours, within 3 hours, or within 1 hour after being reconstituted. In an alternative embodiment, antibodies are supplied in liquid form in a hermetically sealed container indicating the quantity and concentration of the antibody, fusion protein, or conjugated molecule. Preferably, the liquid form of the antibodies are supplied in a hermetically sealed container at least 1 mg/ml, more preferably at least 2.5 mg/ml, at least 5 mg/ml, at least 8 mg/ml, at least 10 mg/ml, at least 15 mg/kg, at least 25 mg/ml, at least 50 mg/ml, at least 100 mg/ml, at least 150 mg/ml, at least 200 mg/ml of the antibodies.

[00167] The precise dose to be employed in the formulation will also depend on the route of administration, and the seriousness of the condition, and should be decided according to the judgment of the practitioner and each patient's circumstances. Effective doses may be extrapolated from dose-response curves derived from *in vitro* or animal model test systems. For the disclosed antibodies, the dosage administered to a patient is typically 0.0001 mg/kg to 100 mg/kg of the patient's body weight. Preferably, the dosage administered to a patient is between 0.0001 mg/kg and 20 mg/kg, 0.0001 mg/kg and 10 mg/kg, 0.0001 mg/kg and 5 mg/kg, 0.0001 and 2 mg/kg, 0.0001 and 1 mg/kg, 0.0001 mg/kg and 0.75 mg/kg, 0.0001 mg/kg and 0.5 mg/kg, 0.0001 mg/kg to 0.25 mg/kg, 0.0001 to 0.15 mg/kg, 0.0001 to 0.10 mg/kg, 0.001 to 0.5 mg/kg, 0.01 to 0.25 mg/kg or 0.01 to 0.10 mg/kg of the patient's body weight. Generally, human antibodies have a longer half-life within the human body than antibodies from other species due to the immune response to the foreign polypeptides. Thus, lower dosages of human antibodies and less frequent administration is often possible. Further, the dosage and frequency of administration of antibodies or fragments thereof may be reduced by enhancing uptake and tissue penetration of the antibodies by modifications such as, for example, lipidation.

[00168] In yet another embodiment, the compositions can be delivered in a controlled release or sustained release system. Any technique known to one of skill in the art can be used to produce sustained release formulations including one or more antibodies. *See, e.g.*, U.S. Patent No. 4,526,938; PCT publication WO 91/05548; PCT publication WO 96/20698; Ning *et al.*, 1996, "Intratumoral Radioimmunotheraphy of a Human Colon Cancer Xenograft Using a Sustained-Release Gel," *Radiotherapy & Oncology* 39:179-189, Song *et al.*, 1995, "Antibody Mediated Lung Targeting of Long-Circulating Emulsions," *PDA Journal of Pharmaceutical Science & Technology* 50:372-397; Cleek *et al.*, 1997, "Biodegradable Polymeric Carriers for a bFGF Antibody for Cardiovascular Application," *Pro. Int'l. Symp. Control. Rel. Bioact. Mater.* 24:853-854; and Lam *et al.*, 1997, "Microencapsulation of Recombinant Humanized Monoclonal Antibody for Local Delivery," *Proc. Int'l. Symp. Control Rel. Bioact. Mater.* 24:759-760. In one embodiment, a pump may be used in a controlled release system (*See* Langer, *supra*; Sefton, 1987, *CRC Crit. Ref. Biomed. Eng.* 14:20; Buchwald *et al.*, 1980, Surgery 88:507; and Saudek *et al.*, 1989, *N. Engl. J. Med.* 321:574). In another embodiment, polymeric materials can be used to achieve controlled release of antibodies (*see e.g.*, Medical Applications of Controlled Release, Langer and Wise (eds.), CRC Pres., Boca Raton, Florida (1974); Controlled Drug Bioavailability, Drug Product Design and Performance, Smolen and Ball (eds.), Wiley, New York (1984); Ranger and Peppas, 1983, J., *Macromol. Sci. Rev. Macromol. Chem.* 23:61; *See* also Levy *et al.*, 1985, *Science* 228:190; During *et al.*, 1989, Ann. Neurol. 25:351; Howard *et al.*, 1989, *J. Neurosurg.* 7 1:105); U.S. Patent No. 5,679,377; U.S. Patent No. 5,916,597; U.S. Patent No. 5,912,015; U.S. Patent No. 5,989,463; U.S. Patent No. 5,128,326; PCT Publication No. WO 99/15154; and PCT Publication No. WO 99/20253). Examples of polymers used in sustained release formulations include, but are not limited to, poly(2-hydroxy ethyl methacrylate), poly(methyl methacrylate), poly(acrylic acid), poly(ethylene-co-vinyl acetate), poly(methacrylic acid), polyglycolides (PLG), polyanhydrides, poly(N-vinyl pyrrolidone), poly(vinyl alcohol), polyacrylamide, poly(ethylene glycol), polylactides (PLA), poly(lactide-co-glycolides) (PLGA), and polyorthoesters. In yet another embodiment, a controlled release system can be placed in proximity of the therapeutic target (*e.g.*, the lungs), thus requiring only a fraction of the systemic dose (*see, e.g.*, Goodson, in Medical Applications of Controlled Release, *supra*, vol. 2, pp. 115-138 (1984)). In another embodiment, polymeric compositions useful as controlled release implants are used according to Dunn *et al.* (*See* U.S. 5,945,155). This particular method is based upon the therapeutic effect of the in situ controlled release of the bioactive material from the polymer system. The implantation can

generally occur anywhere within the body of the patient in need of therapeutic treatment. In another embodiment, a non-polymeric sustained delivery system is used, whereby a non-polymeric implant in the body of the subject is used as a drug delivery system. Upon implantation in the body, the organic solvent of the implant will dissipate, disperse, or leach from the composition into surrounding tissue fluid, and the non-polymeric material will gradually coagulate or precipitate to form a solid, microporous matrix (*See* U.S. 5,888,533). Controlled release systems are discussed in the review by Langer (1990, *Science* 249:1527-1533). Any technique known to one of skill in the art can be used to produce sustained release formulations including one or more therapeutic agents. *See, e.g.*, U.S. Patent No. 4,526,938; International Publication Nos. WO 91/05548 and WO 96/20698; Ning *et al.*, 1996, *Radiotherapy & Oncology* 39:179-189; Song *et al.*, 1995, *PDA Journal of Pharmaceutical Science &* Technology 50:372-397; Cleek *et al.*, 1997, *Pro. Int'l. Symp. Control. Rel. Bioact. Mater.* 24:853-854; and Lam *et al.*, 1997, *Proc. Int'l. Symp. Control Rel. Bioact. Mater.* 24:759-760.

[00169] In a specific embodiment wherein the therapeutic or prophylactic composition is a nucleic acid encoding a disclosed antibody or an antigen-binding fragment thereof, the nucleic acid can be administered *in vivo* to promote expression of its encoded antibody, by constructing it as part of an appropriate nucleic acid expression vector and administering it so that it becomes intracellular, *e.g.*, by use of a retroviral vector (*See* U.S. Patent No. 4,980,286), or by direct injection, or by use of microparticle bombardment (*e.g.*, a gene gun; Biolistic, Dupont), or coating with lipids or cell-surface receptors or transfecting agents, or by administering it in linkage to a homeobox-like peptide which is known to enter the nucleus (*See e.g.*, Joliot *et al.*, 1991, *Proc. Natl. Acad. Sci. USA* 88:1864-1868), *etc.* Alternatively, a nucleic acid can be introduced intracellularly and incorporated within host cell DNA for expression by homologous recombination.

[00170] Treatment of a subject with a therapeutically or prophylactically effective amount of the disclosed antibodies can include a single treatment or, preferably, can include a series of treatments.

G. Pharmaceutical Compositions

[00171] The disclosed compositions can include bulk drug compositions useful in the manufacture of pharmaceutical compositions (*e.g.*, impure or non-sterile compositions) and pharmaceutical compositions (*i.e.*, compositions that are suitable for administration to a subject or patient) which can be used in the preparation of unit dosage forms. Such

compositions can include a prophylactically or therapeutically effective amount of a prophylactic and/or therapeutic agent disclosed herein or a combination of those agents and a pharmaceutically acceptable carrier. Preferably, the compositions include a prophylactically or therapeutically effective amount of humanized antibodies and a pharmaceutically acceptable carrier.

[00172] In a specific embodiment, the term "pharmaceutically acceptable" means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly in humans. The term "carrier" refers to a diluent, adjuvant (*e.g.*, Freund's adjuvant (complete and incomplete), excipient, or vehicle with which the therapeutic is administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. Water is a preferred carrier when the pharmaceutical composition is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid carriers, particularly for injectable solutions. Suitable pharmaceutical excipients include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. The composition, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents. These compositions can take the form of solutions, suspensions, emulsion, tablets, pills, capsules, powders, sustained-release formulations and the like.

[00173] Generally, the ingredients of compositions can be supplied either separately or mixed together in unit dosage form, for example, as a dry lyophilized powder or water free concentrate in a hermetically sealed container such as an ampoule or sachette indicating the quantity of active agent. Where the composition is to be administered by infusion, it can be dispensed with an infusion bottle containing sterile pharmaceutical grade water or saline. Where the composition is administered by injection, an ampoule of sterile water for injection or saline can be provided so that the ingredients may be mixed prior to administration.

[00174] The compositions can be formulated as neutral or salt forms. Pharmaceutically acceptable salts include, but are not limited to, those formed with anions such as those derived from hydrochloric, phosphoric, acetic, oxalic, tartaric acids, etc., and those formed with cations such as those derived from sodium, potassium, ammonium, calcium, ferric hydroxides, isopropylamine, triethylamine, 2-ethylamino ethanol, histidine, procaine, *etc.*

H. Kits

[00175] Another embodiment provides a pharmaceutical pack or kit including one or more containers filled with of the disclosed humanized antibodies. Additionally, one or more other prophylactic or therapeutic agents useful for the treatment of a disease can also be included in the pharmaceutical pack or kit. The pharmaceutical pack or kit can include one or more containers filled with one or more of the ingredients of the disclosed pharmaceutical compositionsOptionally associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration.

[00176] The kits that can be used in the above methods. In one embodiment, a kit can include one or more of the disclosed humanized antibodies. In another embodiment, a kit further includes one or more other prophylactic or therapeutic agents useful for the treatment of cancer, in one or more containers. In another embodiment, a kit further includes one or more cytotoxic antibodies that bind one or more cancer antigens associated with cancer. In certain embodiments, the other prophylactic or therapeutic agent is a chemotherapeutic. In other embodiments, the prophylactic or therapeutic agent is a biological or hormonal therapeutic.

I. Diagnostic Methods

[00177] The disclosed antibodies and their antigen-binding fragments can be used for diagnostic purposes, such as to detect, diagnose, or monitor diseases, disorders or infections associated with H7CR expression. The detection or diagnosis of a disease, disorder or infection, particularly an autoimmune disease can be performed by: (a) assaying the expression of H7CR in cells or in a tissue sample of a subject using one or more antibodies (or fragments thereof) that immunospecifically bind to such antigens; and (b) comparing the level of the antigen with a control level, *e.g.*, levels in normal tissue samples or levels in tissue at a different point in time, whereby an increase or decrease in the assayed level of antigen compared to the control level of the antigen is indicative of the disease, disorder or infection. Such antibodies and fragments are preferably employed in immunoassays, such as the enzyme linked immunosorbent assay (ELISA), the radioimmunoassay (RIA) and fluorescence-activated cell sorting (FACS).

[00178] One aspect relates to the use of such antibodies and fragments, and particularly such antibodies and fragments that bind to human H7CR, as reagents for IHC analysis in cells of

an *in vitro* or *in situ* tissue sample or *in vivo*. Thus, the antibodies and fragments of the have utility in the detection and diagnosis of a disease, disorder, or infection in a human. In one embodiment, such diagnosis includes: a) administering to a subject (for example, parenterally, subcutaneously, or intraperitoneally) an effective amount of a labeled antibody or antigen-binding fragment that immunospecifically binds to H7CR; b) waiting for a time interval following the administration for permitting the labeled molecule to preferentially concentrate at sites in the subject where H7CR is expressed (and for unbound labeled molecule to be cleared to background level); c) determining background level; and d) detecting the labeled antibody in the subject, such that detection of labeled antibody above the background level indicates that the subject has the disease, disorder, or infection. In accordance with this embodiment, the antibody is labeled with an imaging moiety which is detectable using an imaging system known to one of skill in the art. Background level can be determined by various methods including, comparing the amount of labeled molecule detected to a standard value previously determined for a particular system.

[00179] It will be understood in the art that the size of the subject and the imaging system used will determine the quantity of imaging moiety needed to produce diagnostic images. *In vivo* tumor imaging is described in S.W. Burchiel *et al.*, "*Immunopharmacokinetics of Radiolabeled Antibodies and Their Fragments*," (Chapter 13 in TUMOR IMAGING: THE RADIOCHEMICAL DETECTION OF CANCER, S.W. Burchiel and B. A. Rhodes, eds., Masson Publishing Inc. (1982).

[00180] Depending on several variables, including the type of label used and the mode of administration, the time interval following the administration for permitting the labeled molecule to preferentially concentrate at sites in the subject and for unbound labeled molecule to be cleared to background level is 6 to 48 hours or 6 to 24 hours or 6 to 12 hours. In another embodiment the time interval following administration is 5 to 20 days or 5 to 10 days.

[00181] In one embodiment, monitoring of a disease, disorder or infection is carried out by repeating the method for diagnosing the disease, disorder or infection, for example, one month after initial diagnosis, six months after initial diagnosis, one year after initial diagnosis, etc.

[00182] Presence of the labeled molecule can be detected in the subject using methods known in the art for *in vivo* scanning. These methods depend upon the type of label used. Skilled artisans will be able to determine the appropriate method for detecting a particular label. Methods and devices that may be used in the diagnostic methods include, but are not

limited to, computed tomography (CT), whole body scan such as position emission tomography (PET), magnetic resonance imaging (MRI), and sonography.

[00183] In a specific embodiment, the molecule is labeled with a radioisotope and is detected in the patient using a radiation responsive surgical instrument (Thurston *et al.*, U.S. Patent No. 5,441,050). In another embodiment, the molecule is labeled with a fluorescent compound and is detected in the patient using a fluorescence responsive scanning instrument. In another embodiment, the molecule is labeled with a positron emitting metal and is detected in the patient using positron emission-tomography. In yet another embodiment, the molecule is labeled with a paramagnetic label and is detected in a patient using magnetic resonance imaging (MRI).

[00184] Having now generally described the invention, the same will be more readily understood through reference to the following examples, which are provided by way of illustration and are not intended to be limiting of the present invention unless specified.

Example 1
Characterization of Anti-Human H7CR Antibodies and expression pattern of H7CR

Materials and Methods

[00185] For binding affinity estimation, 0.2 million CHO.hH7CR transfectants(Figure 2), naïve CD4+ CD45RA+ T cells (Figure 3A) or naïve CD8+ CD45RA+ T cells (Figure 3B) were resuspended in 100µl flow cytometry buffer (PBS+2%FBS). A serial dilution of chimeric 1.3 and 4.5 of 0, 0.1ng, 0.3ng, 1ng, 3ng, 10ng, 30ng, 100ng, 300ng, 1µg, 3µg and 10µg were added to the cells and incubated at 4°C for 30 min. Cells were then washed twice with 2ml flow cytometry buffer, and resuspended in 100µl flow cytometry buffer. 1µl anti-hIg PE secondary antibody (Biolegend) was added and incubated with the cells for 15mins. Samples were then washed and resuspended in 100µl flow cytometry buffer. Flow Cytometry data was acquired using BD Canto (BD Biosciences) in plate format and analyzed by FlowJo software. Staining data (MFI) was then input into Prism 5 software to generate binding curve. Curve-fit using one-site specific binding algorithm calculates individual K_D for each antibody.

5 µg/ml H7CR 1.3, 4.5 and 7.8 mAbs was used to stain H7CR stable transfectants to show binding specificity (Figure 4). 10 µg/ml B7-H7mIg fusion protein was also used to stain H7CR CHO transfectants. H7CR mAbs were added to the system to evaluate the blocking capability of H7CR mAbs on B7-H7-H7CR interactions (Figure 5).

Immunohistochemistry staining for H7CR on human tonsil paraffin-embedded section was performed with 4.5 antibody at a concentration of 5 μg/ml using a standard protocol (Figure 6). For cell surface staining and analysis by flow cytometry, cells were incubated with the indicated mAb for 30 min at 4°C, washed with buffer and analyzed. Expression of H7CR on human and mouse PBMC was evaluated by lineage marker and 1.3 antibody staining (Figure 7-11). Expression of B7-H7 on activated monocyte-derived DC was evaluated by anti-B7-H7 antibody staining (Figure 12).

Results

[00186] Hamster antibodies 1.3, 4.5 and 7.8 were found to be capable of immunospecifically binding to human H7CR. **Figure 2** shows the respective binding affinities of anti-H7CR antibodies 1.3 and 4.5. Antibody 4.5 was found to have a Kd of 3.5 nM. Antibody 1.3 was found to have a Kd of 5.9 nM. H7CR mAb binding curves to naïve CD4 and CD8 T cells indicated that the receptor saturation dose for both antibodies was 1μg/ml (**Figure 3, Panels A and B**).

[00187] **Figure 4 (Panels A-C)** show the ability of the antibodies 1.3, 4.5 and 7.8 to bind to human H7CR expressed on the surface of CHO cells. The antibodies were tested for their ability to block H7CR's interaction with B7-H7 by incubating the antibodies with H7CR CHO transfectants in the presence of a B7-H7-murine IgG2a fusion protein. As shown in **Figure 5 (Panels A-D)**, the presence of H7CR antibodies did not disrupt the ability of the B7-H7 Ig to bind to H7CR. Thus, these three antibodies were substantially incapable of blocking H7CR's interaction with B7-H7. As shown in **Figure 6**, the anti-human H7CR antibody (Clone 4.5) was found to be capable of binding to H7CR as endogenously expressed on the surface of human tonsil tissue.

[00188] The anti-H7CR antibodies permitted a determination of the expression profiles of H7CR and B7-H7. **Figure 7** shows that H7CR expression was associated with a naïve T cell phenotype in T and NK cells. **Figure 8 (Panels A-H)** shows the expression profiles of H7CR and B7-H7 of four healthy PMBC donors (Donor 1, **Panels A and B**; Donor 2, **Panels C and D**; Donor 3 (**Panels E and F**) and Donor 4 (**Panels G and H**)). **Figure 9 (Panels A-H)** shows the expression profiles of H7CR and B7-H7 of four healthy PMBC donors (Donor 1, **Panels A and B**; Donor 2, **Panels C and D**; Donor 3 (**Panels E and F**) and Donor 4 (**Panels G and H**)). **Figure 10 (Panels A-AD)** shows the expression of H7CR and B7-H7 by human monocytes, CD8+ CD3+ lymphocytes, CD8– CD3+ lymphocytes, CD16+ NK cells, and CD3– CD8– cells. **Figure 11 (Panels A-AD)** shows the expression of H7CR and B7-H7 by cynomolgus monkey monocytes, CD8+ CD3+ lymphocytes, CD8– CD3+ lymphocytes,

CD16+ NK cells, and CD3– CD8– cells, and indicates that cynomolgus monkey is a relevant species for *in vivo* and toxicology studies.

[00189] An *in vitro* functional analysis of expression of B7-H7 was conducted. Matured monocyte-derived dendritic cells were evaluated for their ability to express B7-H7 and other activation markers. The results of this study (**Figure 12, Panels A-K**) confirm the expression of such markers and show that matured dendritic cells are relevant for *in vitro* functional testing.

Example 2

Anti-H7CR Antibodies Promote Antigen Specific Memory T cell Responses

Materials and Methods

[00190] In order to further characterize the anti-H7CR antibodies, a tetanus toxoid (TT) memory recall response assay was conducted. Monocyte-derived immature DC were matured by incubation with 1ng/ml TNFα and 1μg/ml PGE2 for two days, and were incubated in the presence of 50 μg/ml tetanus toxoid (TT) overnight on the second day of DC maturation. The dendritic cells were washed three times with X-Vivo media and then incubated in the presence of carboxyfluorescein succinimidyl ester (CFSE)-labeled autologous T cells at a ratio of 1:20 for two weeks in the presence of 100 ng/ml TT and 10 μg/ml H7CR1.3, 4.5 or 7.8 monoclonal antibody (Figure 13), or humanized 1.3 variants (Figure 23) . Cellular proliferation was monitored by CFSE dilution using flow cytometry. In some experiments, intracellular staining of human IFNγ and TNFα were performed. Golgi Blocker Brefeldin A (eBioscience) was added into DC-T cell culture system for 8 hours. Activated human T cells were harvested and washed with cold PBS. Cell surface markers were first stained. Intracellular staining for IFNγ and TNFα was preformed according to manufacturer's protocol (Cytofix/Cytoperm, BD).

[00191] Culture supernatants were collected at different time points for total cytokine analysis by Bio-Plex Pro Human Cytokine 17-Plex kit (M5000031YV, BioRad) according to Manufacturer's manual. Data were collected and analysized by Bio-Plex 200 system (BioRad).

Results

[00192] The results of this analysis (**Figure 13**) show that the anti-H7CR antibodies promote antigen specific memory T cell responses. The day 7 supernatants were evaluated in order to

determine the nature and levels of cytokines expressed by the cells. The results of this analysis are shown in **Figure 14 (Panels A-L)**. The results show that anti-H7CR antibodies 1.3, 4.5 and 7.8 mediated non-identical cytokine expression profiles. Notably, antibody 1.3 mediated high levels of IFNγ, TNFα, GM-CSF and IL-10 and antibody 4.5 mediated high levels of IL-5 and IL-13.

[00193] Cells were subjected to intracellular staining after 5 hr incubation with Golgi Block (without PMA and Ionmycin) and their intracellular expression of IFNγ and carboxyfluorescein succinimidyl ester (CSFE) dilution were assessed. The results of this investigation revealed that treatment with anti-H7CR antibodies enhanced proliferation as represented by CFSE dilution and IFNγ expression in antigen-specific T cells (**Figures 15A and 15B**). The IFNγ+ percentage in divided T cells increased from 0.15% (**Figure 15A**; control) to 0.96% (**Figure 15B**; antibody 1.3 treated).

[00194] Among 1.3 humanized variants (Figure 23), variant 1, 3 and 5 showed comparable enhancement of CFSE dilution with the parental chimeric 1.3 antibody of the TT-specific T cells.

Example 3

The Interaction Of B7-H7:H7CR Regulates Antigen-Specific Human T Cell Responses

Materials and Methods

[00195] In order to determine the role of the B7-H7:H7CR pathway on the antigen-specific T cell response, purified human $CD4^+$ T cells were labeled with CFSE, and cultured with autologous monocyte-derived dendritic cells that had been pre-incubated with 50 μg/ml tetanus toxoid ("**TT**") as antigen. The dendritic cells were washed three times with X-Vivo media and then incubated in the presence of carboxyfluorescein succinimidyl ester (CFSE)-labeled autologous T cells at a ratio of 1:20 for two weeks in the presence of 100 ng/ml TT and 10 μg/ml H7CR monoclonal antibody. Cellular proliferation was monitored by CFSE dilution using flow cytometry.

Results

[00196] A TT-specific T cell proliferation was found to be strongly augmented when agonistic anti-H7CR mAb were included in the culture (to amplify H7CR signal on T cells) (**Figure 16A**). Inclusion of CTLA4-Ig, a fusion protein blocking B7:CD28 interactions, in the beginning of cell culture greatly inhibited T cell proliferation, even in the presence of agonistic anti-H7CR mAb. These results indicate that H7CR co-stimulation is dependent on endogenous B7:CD28 interaction.

[00197] Cells incubated in the presence of the agonistic anti-H7CR mAb exhibited a substantial enhancement of cytokine production, including IFN-γ (**Figure 16B, Panel A**) and IL-5, IL-10, TNF-α and IL-17 (**Figure 16B, Panel B**). These results indicate that H7CR co-stimulation is not specific for a subset of $CD4^+$ T helper cells. Together, these results indicate that the H7CR signal promotes the growth and differentiation of pan human $CD4^+$ T cells, a feature similar to CD28 co-stimulation.

Example 4
Humanization of Anti-H7CR Antibodies 1.3 and 4.5

[00198] Hamster anti-H7CR antibodies 1.3 and 4.5 were humanized using a process that included generating a homology modeled antibody 3D structure and creating a profile of the parental antibody based on structure modeling. A set of humanized heavy and light chain variable region sequences were generated, each of which combined specific regions of the parental antibody sequence with the majority of the human framework sequence. A total of 6 humanized heavy chain sequences and 6 humanized light chain sequences were produced.

[00199] Sequence alignments comparing the variable domains of antibody 1.3 to the human germline framework sequence database were generated using Geneious. Preferred acceptor frameworks were identified based on the overall sequence identity across the framework, matching interface position, similarly classed CDR canonical positions, and presence of N-glycosylation sites that would have to be removed.

[00200] A structural model of the variable light and heavy chains of the antibodies was generated in Discovery Studio. Template structures were identified by searching the PDB database with the 1.3 light chain and heavy chain variable domain sequences with and without their CDRs. The alignment of the 1.3 sequences to the templates and modeling the structures based on homology were carried out using MODELLER (Sali, A. et al. (1993) "*Comparative Protein Modelling By Satisfaction Of Spatial Restraints*," J. Molec. Biol. 234(3):779-815).

[00201] A number of hybrid sequences that combined different regions of the parental antibody sequence with that of the human frameworks were systematically analyzed using the 3D model to identify the hybrid sequences that were predicted to have the least impact on the defined structure of the CDRs (Chothia, C. *et al.* (1987) "*Canonical Structures For The Hypervariable Regions Of Immunoglobulins*," J. Mol. Biol. 196:901-917; Martin, A.C. *et al.* (1996) "*Structural Families In Loops Of Homologous Proteins: Automatic Classification, Modelling And Application To Antibodies*," J. Molec. Biol. 263(5):800-815). Particular attention was given to hybrid sequences that contained amino acids from the human

framework that were within 5Å of CDR loops, in the Vernier zone, in the VH/VL interchain interface, or in CDR canonical class determining positions, as these hybrid sequences are judged more likely to have a detrimental effect on the function of the resulting humanized antibody.

[00202] A profile of the parental antibody was created based on CDR analysis and structure modeling. Human acceptor frameworks were identified based on sequence and homology comparisons. Humanized antibodies were designed by creating multiple hybrid sequences that fuse parts of the parental antibody sequence with the human framework sequences. Using the 3D model, these humanized sequences were methodically analyzed by eye and by computer modeling to isolate the sequences that would most likely retain antigen binding. The goal was to maximize the amount of human sequence in the final humanized antibody while retaining the original antibody specificity.

[00203] Collier de Perles is a 2D representation of variable domains and provides information on the amino acid positions in beta-strands and loops in the variable domains (Ruiz, M. *et al.* (2002) "*IMGT Gene Identification And Colliers de Perles Of Human Immunoglobulins With Known 3D Structures*," Immunogenetics 53(10-11):857-883). Collier de Perles of antibody 1.3 light chain and heavy chain variable regions are shown in **Figure 17A** and **Figure 17B**, respectively. **Figures 18A** and **18B** show the Collier de Perles of the antibody 4.5 light chain and heavy chain variable regions, respectively. The three CDR loops of the chains are shown at the top of the diagrams. There are no free Cys residues or N-linked glycosylation sites in the variable light or heavy chain regions.

Humanization of Antibody 1.3

[00204] Sequence alignments comparing hamster antibody 1.3 variable domains to the human germline database were generated. Based on the overall sequence identity, matching interface position, and similarly classed CDR canonical positions, two germline families were identified as possible acceptor frameworks for the light chain: **IGKV4-1*01** and **IGKV2D-28*01**. The J-segment genes were compared to the parental sequence over FR4 and J-segments, and **IGKJ2*01** was selected for the light chain. Alignment of the parental 1.3 VL chain to these acceptor frameworks is shown in **Table 6**, with non-identical residues shown underlined.

Table 6

Variable Light Chain	SEQ ID #	Sequence
		10 20 30 40
Hamster 1.3	**60**	DIVMTQSPSS LAVSAGEKVT ISCLSSQSLF SSNTNRNYLN
IGKV4-1*01	**61**	DIVMTQSP**D**S LAVS**L**GE**RA**T I**N**C**K**SSQS**VL** **Y**S**SN**N**K**NYL**A**

Table 6		
Variable Light Chain	**SEQ ID #**	**Sequence**
IGKV2D-28*01	**62**	DIVMTQSPLS LPVTPGEPAS ISCRSSQSLL HSN-GYNYLD
		50 60 70 80
Hamster 1.3	**63**	WYLQKPGQSP KLLIYHASTR LTGVPDRFIG SGSGTDFTLT
IGKV4-1*01	**64**	WYQQKPGQPP KLLIYWASTR ESGVPDRFSG SGSGTDFTLT
IGKV2D-28*01	**65**	WYLQKPGQSP QLLIYLGSNR ASGVPDRFSG SGSGTDFTLK
		90 100 110
Hamster 1.3	**66**	ISSVQAEDLG DYYCQHHYET PLTFGDGTKL EIK
IGKV4-1*01	**67**	ISSLQAEDVA VYYCQQYYST PYT
IGKV2D-28*01	**68**	ISRVEAEDVG VYYCMQALQT PYT
IGKJ2*01	**69**	FGQGTKL EIK

[00205] The heavy chain of hamster antibody 1.3 was found to be most similar to the germline **IGHV4-31*02**. In the top 50 closest germlines to antibody 1.3 heavy chain, none of the CDR H3 have the same length as the 1.3 heavy chain. Therefore, a rearranged heavy chain was selected as the second acceptor framework (**AAY33199.1**) based on overall similarity, CDR lengths, and CDR canonical structures. The J-segment genes were compared to the Parental sequence over FR4 and J-segments, and **IGHJ3*01** was selected for the heavy chain. Alignment of the parental VH chain to these acceptor frameworks is shown in **Table 7**, with non-identical residues shown underlined.

Table 7		
Variable Heavy Chain	**SEQ ID #**	**Sequence**
		10 20 30 40
Hamster 1.3	**70**	QIQLQESGPG LVKPSQSLSL TCSVTGFSIS TSGYYWTWIR
IGHV4-31*02	**71**	QVQLQESGPG LVKPSQTLSL TCTVSGGSIS SGGYYWSWIR
AAY33199.1	**72**	QVQLQESGPG LVKPAQTLSL TCTVSGGSIS SVNYYWSWIR
		50 60 70 80
Hamster 1.3	**73**	QFPGKRLEWM GYINYGGGTS YNPSLKSRIS ITRDTSKNQF
IGHV4-31*02	**74**	QHPGKGLEWI GYIYYSGSTY YNPSLKSRVT ISVDTSKNQF
AAY33199.1	**75**	QYPGKGLEWI GYIYYRGSTY YNPSLKSRVT ISVDTSKNQF
		90 100 110 120
Hamster 1.3	**76**	LLHLNSVTTE DTATYCCATM ADRFAFFDVW GQGIQVTVSS
IGHV4-31*02	**77**	SLKLSSVTAA DTAVYYCAR
AAY33199.1	**78**	SLKLTSVTAA DTAVYHCARE RTMTGAFDIW GQGTMVTVSS
IGHJ3*01	**79**	DAFDVW GQGTMVTVSS

[00206] For the light chain, three humanized chains were created for each of the two acceptor frameworks **IGKV4-1*01** and **IGKV2D-28*01** to thereby form six humanized 1.3 light chains. The first humanized chain for each acceptor framework (VL1A, VL2A) contains the most human framework (**Humanized Light Chain 1**). The second humanized chain for each acceptor framework (VL1B, VL2B) contains some amount of parental sequence fused with the human framework sequence, which should help retain the original

CDR conformation (**Humanized Light Chain 2**). The third humanized chain for each of the acceptor frameworks (VL1C, VL2C) contains even more parental sequence fused with the human framework, which should help maintain the original antibody specificity and CDR structure (**Humanized Light Chain 3**). The amino acid sequences of these chains are as indicated below.

[00207] Amino Acid Sequences of the **Light Chain Variable Region** of the humanized variants of anti-human H7CR antibody 1.3, as derived from the **IGKV4-1*01** acceptor framework (CDRs are shown underlined):

1. VL1A IGKV4-1*01 (Humanized 1):

DIVMTQSPDS LAVSLGERAT INCKSS**QSLF** **SSNTNRNY**LA WYQQKPGQPP KLLIY**HAS**TR ESGVPDRFSG SGSGTDFTLT ISSLQAEDVA VYYC**QHHYET** **PLT**FGQGTKL EIK **(SEQ ID NO:17)**

2. VL1B IGKV4-1*01 (Humanized 2):

DIVMTQSPDS LAVSLGERAT INCKSS**QSLF** **SSNTNRNY**LN WYQQKPGQSP KLLIY**HAS**TR LSGVPDRFSG SGSGTDFTLT ISSLQAEDVA DYYC**QHHYET** **PLT**FGDGTKL EIK **(SEQ ID NO:18)**

3. VL1C IGKV4-1*01 (Humanized 3):

DIVMTQSPDS LAVSLGERAT INCLSS**QSLF** **SSNTNRNY**LN WYLQKPGQSP KLLIY**HAS**TR LSGVPDRFIG SGSGTDFTLT ISSLQAEDVG DYYC**QHHYET** **PLT**FGDGTKL EIK **(SEQ ID NO:19)**

[00208] Amino Acid Sequences of the **Light Chain Variable Region** of the humanized variants of anti-human H7CR antibody 1.3, as derived from the **IGKV2D-28*01** acceptor framework (CDRs are shown underlined):

1. VL2A IGKV2D-28*01 (Humanized 1):

DIVMTQSPLS LPVTPGEPAS ISCRSS**QSLF** **SSNTNRNY**LD WYLQKPGQSP QLLIY**HAS**NR ASGVPDRFSG SGSGTDFTLK ISRVEAEDVG VYYC**QHHYET** **PLT**FGDGTKL EIK **(SEQ ID NO:20)**

2. VL2B IGKV2D-28*01 (Humanized 2):

DIVMTQSPLS LPVTPGEPAS ISCRSS**QSLF** **SSNTNRNY**LN WYLQKPGQSP KLLIY**HAS**TR ASGVPDRFSG SGSGTDFTLK ISRVEAEDVG VYYC**QHHYET** **PLT**FGDGTKL EIK **(SEQ ID NO:21)**

3. VL2C IGKV2D-28*01 (Humanized 3):

DIVMTQSPLS LPVTPGEPAS ISCLSS**QSLF** **SSNTNRNY**LN WYLQKPGQSP KLLIY**HAS**TR LSGVPDRFSG SGSGTDFTLK ISRVEAEDVG DYYC**QHHYET** **PLT**FGDGTKL EIK **(SEQ ID NO:22)**

[00209] For the heavy chain, three humanized chains were created for each of the **IGHV4-31*02** and **AAY33199.1** acceptor frameworks identified above. In a similar fashion to the light chain, the first humanized chain for each acceptor framework (VH1A, VH2A) contains the most human sequence (Humanized 1). The second humanized chain for each acceptor

framework (VH1B, VH2B) should help retain the original CDR conformation (Humanized 2). The third chain for each of the acceptor frameworks (VH1C, VH2C) should help maintain the original antibody specificity and CDR structure (Humanized 3). The amino acid sequences of these chains are as indicated below.

[00210] Amino Acid Sequences of the **Heavy Chain Variable Region** of the humanized variants of anti-human H7CR antibody 1.3, as derived from the **IGHV4-31*02** acceptor framework (CDRs are shown underlined):

1. VH1A IGHV4-31*02 (Humanized 1):

QVQLQESGPG LVKPSQTLSL TCTVS**GFSIS** **TSG**YYWSWIR QHPGKGLEWI
GY**INYGGGT**Y YNPSLKSRVT ISVDTSKNQF SLKLSSVTAA DTAVYYC**ATM**
ADRFAFFDVW GQGTMVTVSS **(SEQ ID NO:23)**

2. VH1B IGHV4-31*02 (Humanized 2):

QVQLQESGPG LVKPSQTLSL TCTVS**GFSIS** **TSG**YYWSWIR QHPGKRLEWI
GY**INYGGGT**S YNPSLKSRVT ISRDTSKNQF SLKLSSVTAA DTAVYCC**ATM**
ADRFAFFDVW GQGTMVTVSS **(SEQ ID NO:24)**

3. VH1C IGHV4-31*02 (Humanized 3):

QVQLQESGPG LVKPSQTLSL TCTVS**GFSIS** **TSG**YYWSWIR QFPGKRLEWM
GY**INYGGGT**S YNPSLKSRVT ISRDTSKNQF SLKLSSVTAA DTATYCC**ATM**
ADRFAFFDVW GQGTMVTVSS **(SEQ ID NO:25)**

[00211] Amino Acid Sequences of the **Heavy Chain Variable Region** of the humanized variants of anti-human H7CR antibody 1.3, as derived from the **AAY33199.1** acceptor framework (CDRs are shown underlined):

1. VH2A AAY33199.1 (Humanized 1):

QVQLQESGPG LVKPAQTLSL TCTVS**GFSIS** **TSG**YYWSWIR QYPGKGLEWI
GY**INYGGGT**Y YNPSLKSRVT ISVDTSKNQF SLKLTSVTAA DTAVYHC**ATM**
ADRFAFFDVW GQGTMVTVSS **(SEQ ID NO:26)**

2. VH2B AAY33199.1 (Humanized 2):

QVQLQESGPG LVKPAQTLSL TCTVS**GFSIS** **TSG**YYWSWIR QYPGKRLEWI
GY**INYGGGT**S YNPSLKSRVT ISRDTSKNQF SLKLTSVTAA DTATYCC**ATM**
ADRFAFFDVW GQGTMVTVSS **(SEQ ID NO:27)**

3. VH2C AAY33199.1 (Humanized 3):

QVQLQESGPG LVKPAQTLSL TCTVS**GFSIS** **TSG**YYWSWIR QFPGKRLEWM
GY**INYGGGT**S YNPSLKSRVT ISRDTSKNQF SLKLTSVTAA DTATYCC**ATM**
ADRFAFFDVW GQGTMVTVSS **(SEQ ID NO:28)**

[00212] Preferred antibodies and their antigen-binding fragments include any of the 36 combinations of the above-described humanized variants of anti-human H7CR antibody 1.3. Specifically, such antibodies contain the combinations shown in **Table 4**. All 36 such humanized variants of anti-human H7CR antibody 1.3 were evaluated for their respective

ability to bind human H7CR molecules as ectopically expressed on the surface of a CHO cell and 28 out of 36 are found to be able to bind to such human H7CR molecules.

Humanization of Anti-H7CR Antibody 4.5

[00213] Sequence alignments comparing hamster antibody 4.5 variable domains to the human germline database were generated. Based on the overall sequence identity, matching interface position, and similarly classed CDR canonical positions, two germline families were identified as possible acceptor frameworks for the light chain: **IGKV4-1*01** and **IGKV2D-40*01**. The J-segment genes were compared to the parental sequence over FR4 and J-segments, and **IGKJ5*01** was selected for the light chain. Alignment of the parental 1.3 VL chain to these acceptor frameworks is shown in **Table 8**, with non-identical residues shown underlined.

Table 8

Variable Light Chain	SEQ ID #	Sequence
		10 20 30 40
Hamster 4.5	**80**	DIVMTQSPSS LAVSAGEKVT ISCLSSQSLF SSNTKRNYLN
IGKV4-1*01	**81**	DIVMTQSPDS LAVSLGERAT INCKSSQSVL YSSNMKNYLA
IGKV2D-40*01	**82**	DIVMTQTPLS LPVTPGEPAS ISCRSSQSLL DSDDGNTYLD
		50 60 70 80
Hamster 4.5	**83**	WYLQKPGQSP KLLIYHASTR LTGVPGRFIG SGSGTDFTLT
IGKV4-1*01	**84**	WYQQKPGQPP KLLIYWASTR ESGVPDRFSG SGSGTDFTLT
IGKV2D-40*01	**85**	WYLQKPGQSP QLLIYTLSYR ASGVPDRFSG SGSGTDFTLK
		90 100 110
Hamster 4.5	**86**	VSTVQAEDLG DYFCQQHYET PLTFGDGTRL EIK
IGKV4-1*01	**87**	ISSLQAEDVA VYYCQQYYST PYT
IGKV2D-40*01	**88**	ISRVEAEDVG VYYCMQRIEF P
IGKJ5*01	**89**	ITFGQGTRL EIK

[00214] The heavy chain of hamster antibody 4.5 was found to be most similar to the germline **IGHV4-31*02**. In the top 50 closest germlines to antibody 4.5 heavy chain, the second acceptor framework that had a similar canonical structure is **IGHV2-5*01**. The J-segment genes were compared to the Parental sequence over FR4 and J-segments, and **IGHJ5*01** was selected for the heavy chain. Alignment of the parental VH chain to these acceptor frameworks is shown in **Table 9**, with non-identical residues shown underlined.

Table 9

Variable Heavy Chain	SEQ ID #	Sequence
		10 20 30 40
Hamster 4.5	**90**	QIQLQESGPG LVKPSQSLSL TCSVTGFSIT TGGYYWNWIR
IGHV4-31*02	**91**	QVQLQESGPG LVKPSQTLSL TCTVSGGSIS SGGYYWSWIR
IGHV2-5*01	**92**	QITLKESGPT LVKPTQTLTL TCTFSGFSLS TSGVGVGWIR
		50 60 70 80
Hamster 4.5	**93**	QFPGKKLEWM GYIYTSGRTS YNPSLKSRIS ITRDTSKNQF

Table 9		
Variable Heavy Chain	**SEQ ID #**	**Sequence**
IGHV4-31*02	**94**	QHPGKGLEWI GYIYYSGSTY YNPSLKSRVT ISVDTSKNQF
IGHV2-5*01	**95**	QPPGKALEWL ALIYWNDDKR YSPSLKSRLT ITKDTSKNQV
		90 100 110 120
Hamster 4.5	**96**	FLQLNSMTTE DTATYYCADM ADKGGWFAYW GQGTLVTVSS
IGHV4-31*02	**97**	SLKLSSVTAA DTAVYYCA-- --R
IGHV2-5*01	**98**	VLTMTNMDPV DTATYYCA-- --HR
IGHJ5*01	**99**	NWFDSW GQGTLVTVSS

[00215] For the light chain, three humanized chains were created for each of the two acceptor frameworks **IGKV4-1*01** and **IGKV2D-40*01** to thereby form six humanized 4.5 light chains. The first humanized chain for each acceptor framework (VL1A, VL2A) contains the most human framework (**Humanized Light Chain 1**). The second humanized chain for each acceptor framework (VL1B, VL2B) contains some amount of parental sequence fused with the human framework sequence, which should help retain the original CDR conformation (**Humanized Light Chain 2**). The third humanized chain for each of the acceptor frameworks (VL1C, VL2C) contains even more parental sequence fused with the human framework, which should help maintain the original antibody specificity and CDR structure (**Humanized Light Chain 3**). The amino acid sequences of these chains are as indicated below.

[00216] Amino Acid Sequences of the **Light Chain Variable Region** of the humanized variants of anti-human H7CR antibody 4.5, as derived from the **IGKV4-1*01** acceptor framework (CDRs are shown underlined):

1. VL1A IGKV4-1*01 (Humanized 1):

   DIVMTQSPDS LAVSLGERAT INCKSSQSLF SSNTKRNYLA WYQQKPGQPP KLLIYHASTR ESGVPDRFSG SGSGTDFTLT ISSLQAEDVA VYYCQQHYET PLTFGQGTRLEIK **(SEQ ID NO:33)**

2. VL1B IGKV4-1*01 (Humanized 2):

   DIVMTQSPDS LAVSLGERAT INCKSSQSLF SSNTKRNYLN WYQQKPGQPP KLLIYHASTR LSGVPDRFSG SGSGTDFTLT ISSLQAEDVA DYFCQQHYET PLTFGDGTRL EIK **(SEQ ID NO:34)**

3. VL1C IGKV4-1*01 (Humanized 3):

   DIVMTQSPDS LAVSLGERAT INCLSSQSLF SSNTKRNYLN WYQQKPGQSP KLLIYHASTR LSGVPDRFSG SGSGTDFTLT ISSLQAEDVA DYFCQQHYET PLTFGDGTRL EIK **(SEQ ID NO:35)**

[00217] Amino Acid Sequences of the **Light Chain Variable Region** of the humanized variants of anti-human H7CR antibody 4.5, as derived from the **IGKV2D-40*01** acceptor framework (CDRs are shown underlined):

1. VL2A IGKV2D-40*01 (Humanized 1):

DIVMTQTPLS LPVTPGEPAS ISCRSS**QSLF** **SSNTKRNY**LD WYLQKPGQSP QLLIY**HAS**YR ASGVPDRFSG SGSGTDFTLK ISRVEAEDVG VYYC**QQHYET** **PLT**FGQGTRL EIK **(SEQ ID NO:36)**

2. VL2B IGKV2D-40*01 (Humanized 2):

DIVMTQTPLS LPVTPGEPAS ISCRSS**QSLF** **SSNTKRNY**LN WYLQKPGQSP KLLIY**HAS**TR LSGVPDRFSG SGSGTDFTLK ISRVEAEDVG DYFC**QQHYET** **PLT**FGDGTRL EIK **(SEQ ID NO:37)**

3. VL2C IGKV2D-40*01 (Humanized 3):

DIVMTQTPSS LPVTPGEPAS ISCLSS**QSLF** **SSNTKRNY**LN WYLQKPGQSP KLLIY**HAS**TR LSGVPDRFSG SGSGTDFTLK ISRVEAEDVG DYFC**QQHYET** **PLT**FGDGTRL EIK **(SEQ ID NO:38)**

[00218] For the heavy chain, three humanized chains were created for each of the **IGHV4-31*02** and **IGHV2-5*01** acceptor frameworks identified above. In a similar fashion to the light chain, the first humanized chain for each acceptor framework (VH1A, VH2A) contains the most human sequence (Humanized 1). The second humanized chain for each acceptor framework (VH1B, VH2B) should help retain the original CDR conformation (Humanized 2). The third chain for each of the acceptor frameworks (VH1C, VH2C) should help maintain the original antibody specificity and CDR structure (Humanized 3). The amino acid sequences of these chains are as indicated below.

[00219] Amino Acid Sequences of the **Heavy Chain Variable Region** of the humanized variants of anti-human H7CR antibody 4.5, as derived from the **IGHV4-31*02** acceptor framework (CDRs are shown underlined):

1. VH1A IGHV4-31*02 (Humanized 1):

QVQLQESGPG LVKPSQTLSL TCTVS**GFSIT** **TGGYY**WSWIR QHPGKGLEWI GY**IYTSGRT**Y YNPSLKSRVT ISVDTSKNQF SLKLSSVTAA DTAVYYC**ADM** **ADKGGWFAY**W GQGTLVTVSS **(SEQ ID NO:39)**

2. VH1B IGHV4-31*02 (Humanized 2):

QVQLQESGPG LVKPSQTLSL TCTVS**GFSIT** **TGGYY**WNWIR QHPGKKLEWI GY**IYTSGRT**S YNPSLKSRVT ISRDTSKNQF SLKLSSVTAA DTAVYYC**ADM** **ADKGGWFAY**W GQGTLVTVSS **(SEQ ID NO:40)**

3. VH1C IGHV4-31*02 (Humanized 3):

QVQLQESGPG LVKPSQTLSL TCTVS**GFSIT** **TGGYY**WNWIR QFPGKKLEWM GY**IYTSGRT**S YNPSLKSRVT ISRDTSKNQF SLKLSSVTAA DTAVYYC**ADM** **ADKGGWFAY**W GQGTLVTVSS **(SEQ ID NO:41)**

[00220] Amino Acid Sequences of the **Heavy Chain Variable Region** of the humanized variants of anti-human H7CR antibody 4.5 as derived from the **IGHV2-5*01** acceptor framework (CDRs are shown underlined):

1. VH2A IGHV2-5*01 (Humanized 1):

QITLKESGPT LVKPTQTLTL TCTFS**GFSIT** **TGGYY**VGWIR QPPGKALEWL
AL**IYTSGRT**R YSPSLKSRLT ITKDTSKNQV VLTMTNMDPV DTATYYC**ADM**
ADKGGWFAYW GQGTLVTVSS **(SEQ ID NO:42)**

2. VH2B IGHV2-5*01 (Humanized 2):

QITLKESGPT LVKPTQTLTL TCTVS**GFSIT** **TGGYY**WNWIR QPPGKKLEWL
AL**IYTSGRT**S YNPSLKSRLT ITKDTSKNQV VLTMTNMDPV DTATYYC**ADM**
ADKGGWFAYW GQGTLVTVSS **(SEQ ID NO:43)**

3. VH2C IGHV2-5*01 (Humanized 3):

QIQLKESGPT LVKPTQTLTL TCTVS**GFSIT** **TGGYY**WNWIR QPPGKKLEWM
AL**IYTSGRT**S YNPSLKSRLT ITKDTSKNQV VLTMTNMDPV DTATYYC**ADM**
ADKGGWFAYW GQGTLVTVSS **(SEQ ID NO:44)**

[00221] Preferred antibodies and their antigen-binding fragments include any of the 36 combinations of the above-described humanized variants of anti-human H7CR antibody 4.5. Specifically, such antibodies include the combinations shown in **Table 5**. All 36 such humanized variants of anti-human H7CR antibody 4.5 are evaluated for their respective ability to bind human H7CR molecules as endogenously expressed on the surface of a cell and all are found to be able to bind to such human H7CR molecules.

Example 5

Antibody 1.3 Increases T Cell Functionality In vivo

Materials and Methods

[00222] NOD-SCID Il2rg-/- (NSG) mice (Jackson Lab) were intraperitoneally transferred with 15~20 million human PBMCs or 10 million purified naïve CD4+ human T cells. On day 0 and day 2, each mouse was inoculated peritoneally with 300µg control or H7CR mAb 1.3. 6 days after transfer, splenocytes were harvested. Human T cells were detected by staining for human CD45, CD3, and CD8. To monitor cell division, hPBMCs were labeled with CFSE before transfer.

Results

[00223] Flow cytometric analysis revealed that antibody 1.3 expanded human anti-mouse xeno-reactive T cells as evidenced by increased population of CFSE diluted population in both human CD4+ and CD8+ T cells. (Figures 19A-19D)

Example 6

Antibody 1.3 Increase CD40L, IFNγ, and CD107a Expression in vivo: Xeno GvDH Model

Materials and Methods

[00224] NOD-*SCID Il2rg*$^{-/-}$ (NSG) mice (Jackson Lab) were intraperitoneally transferred with 15~20 million human PBMCs or 10 million purified naïve CD4+ human T cells. On day 0 and day 2, each mouse was inoculated peritoneally with 300μg control or H7CR mAb 1.3. 6 days after transfer, splenocytes were harvested. Human T cells were detected by staining for human CD45, CD3, and CD8. Splenocytes were restimulated *in vitro* with PMA plus ionomycin to detect IFN-γ or CD107a-producing cells. To monitor cell division, hPBMCs were labeled with CFSE before transfer.

Results

[00225] Figures 20A-20H are scatter plots of FACS analysis showing increased expression of of CD40L, IFNγ and CD107a in an NGS mouse injected with antibody 1.3. 1.3 antibody significantly enhanced CD4+ T cell expression of membrane-bound CD40L and IFN-γ production, compared with control antibody treated mice. 1.3 antibody treatment also increased the expression of CD107a on CD8+ T cells indicative of cytolytic activity, as well as IFN-γ-production. In summary, 1.3 antibody treatment promoted the expansion and effector function of xeno-reactive CD4+ and CD8+ T cells.

Example 7

Characterization of Variants of Antibody 1.3

Materials and Methods

[00226] 100μl 1μg/ml H7CRECD human IgG1 Fc fusion protein diluted in PBS was immobilized on flat bottom 96 well plate (Costar 9017) overnight at 4°C. Plates were washed twice with PBS+0.1% PS-20 and blocked with 200μl/well PBS 10% FBS at RT for 1hr. 100μl human IgG4 Fc chimeric 1.3 and 14 selected 1.3 humanized variants diluted in PBS 10%FBS were added to each well and incubated at RT for 1hr. Plates were washed three times and 100μl 1μg/ml anti-human IgG4 HRP (Southern Biotech) was added to each well and incubated at RT for 1hr. Plates were washed six times and 100μl TMB substrate (SurModics) was added to each well for 5-15mins. 100μl stop solution (0.1M Sulfuric acid) was added to each well. Plates were read at Absorbance 450nm by PerkinElmer EnVision 2104 Multilabel Reader.

[00227] The binding affinities for 14 variants of antibody 1.3 were investigated using an ELISA assay to a H7CR fusion protein.

Results

[00228] The binding affinity results are shown in Table 10.

Table 10

ANTIBODY	HEAVY CHAIN	LIGHT CHAIN	EC_{50} (nM)
chimeric			0.055
VI	1A SEQ ID NO:23	1A SEQ ID NO:17	0.84
V2	1B SEQ ID NO:24	1A SEQ ID NO:17	0.23
V3	1C SEQ ID NO:25	1A SEQ ID NO:17	0.38
V4	2A SEQ ID NO:26	1A SEQ ID NO:17	1.08
V5	2B SEQ ID NO:27	1A SEQ ID NO:17	0.28
V6	2C SEQ ID NO:28	1A SEQ ID NO:17	0.30
V7	1B SEQ ID NO:24	1B SEQ ID NO:18	1.01
V8	1C SEQ ID NO:25	1B SEQ ID NO:18	0.74
V9	2B SEQ ID NO:27	1B SEQ ID NO:18	2.43
V10	2C SEQ ID NO:28	1B SEQ ID NO:18	1.18
V11	1B SEQ ID NO:24	1C SEQ ID NO:19	1.04
V12	1C SEQ ID NO:25	1C SEQ ID NO:19	0.75
V13	2B SEQ ID NO:27	1C SEQ ID NO:19	0.45

V14	2C SEQ ID NO:28	1C SEQ ID NO:19	0.32

[00229] Figures 21A and 21B are dot plots of resting or stimulated PMBCs treated with (from left to right) humanized antibody 1.3, negative control, OKT3, OKT3 +CD28, humanized antibody-immobilized, negative control immobilized, and OKT3 – immobilized. No statistically significant increases in cytokine production were observed upon exposure to human chimeric 1.3 antibody. As a result, 1.3 antibody treatment does not induce T cell cytokine storm in this in vitro setting.

[00230] The sequences for chimeric 1.3 antibody is as follows:

Heavy chain nucleic acid sequence:

ATGGAATGGTCCTGGGTGTTCCTGTTCTTCCTGTCCGTGACCACCGGCGTGCACTCCCAG
ATCCAGCTGCAGGAATCTGGCCCTGGCCTCGTGAAGCCTTCCCAGTCCCTGTCCCTGACC
TGCAGCGTGACCGGCTTCTCCATCTCCACCTCCGGCTACTACTGGACCTGGATCCGGCAG
TTCCCTGGCAAGCGGCTGGAATGGATGGGCTACATCAACTACGGCGGAGGCACCTCCTA
CAACCCCAGCCTGAAGTCCCGGATCTCCATCACCCGGGATACCTCCAAGAACCAGTTCCT
GCTGCACCTGAACTCCGTGACAACCGAGGACACCGCCACCTACTGCTGCGCTACCATGGC
CGACAGATTCGCCTTCTTCGACGTGTGGGGCCAGGGCATCCAAGTGACCGTGTCCTCCGC
TTCCACCAAGGGCCCCTCTGTGTTTCCTCTGGCCCCTTGCTCCCGGTCCACCTCTGAGTCT
ACAGCCGCTCTGGGCTGCCTCGTGAAAGACTACTTCCCCGAGCCCGTGACAGTGTCCTGG
AACTCTGGCGCTCTGACCTCTGGCGTGCACACCTTCCCTGCTGTGCTGCAGTCTAGCGGC
CTGTACTCCCTGTCCTCCGTCGTGACCGTGCCTTCCAGCTCTCTGGGCACCAAGACCTACA
CCTGTAACGTGGACCACAAGCCCTCCAACACCAAGGTGGACAAGAGAGTGGAATCTAAG
TACGGCCCTCCCTGCCCCCCTTGTCCTGCCCCTGAATTTCTGGGCGGACCCTCCGTGTTTC
TGTTCCCCCCAAAGCCCAAGGACACCCTGATGATCTCCCGGACCCCCGAAGTGACCTGCG
TGGTGGTGGATGTGTCCCAGGAAGATCCCGAGGTGCAGTTCAATTGGTACGTGGACGGC
GTGGAAGTGCACAACGCCAAGACCAAGCCTAGAGAGGAACAGTTCAACTCCACCTACCG
GGTGGTGTCCGTGCTGACCGTGCTGCACCAGGATTGGCTGAACGGCAAAGAGTACAAGT
GCAAGGTGTCCAACAAGGGCCTGCCCTCCAGCATCGAAAAGACCATCTCCAAGGCTAAG
GGCCAGCCCCGCGAGCCCCAGGTGTACACACTGCCTCCAAGCCAGGAAGAGATGACCAA
GAATCAGGTGTCACTGACCTGTCTCGTGAAGGGCTTCTACCCCTCCGATATCGCCGTGGA
ATGGGAGTCCAACGGCCAGCCCGAGAACAACTACAAGACCACCCCCCCTGTGCTGGACT
CCGACGGCTCCTTCTTTCTGTACTCTCGCCTGACCGTGGACAAGTCCCGGTGGCAGGAAG

GCAACGTGTTCTCCTGCTCTGTGATGCACGAGGCCCTGCACAACCACTACACCCAGAAGT
CCCTGAGCCTGTCCCCCGGCTGATGA **(SEQ ID NO:100).**

[00231] Light chain nucleic acid sequence:

ATGTCCGTGCCCACCCAGGTGCTGGGATTGCTGCTGCTGTGGCTGACCGACGCCA
GATGCGACATCGTGATGACCCAGTCCCCCTCCTCCCTGGCTGTGTCTGCTGGCGA
GAAAGTGACCATCTCCTGCCTGTCCTCCCAGTCCCTGTTCTCCTCCAACACCAACC
GGAACTACCTGAACTGGTATCTGCAGAAGCCCGGCCAGTCCCCTAAGCTGCTGAT
CTACCACGCCTCCACCAGACTGACCGGCGTGCCCGATAGATTCATCGGCTCTGGC
TCCGGCACCGACTTTACCCTGACCATCAGCTCCGTGCAGGCCGAGGACCTGGGCG
ACTACTACTGCCAGCACCACTACGAGACACCCCTGACCTTTGGCGACGGCACCAA
GCTGGAAATCAAGCGGACCGTGGCCGCTCCCTCCGTGTTCATCTTCCCACCTTCC
GACGAGCAGCTGAAGTCTGGCACCGCCTCTGTCGTGTGCCTGCTGAACAACTTCT
ACCCCCGCGAGGCCAAGGTGCAGTGGAAGGTGGACAACGCCCTGCAGTCCGGCA
ACTCCCAGGAATCCGTGACCGAGCAGGACTCCAAGGACAGCACCTACTCCCTGT
CCAGCACCCTGACCCTGTCCAAGGCCGACTACGAGAAGCACAAGGTGTACGCCT
GCGAAGTGACCCACCAGGGCCTGTCTAGCCCCGTGACCAAGTCTTTCAACCGGG
GCGAGTGCTGATGA **(SEQ ID NO:101).**

[00232] Heavy chain protein sequence:

MEWSWVFLFFLSVTTGVHSQIQLQESGPGLVKPSQSLSLTCSVTGFSISTSGYYWTWI
RQFPGKRLEWMGYINYGGGTSYNPSLKSRISITRDTSKNQFLLHLNSVTTEDTATYCC
ATMADRFAFFDVWGQGIQVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFP
EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSN
TKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQE
DPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVS
NKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWE
SNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQ
KSLSLSPG** **(SEQ ID NO:11).**

[00233] Light chain protein sequence:

MSVPTQVLGLLLLWLTDARCDIVMTQSPSSLAVSAGEKVTISCLSSQSLFSSNTNRNY
LNWYLQKPGQSPKLLIYHASTRLTGVPDRFIGSGSGTDFTLTISSVQAEDLGDYYCQH

HYETPLTFGDGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQW KVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPV TKSFNRGEC** **(SEQ ID NO:12).**

Example 8

Humanized H7CR Antibody 4.5 Variants

Materials and Methods

[00234] 5μg/ml antibodies from thirty-six variants were incubated with H7CR-GFP fusion protein transfected CHO cells for 30min at room temperature. Cells were then washed twice with 2ml flow cytometry buffer, and resuspended in 100μl flow cytometry buffer. 1μl anti-hIg PE secondary antibody (Biolegend) was added and incubated with the cells for 15mins. Samples were then washed and resuspended in 100μl flow cytometry buffer. Flow Cytometry data was acquired using BD Canto (BD Biosciences) in plate format and analyzed by FlowJo software. X axis shows H7CR-GFP expression and Y axis shows variant binding to the transfectants.

Results

[00235] Thirty-six humanized variants of H7CR antibody 4.5 were assayed for binding specificity for H7CR. The results are presented in Figure 23. All thirty-six 4.5 humanized variants maintain binding specificity to H7CR.

Table 11: 4.5 antibody humanized variants

4.5 humanized variants				
Variant #	Heavy Chain		Light Chain	
1	HC1-1	**(SEQ ID NO:39)**	LC1-1	**(SEQ ID NO:33)**
2	HC1-1	**(SEQ ID NO:39)**	LC1-2	**(SEQ ID NO:34)**
3	HC1-1	**(SEQ ID NO:39)**	LC1-3	**(SEQ ID NO:35)**
4	HC1-1	**(SEQ ID NO:39)**	LC2-1	**(SEQ ID NO:36)**
5	HC1-1	**(SEQ ID NO:39)**	LC2-2	**(SEQ ID NO:37)**
6	HC1-1	**(SEQ ID NO:39)**	LC2-3	**(SEQ ID NO:38)**
7	HC1-2	**(SEQ ID NO:40)**	LC1-1	**(SEQ ID NO:33)**
8	HC1-2	**(SEQ ID NO:40)**	LC1-2	**(SEQ ID NO:34)**

9	HC1-2	**(SEQ ID NO:40)**	LC1-3	**(SEQ ID NO:35)**
10	HC1-2	**(SEQ ID NO:40)**	LC2-1	**(SEQ ID NO:36)**
11	HC1-2	**(SEQ ID NO:40)**	LC2-2	**(SEQ ID NO:37)**
12	HC1-2	**(SEQ ID NO:40)**	LC2-3	**(SEQ ID NO:38)**
13	HC1-3	**(SEQ ID NO:41)**	LC1-1	**(SEQ ID NO:33)**
14	HC1-3	**(SEQ ID NO:41)**	LC1-2	**(SEQ ID NO:34)**
15	HC1-3	**(SEQ ID NO:41)**	LC1-3	**(SEQ ID NO:35)**
16	HC1-3	**(SEQ ID NO:41)**	LC2-1	**(SEQ ID NO:36)**
17	HC1-3	**(SEQ ID NO:41)**	LC2-2	**(SEQ ID NO:37)**
18	HC1-3	**(SEQ ID NO:41)**	LC2-3	**(SEQ ID NO:38)**
19	HC2-1	**(SEQ ID NO:42)**	LC1-1	**(SEQ ID NO:33)**
20	HC2-1	**(SEQ ID NO:42)**	LC1-2	**(SEQ ID NO:34)**
21	HC2-1	**(SEQ ID NO:42)**	LC1-3	**(SEQ ID NO:35)**
22	HC2-1	**(SEQ ID NO:42)**	LC2-1	**(SEQ ID NO:36)**
23	HC2-1	**(SEQ ID NO:42)**	LC2-2	**(SEQ ID NO:37)**
24	HC2-1	**(SEQ ID NO:42)**	LC2-3	**(SEQ ID NO:38)**
25	HC2-2	**(SEQ ID NO:43)**	LC1-1	**(SEQ ID NO:33)**
26	HC2-2	**(SEQ ID NO:43)**	LC1-2	**(SEQ ID NO:34)**
27	HC2-2	**(SEQ ID NO:43)**	LC1-3	**(SEQ ID NO:35)**
28	HC2-2	**(SEQ ID NO:43)**	LC2-1	**(SEQ ID NO:36)**
29	HC2-2	**(SEQ ID NO:43)**	LC2-2	**(SEQ ID NO:37)**
30	HC2-2	**(SEQ ID NO:43)**	LC2-3	**(SEQ ID NO:38)**
31	HC2-3	**(SEQ ID NO:44)**	LC1-1	**(SEQ ID NO:33)**
32	HC2-3	**(SEQ ID NO:44)**	LC1-2	**(SEQ ID NO:34)**
33	HC2-3	**(SEQ ID NO:44)**	LC1-3	**(SEQ ID NO:35)**
34	HC2-3	**(SEQ ID NO:44)**	LC2-1	**(SEQ ID NO:36)**
35	HC2-3	**(SEQ ID NO:44)**	LC2-2	**(SEQ ID NO:37)**
36	HC2-3	**(SEQ ID NO:44)**	LC2-3	**(SEQ ID NO:38)**

[00236] The sequence data for the chimeric 4.5 antibody is as follows:

[00237] Heavy chain nucleic acid sequence:

ATGGAATGGTCCTGGGTGTTCCTGTTCTTCCTGTCCGTGACCACCGGCGTGCACTC
CCAGATCCAGCTGCAGGAATCTGGCCCTGGCCTCGTGAAGCCTTCCCAGTCCCTG
TCCCTGACCTGCAGCGTGACCGGCTTCTCTATCACAACCGGCGGCTACTACTGGA
ACTGGATCCGGCAGTTCCCCGGCAAGAAACTGGAATGGATGGGCTACATCTATA
CCAGCGGCCGGACCTCCTACAACCCCAGCCTGAAGTCCCGGATCTCCATCACCCG
GGACACCTCCAAGAACCAGTTCTTTCTGCAGCTGAACTCCATGACCACCGAGGAC
ACCGCCACCTACTACTGCGCCGACATGGCCGATAAGGGCGGATGGTTCGCTTACT
GGGGCCAGGGCACACTCGTGACCGTGTCCTCTGCTTCCACCAAGGGCCCCTCCGT
GTTTCCTCTGGCCCCTTGCTCCAGATCCACCTCCGAGTCTACCGCCGCTCTGGGCT
GCCTCGTGAAAGACTACTTCCCCGAGCCCGTGACAGTGTCTTGGAACTCTGGCGC
CCTGACCTCTGGCGTGCACACCTTTCCAGCTGTGCTGCAGTCCTCCGGCCTGTACT
CCCTGTCCTCCGTCGTGACTGTGCCCTCCAGCTCTCTGGGCACCAAGACCTACAC
CTGTAACGTGGACCACAAGCCCTCCAACACCAAGGTGGACAAGCGGGTGGAATC
TAAGTACGGCCCTCCCTGCCCTCCTTGCCCAGCCCCTGAATTTCTGGGCGGACCTT
CTGTGTTTCTGTTCCCCCCAAAGCCCAAGGACACCCTGATGATCTCCCGGACCCC
CGAAGTGACCTGCGTGGTGGTGGATGTGTCCCAGGAAGATCCCGAGGTGCAGTT
CAATTGGTACGTGGACGGCGTGGAAGTGCACAACGCCAAGACCAAGCCTAGAGA
GGAACAGTTCAACTCCACCTACCGGGTGGTGTCCGTGCTGACCGTGCTGCACCAG
GATTGGCTGAACGGCAAAGAGTACAAGTGCAAGGTGTCCAACAAGGGCCTGCCC
AGCTCCATCGAAAAGACCATCTCCAAGGCTAAGGGCCAGCCCCGCGAGCCCCAG
GTGTACACACTGCCTCCAAGCCAGGAAGAGATGACCAAGAATCAGGTGTCACTG
ACCTGTCTCGTGAAGGGCTTCTACCCCTCCGATATCGCCGTGGAATGGGAGTCCA
ACGGCCAGCCCGAGAACAACTACAAGACCACCCCCCCTGTGCTGGACTCCGACG
GCTCCTTCTTTCTGTACTCTCGCCTGACCGTGGACAAGTCCCGGTGGCAGGAAGG
CAACGTGTTCTCCTGCTCTGTGATGCACGAGGCCCTGCACAACCACTACACCCAG
AAGTCCCTGAGCCTGTCCCCCGGCTGATGA **(SEQ ID NO:13).**

[00238] Light chain nucleic acid sequence:

ATGTCCGTGCCCACCCAGGTGCTGGGATTGCTGCTGCTGTGGCTGACCGACGCCA
GATGCGACATCGTGATGACCCAGTCCCCCTCCTCCCTGGCTGTGTCTGCTGGCGA
GAAAGTGACCATCTCCTGCCTGTCCTCCCAGTCCCTGTTCTCCAGCAACACCAAG
CGGAACTACCTGAACTGGTATCTGCAGAAGCCCGGCCAGTCCCCTAAGCTGCTGA

TCTACCACGCCTCCACCAGACTGACCGGCGTGCCCGGAAGATTCATCGGCTCTGG
CTCTGGCACCGACTTCACCCTGACCGTGTCTACCGTGCAGGCCGAGGACCTGGGC
GACTACTTCTGCCAGCAGCACTACGAGACACCCCTGACCTTTGGCGACGGCACCC
GGCTGGAAATCAAGAGAACCGTGGCCGCTCCCTCCGTGTTCATCTTCCCACCTTC
CGACGAGCAGCTGAAGTCCGGCACCGCTTCTGTCGTGTGCCTGCTGAACAACTTC
TACCCCCGCGAGGCCAAGGTGCAGTGGAAGGTGGACAACGCCCTGCAGTCCGGC
AACTCCCAGGAATCCGTGACCGAGCAGGACTCCAAGGACAGCACCTACTCCCTG
TCCTCTACCCTGACCCTGAGCAAGGCCGACTACGAGAAGCACAAGGTGTACGCC
TGCGAAGTGACCCACCAGGGCCTGTCTAGCCCCGTGACCAAGTCTTTCAACCGGG
GCGAGTGCTGATGA **(SEQ ID NO:14).**

[00239] Heavy chain protein sequence:

MEWSWVFLFFLSVTTGVHSQIQLQESGPGLVKPSQSLSLTCSVTGFSITTGGYYWNW
IRQFPGKKLEWMGYIYTSGRTSYNPSLKSRISITRDTSKNQFFLQLNSMTTEDTATYY
CADMADKGGWFAYWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDY
FPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPS
NTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQ
EDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCK
VSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVE
WESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHY
TQKSLSLSPG** **(SEQ ID NO:15).**

[00240] Light chain protein sequence:

MSVPTQVLGLLLLWLTDARCDIVMTQSPSSLAVSAGEKVTISCLSSQSLFSSNTKRNY
LNWYLQKPGQSPKLLIYHASTRLTGVPGRFIGSGSGTDFTLTVSTVQAEDLGDYFCQ
QHYETPLTFGDGTRLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQ
WKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSS
PVTKSFNRGEC** **(SEQ ID NO:16).**

[00241] All publications and patents mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference in its entirety. While the invention has been described in connection with specific embodiments thereof, it will be understood that it is capable of further modifications and this application is intended to cover

any variations, uses, or adaptations of the invention following, in general, the principles of the invention and including such departures from the present disclosure as come within known or customary practice within the art to which the invention pertains and as may be applied to the essential features hereinbefore set forth.

[00242] Throughout the specification and claims, unless the context requires otherwise, the word "comprise" or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated integer or group of integers but not the exclusion of any other integer or group of integers.

We claim:

1. An antibody or an antigen-binding fragment thereof that specifically binds to a human B7-H7CR, wherein the antibody or an antigen binding fragment thereof is genetically engineered and comprises:

(1) a light chain variable region comprising amino acid sequence **SEQ ID NO:17** and a heavy chain variable region comprising amino acid sequence **SEQ ID NO:23**;

(2) a light chain variable region comprising amino acid sequence **SEQ ID NO:17** and a heavy chain variable region comprising amino acid sequence **SEQ ID NO:24**;

(3) a light chain variable region comprising amino acid sequence **SEQ ID NO:17** and a heavy chain variable region comprising amino acid sequence **SEQ ID NO:25**;

(4) a light chain variable region comprising amino acid sequence **SEQ ID NO:17** and a heavy chain variable region comprising amino acid sequence **SEQ ID NO:26**;

(5) a light chain variable region comprising amino acid sequence **SEQ ID NO:17** and a heavy chain variable region comprising amino acid sequence **SEQ ID NO:27**;

(6) a light chain variable region comprising amino acid sequence **SEQ ID NO:17** and a heavy chain variable region comprising amino acid sequence **SEQ ID NO:28**;

(7) a light chain variable region comprising amino acid sequence **SEQ ID NO:18** and a heavy chain variable region comprising amino acid sequence **SEQ ID NO:24**;

(8) a light chain variable region comprising amino acid sequence **SEQ ID NO:18** and a heavy chain variable region comprising amino acid sequence **SEQ ID NO:25**;

(9) a light chain variable region comprising amino acid sequence **SEQ ID NO:18** and a heavy chain variable region comprising amino acid sequence **SEQ ID NO:27**;

(10) a light chain variable region comprising amino acid sequence **SEQ ID NO:18** and a heavy chain variable region comprising amino acid sequence **SEQ ID NO:28**;

(11) a light chain variable region comprising amino acid sequence **SEQ ID NO:19** and a heavy chain variable region comprising amino acid sequence **SEQ ID NO:24**;

(12) a light chain variable region comprising amino acid sequence **SEQ ID NO:19** and a heavy chain variable region comprising amino acid sequence **SEQ ID NO:25**;

(13) a light chain variable region comprising amino acid sequence **SEQ ID NO:19** and a heavy chain variable region comprising amino acid sequence **SEQ ID NO:27**; or

(14) a light chain variable region comprising amino acid sequence **SEQ ID NO:19** and a heavy chain variable region comprising amino acid sequence **SEQ ID NO:28**.

2. The antibody or an antigen binding fragment thereof that specifically binds to a human B7-H7CR of claim 1, wherein the specifically bound H7CR is:

(A) arrayed on the surface of a live cell; or

(B) expressed at an endogenous concentration.

3. The antibody or an antigen binding fragment thereof of claim 2, wherein said live cell is a T cell, an NK cell, or a plasmacytoid dendritic cell.

4. The antibody or an antigen binding fragment thereof of claim 1, wherein the antibody or an antigen binding fragment thereof is substantially incapable of blocking B7-H7CR's interaction with B7-H7.

5. The antibody or an antigen binding fragment thereof of claim 1, wherein the antibody or an antigen binding fragment thereof modulates or agonizes H7CR activity.

6. The antibody or an antigen binding fragment thereof of claim 1, wherein the antibody or an antigen binding fragment thereof is a bispecific or multispecific antibody, or an antigen binding fragment thereof.

7. The antibody or an antigen binding fragment thereof of any one of claims 1 to 6, wherein the antigen binding fragment is selected from the group consisting of single-chain Fv (scFv), Fab fragment, F(ab') fragment, $F(ab')_2$ fragment and disulfide-linked bispecific Fv (sdFv).

8. The antibody or an antigen binding fragment thereof of any one of claims 1 to 7, wherein the antibody or an antigen binding fragment thereof is of an immunoglobulin class selected from IgG, IgE, IgM, IgD, IgA, or IgY.

9. The antibody or an antigen binding fragment thereof of claim 8, wherein the IgG is an IgG1, IgG2, IgG3, or IgG4 subtype.

10. The antibody or an antigen binding fragment thereof of claim 1, which is detectably labeled.

11. The antibody or an antigen binding fragment thereof of claim 1, which comprises a conjugated toxin, drug, receptor, enzyme, or receptor ligand.

12. A pharmaceutical composition comprising a therapeutically effective amount of the antibody or an antigen binding fragment thereof of claim 1, and a physiologically acceptable carrier or excipient.

13. A method for treating a disease in a subject exhibiting a symptom of said disease, said method comprising administering to a subject in need thereof, a therapeutically effective amount of the pharmaceutical composition of claim 12.

14. The method of claim 13, wherein said disease is cancer.

15. The method of claim 14, wherein the cancer is selected from the group consisting of leukemia, lymphoma, melanoma, colon cancer, lung cancer, breast cancer, prostate cancer, cervical cancer, liver cancer, testicular cancer, brain cancer, pancreatic cancer and renal cancer.

16. The method of claim 14 or claim 15, wherein one or more additional therapies are administered to the subject with cancer.

17. The method of claim 16, wherein the one or more additional therapies is selected from

(i) administering to the subject one or more anti-cancer agents, cytokines, cellular vaccines, anti-hormonal agents, and/or

(ii) subjecting the subject to surgery, chemotherapy, radiation therapy, or a combination thereof

18. The method of claim 13, wherein said disease is an infectious disease.

19. The method of claim 18, wherein said infectious disease is a chronic viral disease.

20. A method for enhancing an immune response in a subject in need thereof, said method comprising administering to the subject a therapeutically effective amount of the pharmaceutical composition of claim 12.

21. The method of claim 20, wherein said pharmaceutical composition agonizes an H7CR function.

22. The method of claim 20 or claim 21, wherein the pharmaceutical composition is administered by an oral, intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, transdermal, implant, rectal, pulmonary, intestinal, mucosal, or epidural mode of administration.

23. A method for prophylactically treating a disease in a subject in need of prophylactic treatment, said method comprising administering to the subject in advance of exhibiting a symptom of said disease a

prophylactically effective amount of the pharmaceutical composition of claim 12.

24. A method for diagnosing a disease associated with the expression of B7-H7CR in a subject, said method comprising:

(i) assaying cells or tissue obtained from a biological sample of said subject for their ability to bind to the antibody or an antigen binding fragment thereof that specifically binds to a human H7-H7CR of claim 1;,

(ii) Comparing the binding levels of the antibody or an antigen binding fragment thereof to human B7-H7CR expressed by the cells or tissue of the subject's sample; and

(iii) diagnosing disease in the subject based on an increase or a decrease in the B7-H7CR levels compared with levels of B7-H7CR in a suitable control.

25. The method of claim 24, wherein said disease is cancer.

26. An antibody or an antigen binding fragment of an antibody that specifically binds a human B7-H7CR,wherein the antibody or the antigen-binding fragment comprises a light chain CDR1 of SEQ ID NO: 29, a light chain CDR2 of SEQ ID NO: 32 and a light chain CDR3 of SEQ ID NO: 45; and a heavy chain CDR1 of SEQ ID NO: 49; a heavy chain CDR2 of SEQ ID NO: 52 and a heavy chain CDR3 of SEQ ID NO: 56

27. The antibody or an antigen binding fragment thereof of claim 26, wherein the antibody or an antigen binding fragment thereof is a humanized antibody or a humanized monoclonal antibody or an antigen binding fragment thereof.

28. The antibody or antigen binding fragment thereof of claim 27, which is a bispecific or multispecific antibody.

29. The antibody or an antigen binding fragment thereof of claim 26, which is detectably labeled or comprises a conjugated toxin, drug, receptor, enzyme, or receptor ligand.

30. The antibody or an antigen binding fragment thereof of claim 1 or claim 26, which does not block an interaction between B7-H7 and B7-H7CR.

31. The antibody or an antigen binding fragment thereof of claim 1 or claim 26, which promotes antigen-specific memory T lymphocyte responses by T lymphocytes exposed to antigen and the antibody or an antigen binding fragment thereof.

32. The antibody or an antigen binding fragment thereof of claim 31, wherein the exposure of the T lymphocytes to the antibody or an antigen binding fragment thereof elicits production of one or more of cytokines IFNγ, TNFα, GM-CSF and IL-10 by the T lymphocytes.

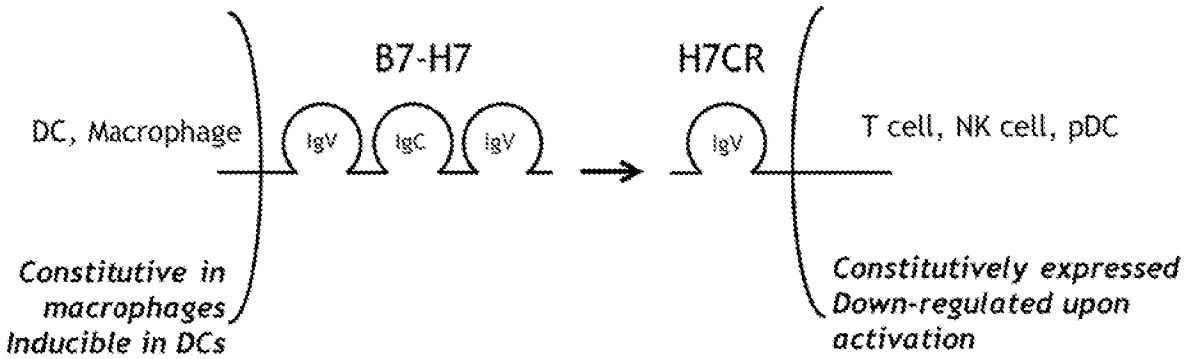

Figure 1

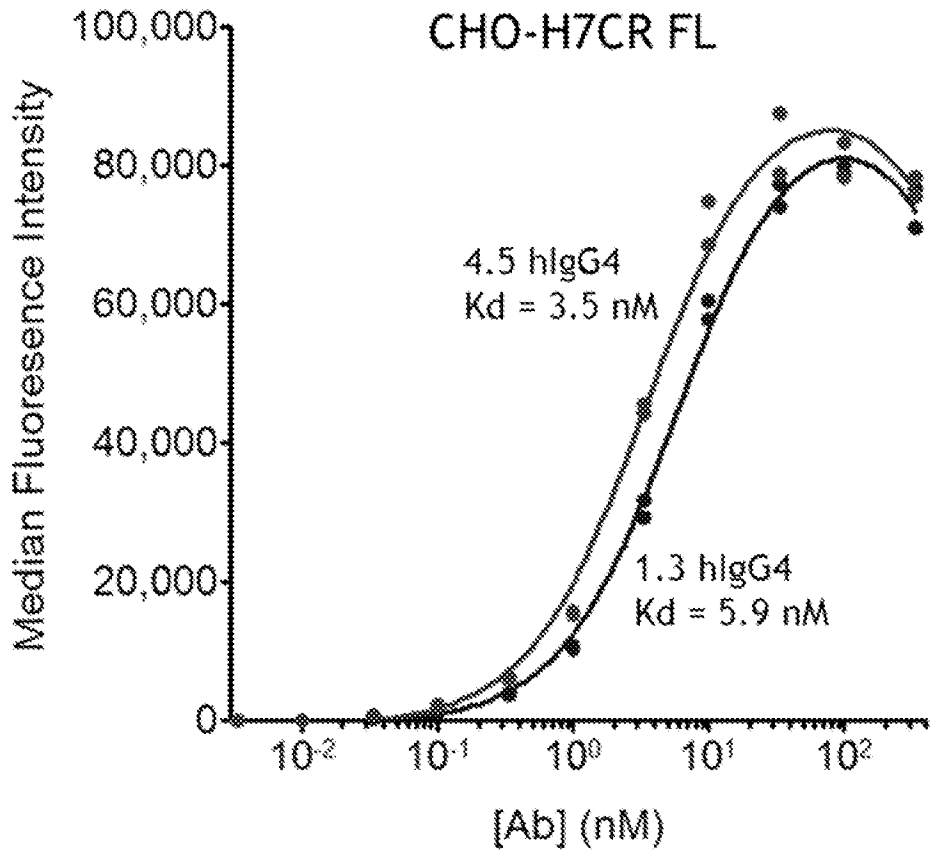

Figure 2

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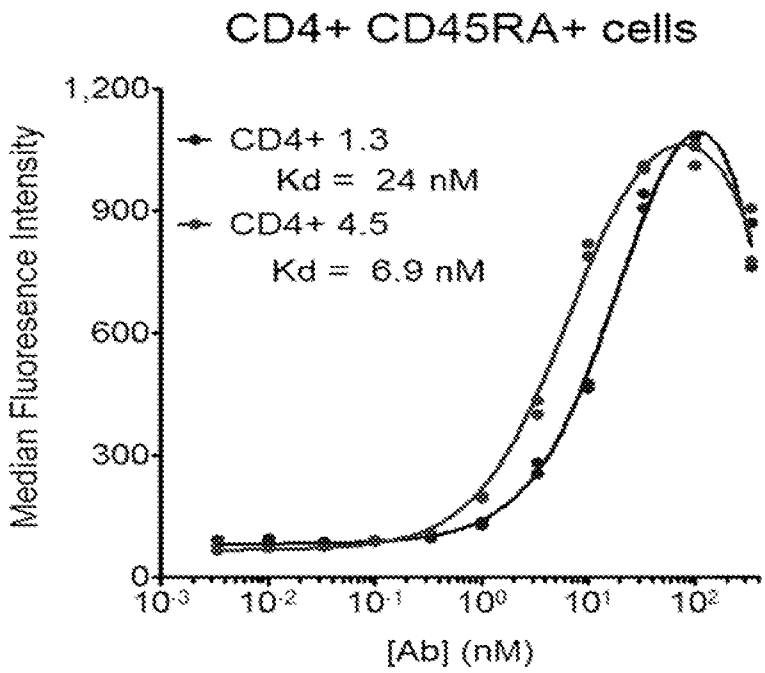

CD4+ CD45RA+ cells
Median Fluorescence Intensity
1,200
900
600
300
0
CD4+ 1.3
Kd = 24 nM
CD4+ 4.5
Kd = 6.9 nM
10-3
10-2
10-1
100
101
102
[Ab] (nM)

B

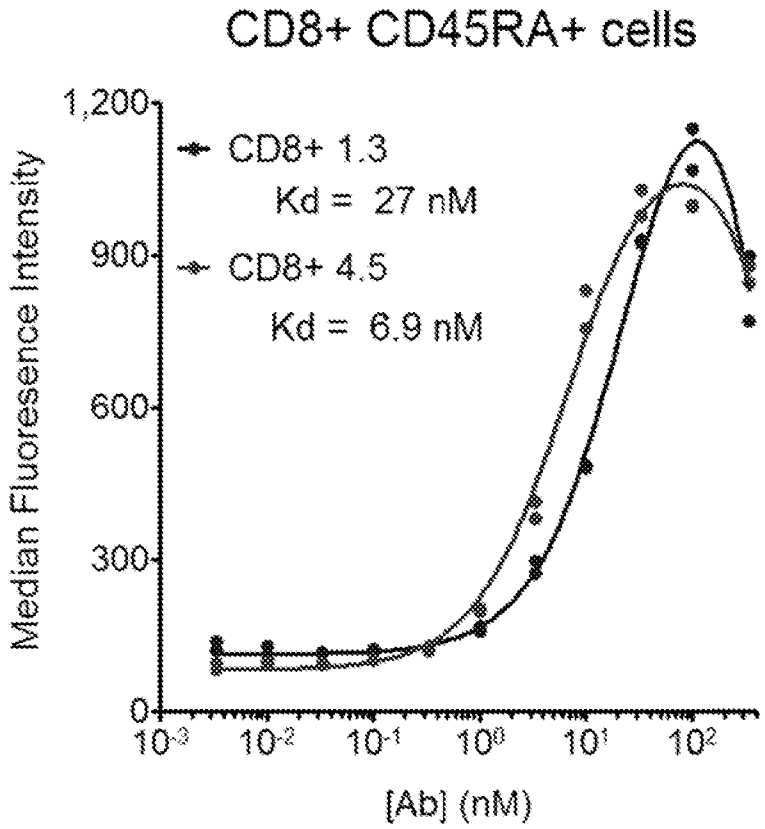

CD8+ CD45RA+ cells
Median Fluorescence Intensity
1,200
900
600
300
0
CD8+ 1.3
Kd = 27 nM
CD8+ 4.5
Kd = 6.9 nM
10-3
10-2
10-1
100
101
102
[Ab] (nM)

Figure 3

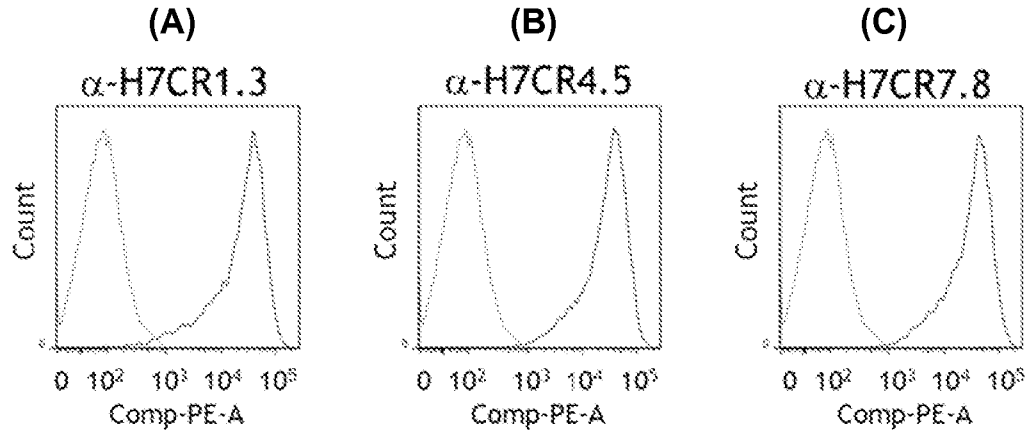


Figure 4

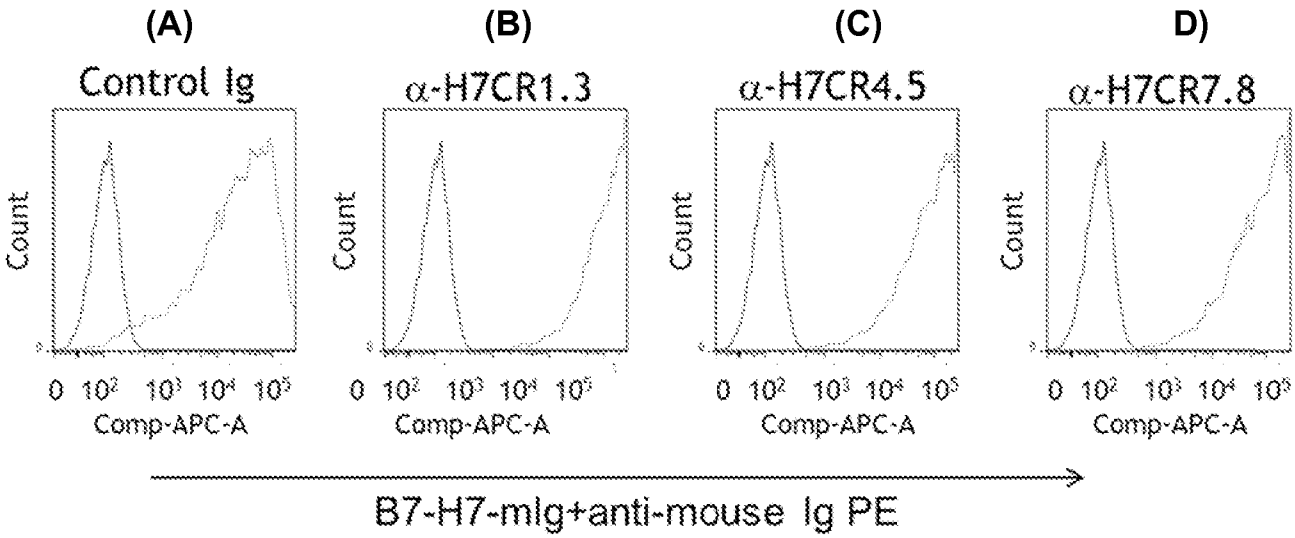


Figure 5

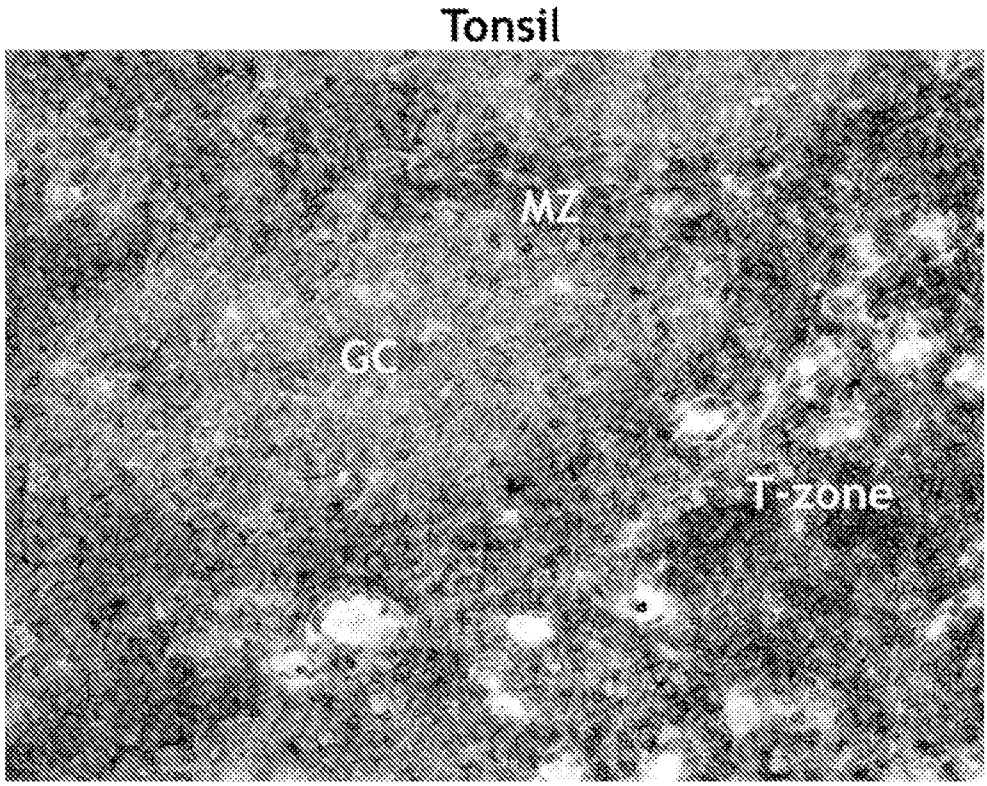


Figure 6

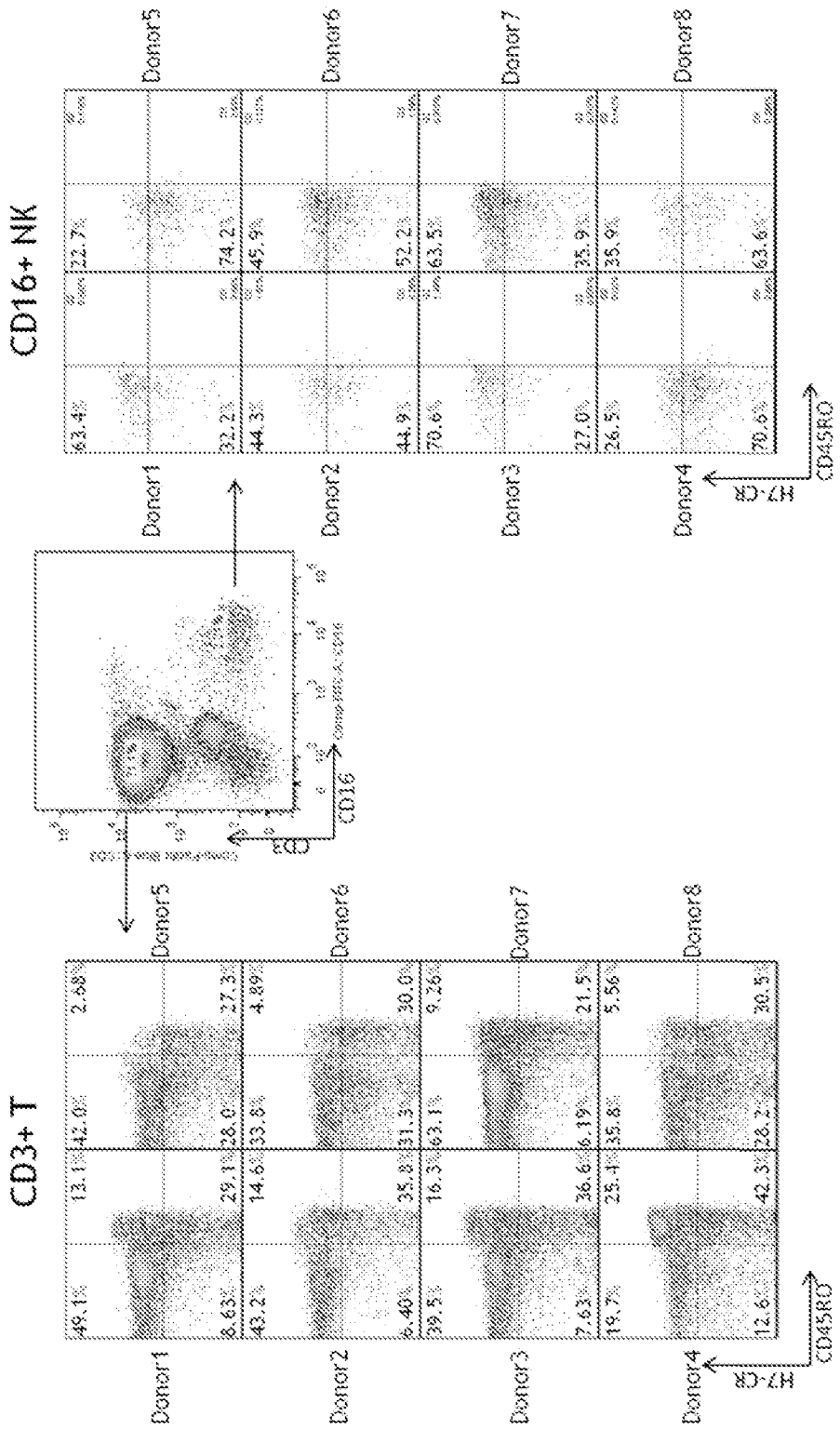

CD16+ NK
Donor5
Donor6
Donor7
Donor8
Donor1
Donor2
Donor3
Donor4
CD16
CD45RO
CD3+ T
Donor5
Donor6
Donor7
Donor8
Donor1
Donor2
Donor3
Donor4
CD45RO

Figure 7

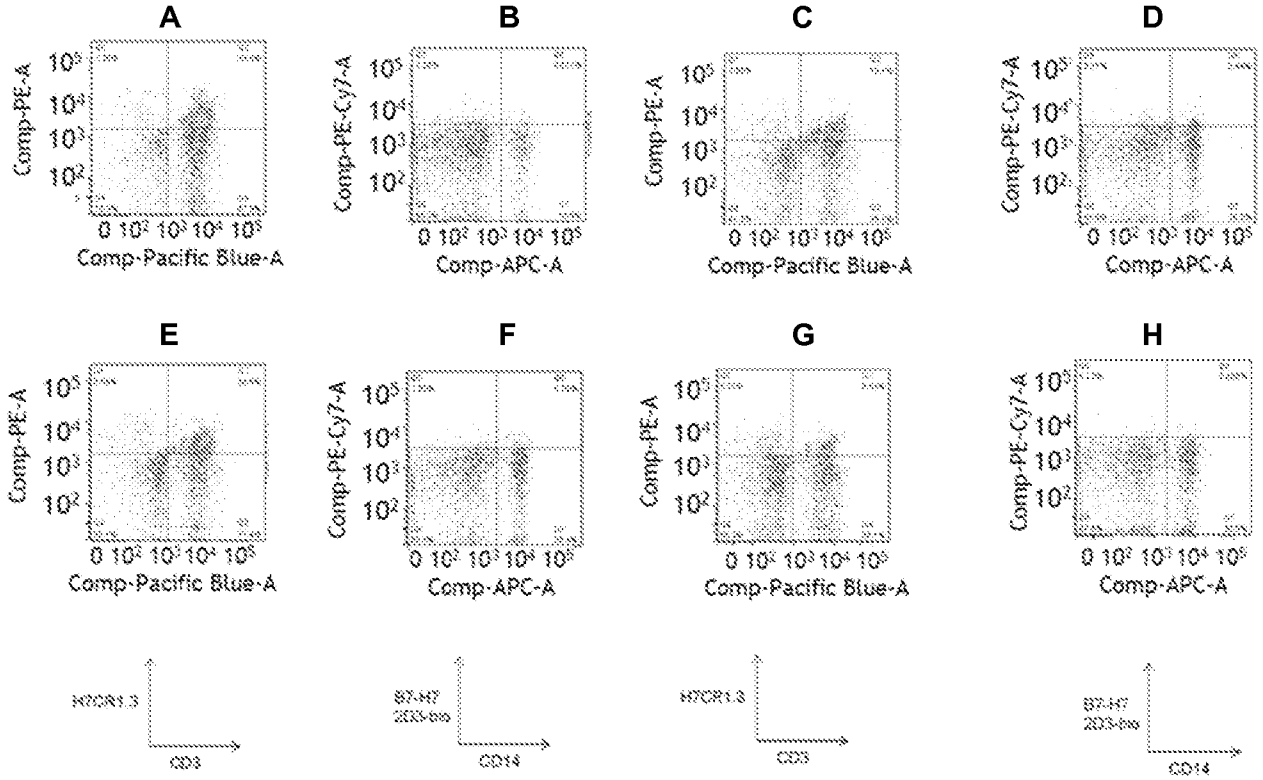


Figure 8

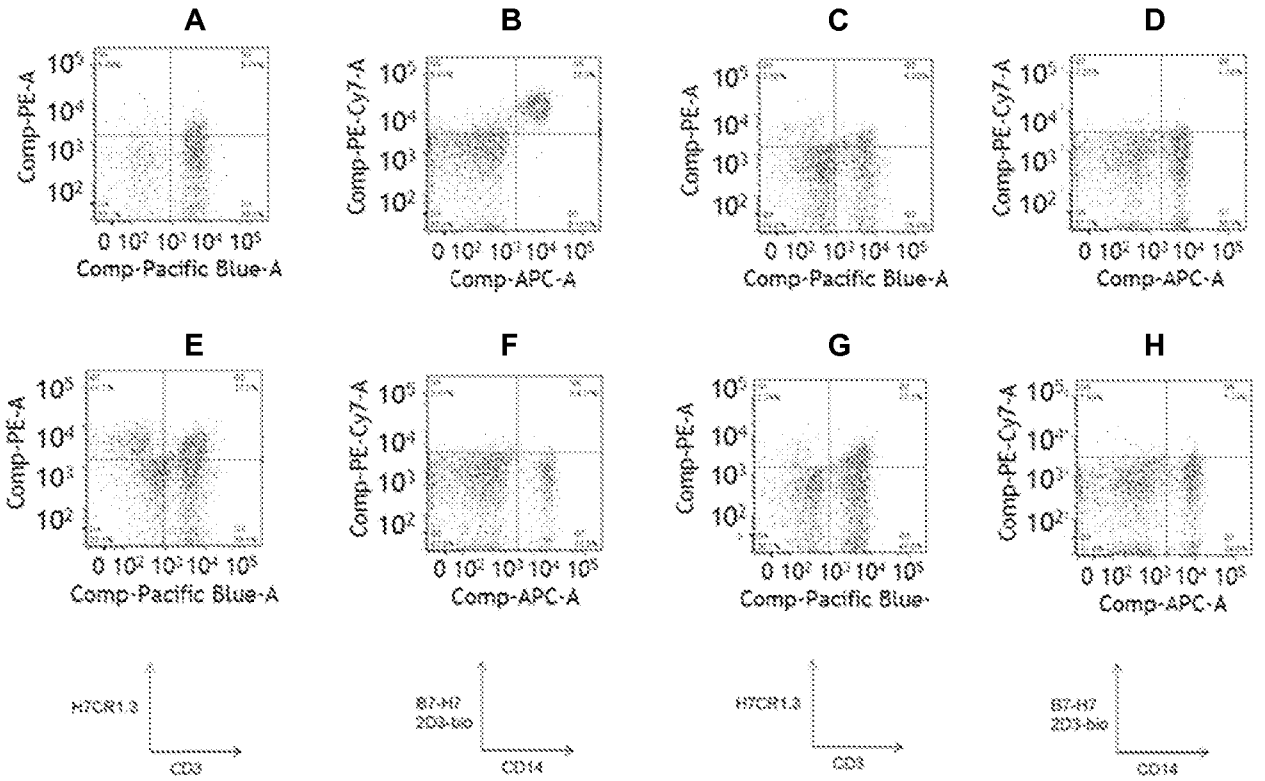


Figure 9

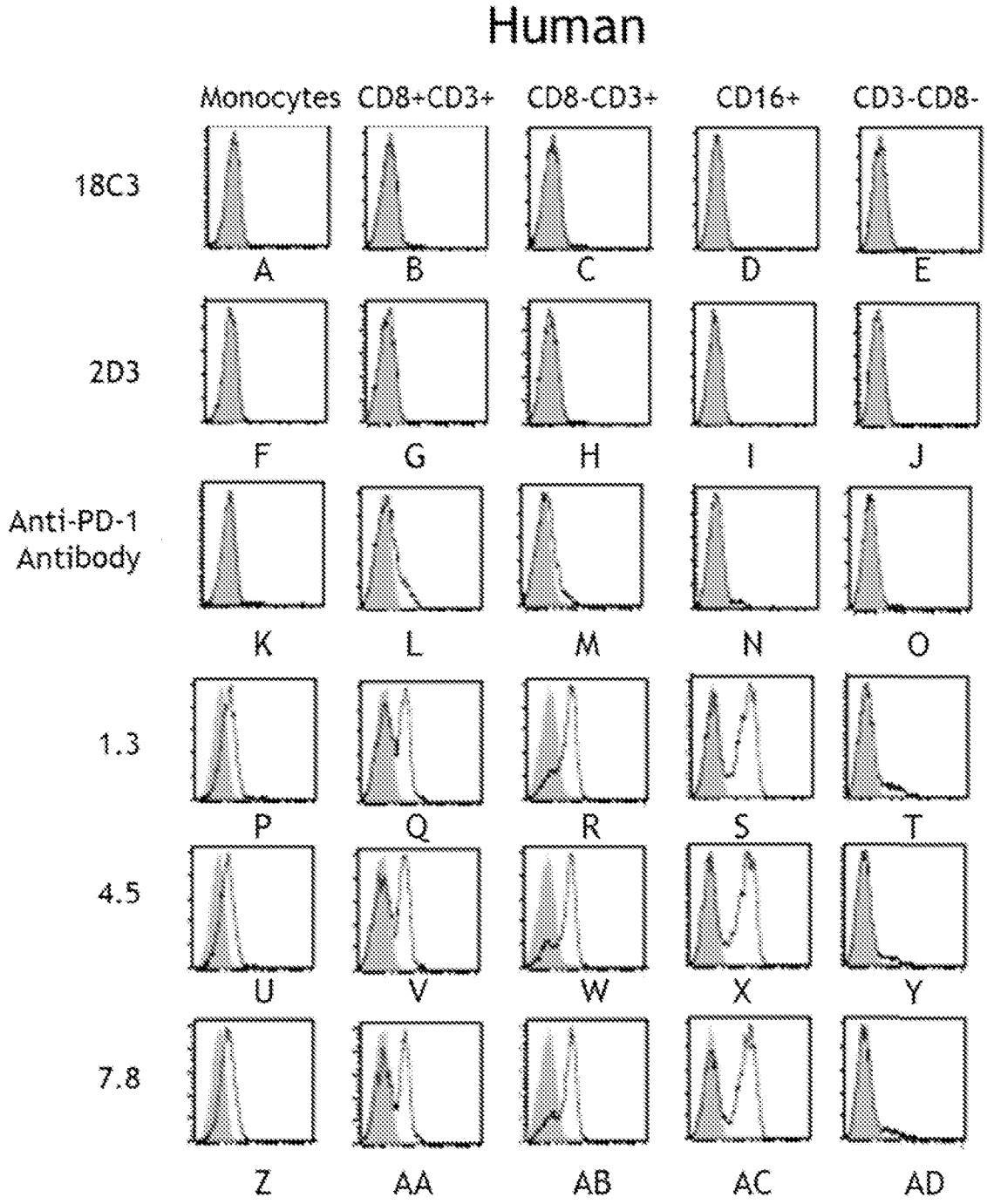

Human
Monocytes
CD8+CD3+
CD8-CD3+
CD16+
CD3-CD8-
18C3
2D3
Anti-PD-1 Antibody
1.3
4.5
7.8
A
B
C
D
E
F
G
H
I
J
K
L
M
N
O
P
Q
R
S
T
U
V
W
X
Y
Z
AA
AB
AC
AD

Figure 10

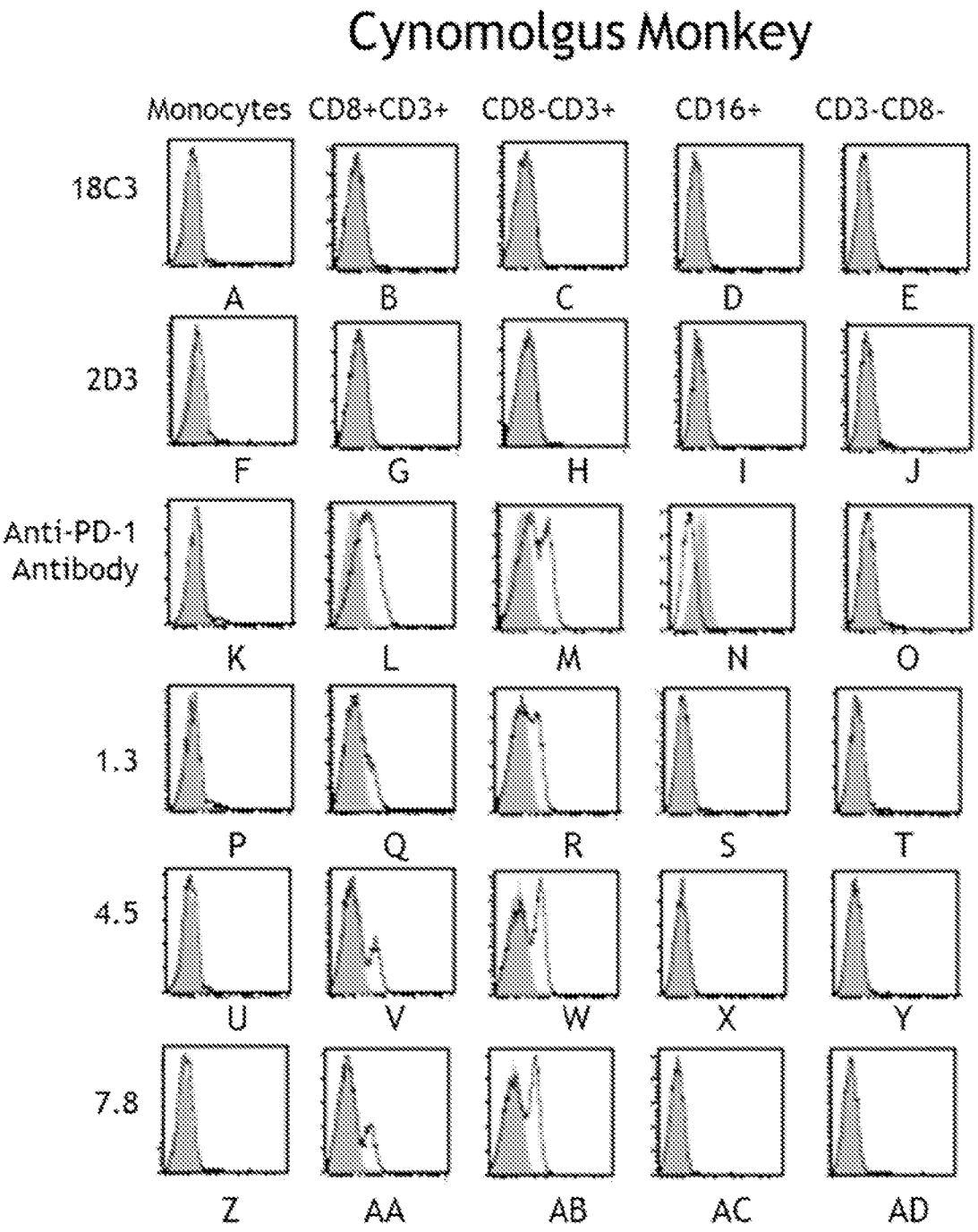

Cynomolgus Monkey
Monocytes
CD8+CD3+
CD8-CD3+
CD16+
CD3-CD8-
18C3
2D3
Anti-PD-1 Antibody
1.3
4.5
7.8
A
B
C
D
E
F
G
H
I
J
K
L
M
N
O
P
Q
R
S
T
U
V
W
X
Y
Z
AA
AB
AC
AD

Figure 11

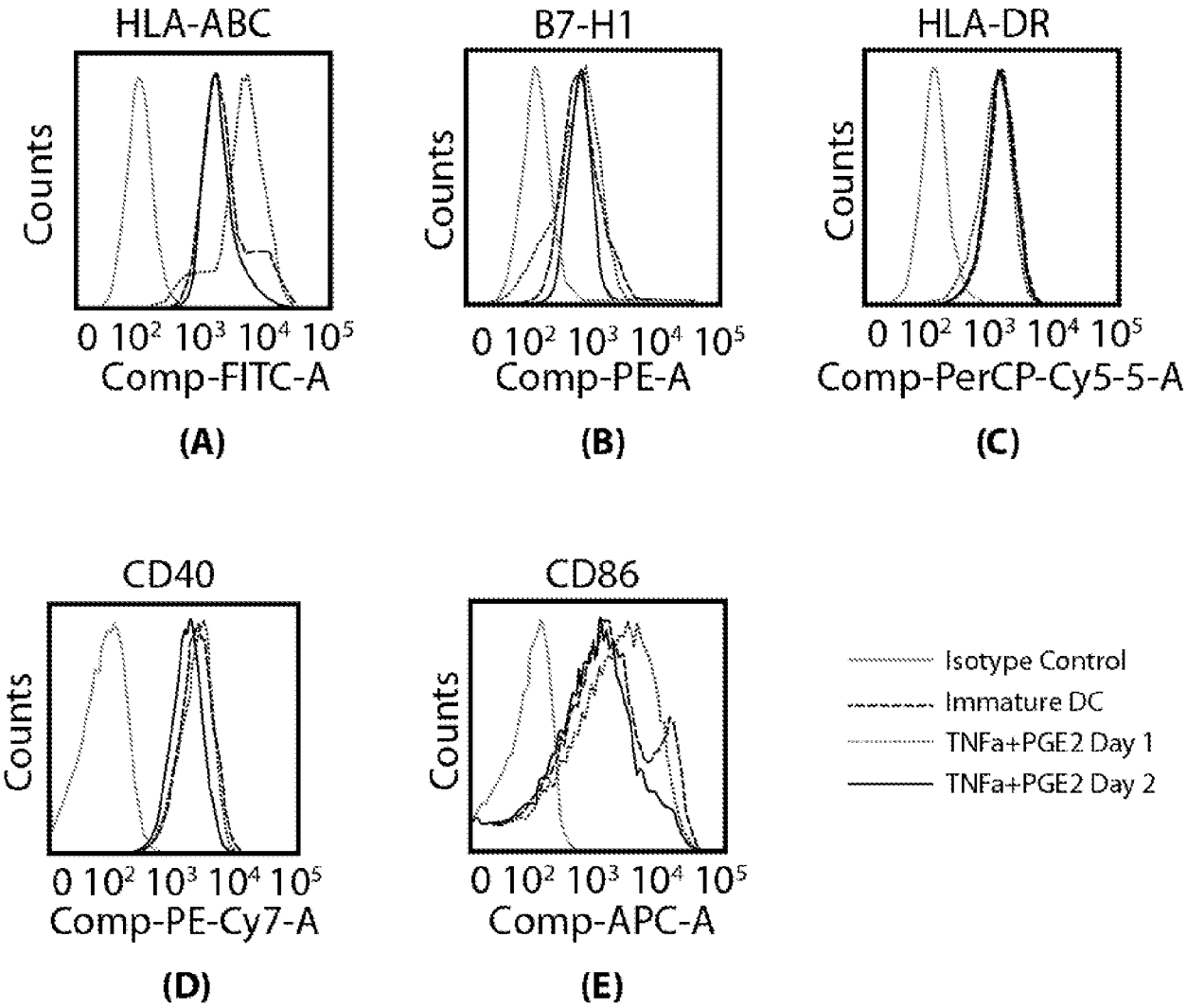

HLA-ABC
Counts
0 10² 10³ 10⁴ 10⁵
Comp-FITC-A
(A)
B7-H1
Counts
0 10² 10³ 10⁴ 10⁵
Comp-PE-A
(B)
HLA-DR
Counts
0 10² 10³ 10⁴ 10⁵
Comp-PerCP-Cy5-5-A
(C)
CD40
Counts
0 10² 10³ 10⁴ 10⁵
Comp-PE-Cy7-A
(D)
CD86
Counts
0 10² 10³ 10⁴ 10⁵
Comp-APC-A
(E)
Isotype Control
Immature DC
TNFa+PGE2 Day 1
TNFa+PGE2 Day 2

Figure 12

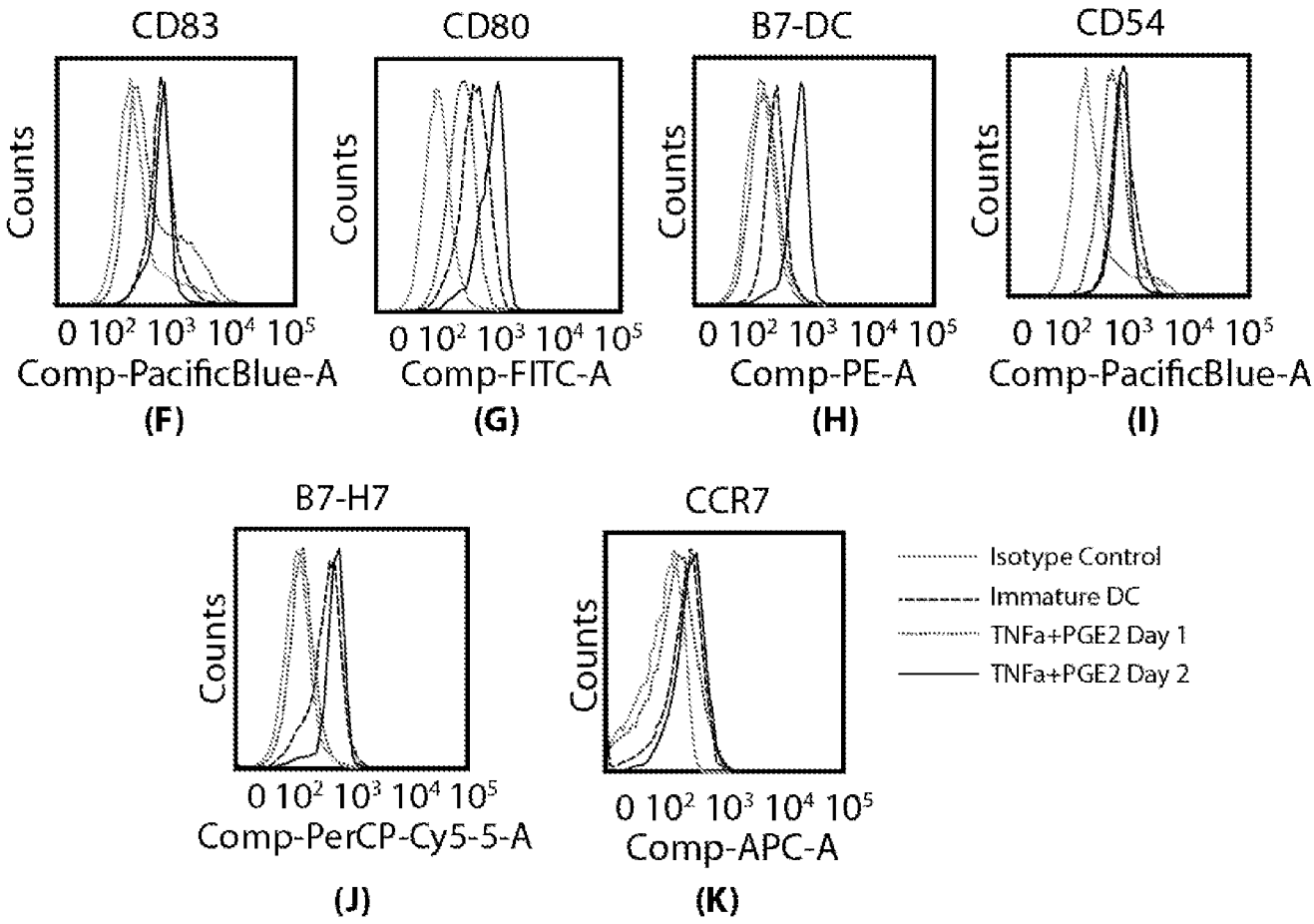


Figure 12 (continued)

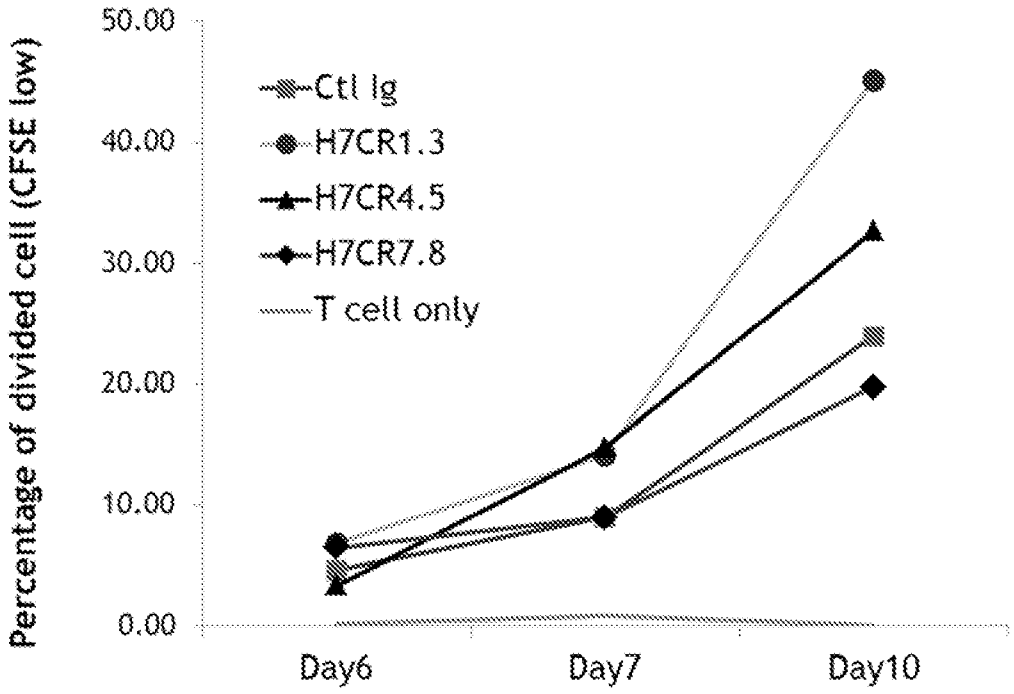

Percentage of divided cell (CFSE low)
50.00
40.00
30.00
20.00
10.00
0.00
Ctl Ig
H7CR1.3
H7CR4.5
H7CR7.8
T cell only
Day6
Day7
Day10

Figure 13

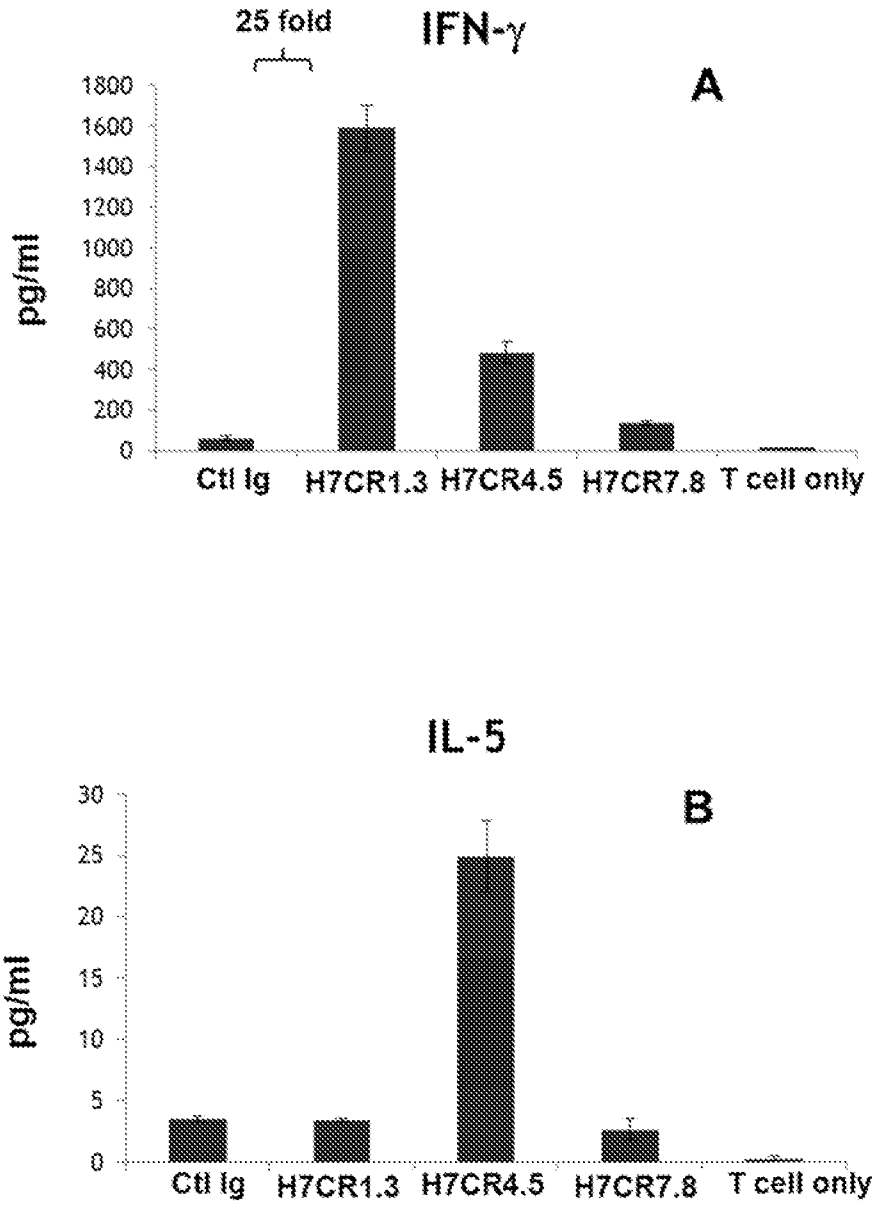

25 fold
IFN-γ
A
pg/ml
1800
1600
1400
1200
1000
800
600
400
200
0
Ctl Ig
H7CR1.3
H7CR4.5
H7CR7.8
T cell only
IL-5
B
pg/ml
30
25
20
15
10
5
0
Ctl Ig
H7CR1.3
H7CR4.5
H7CR7.8
T cell only

Figure 14

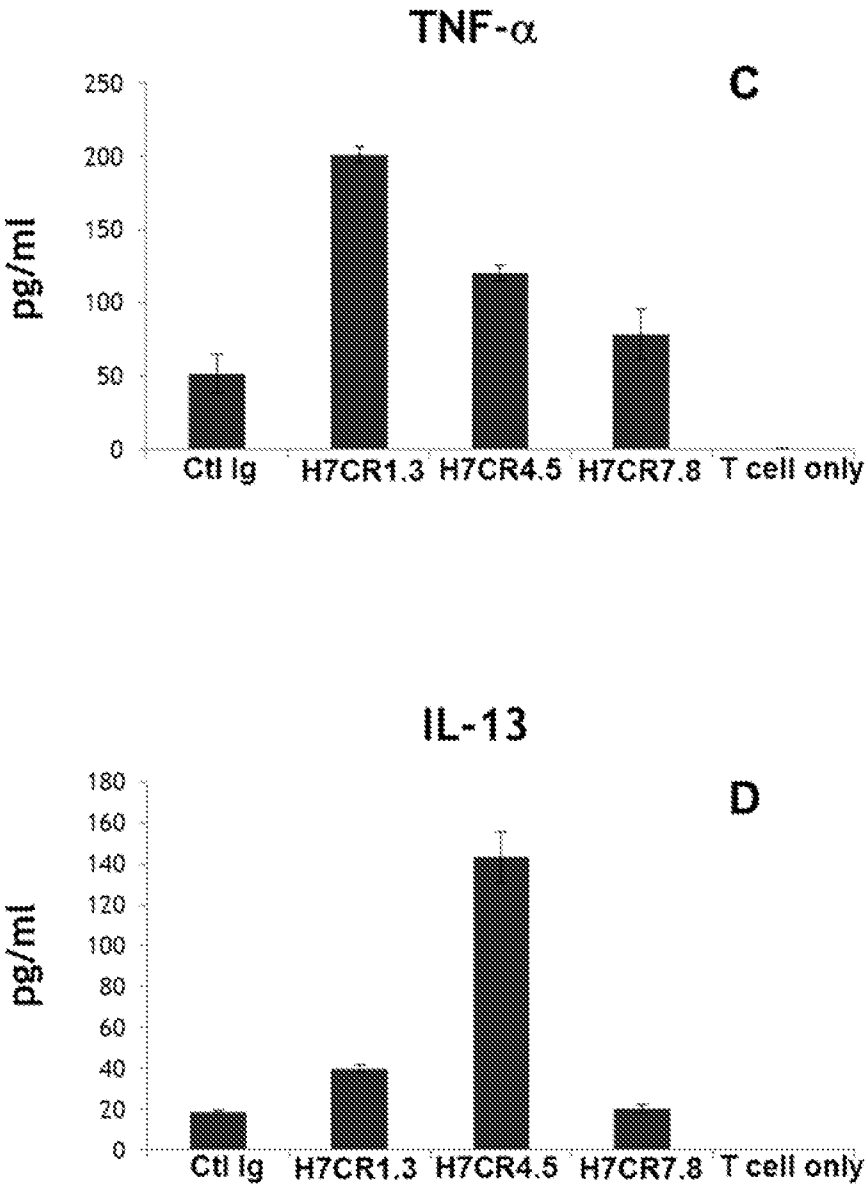


Figure 14 (continued)

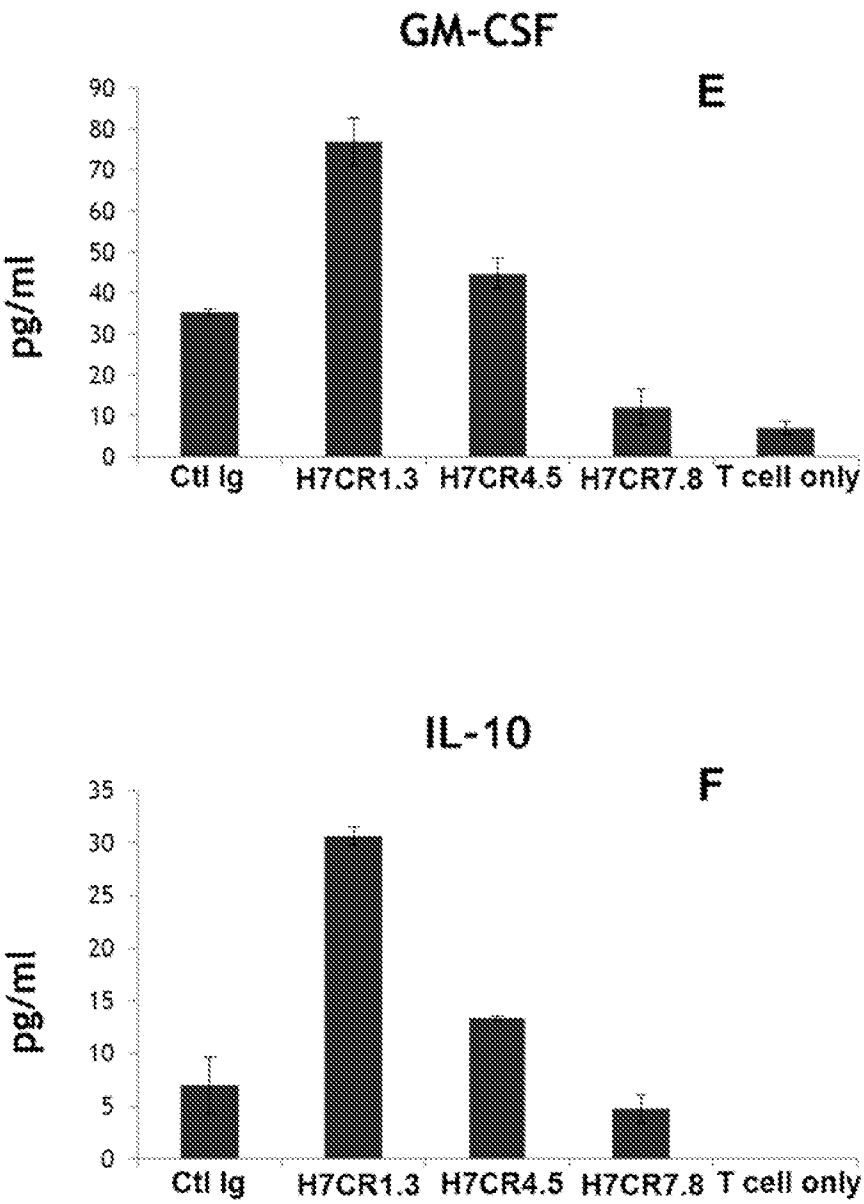


Figure 14 (continued)

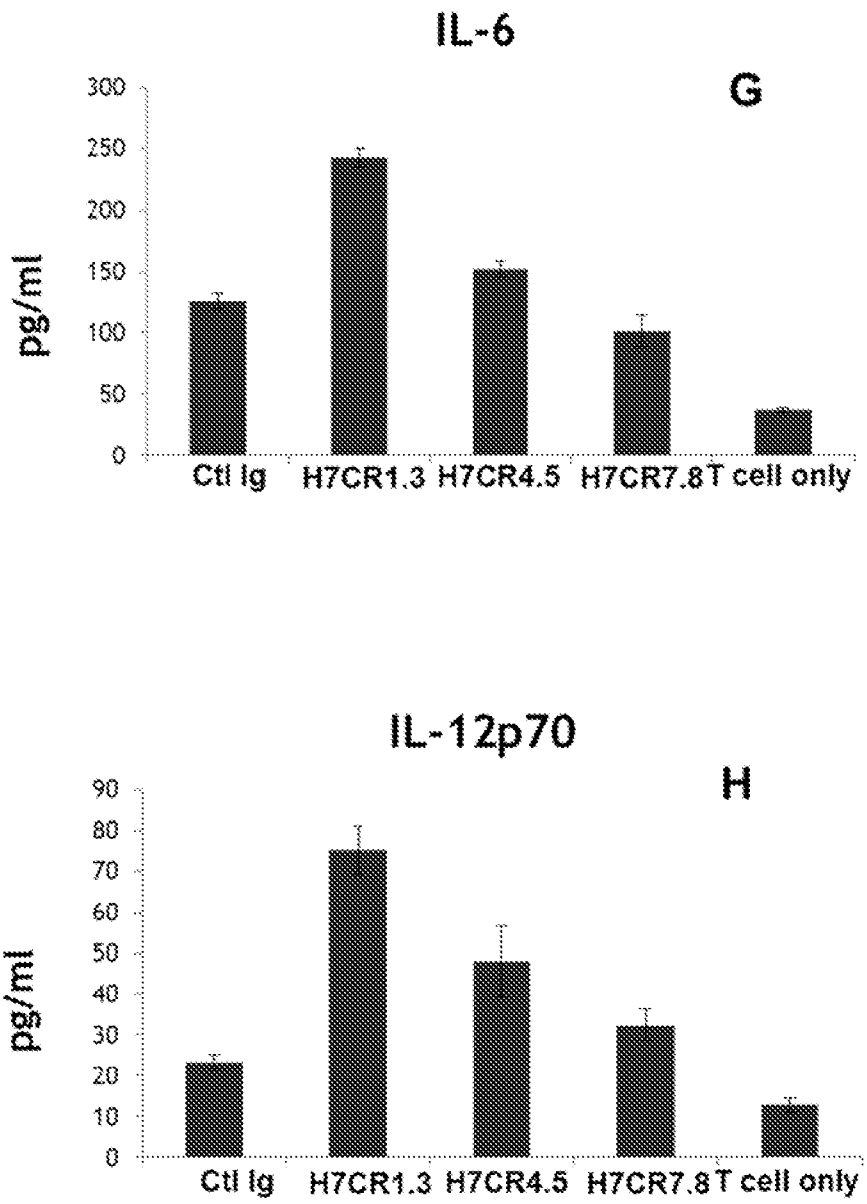
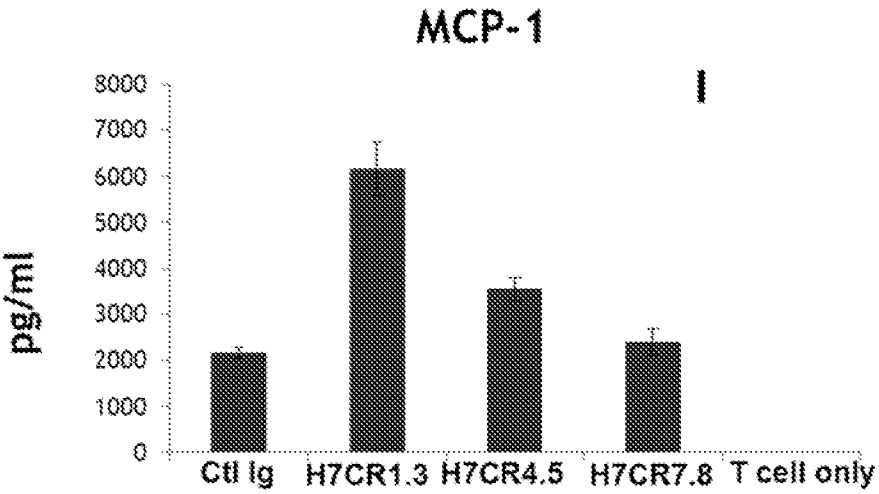
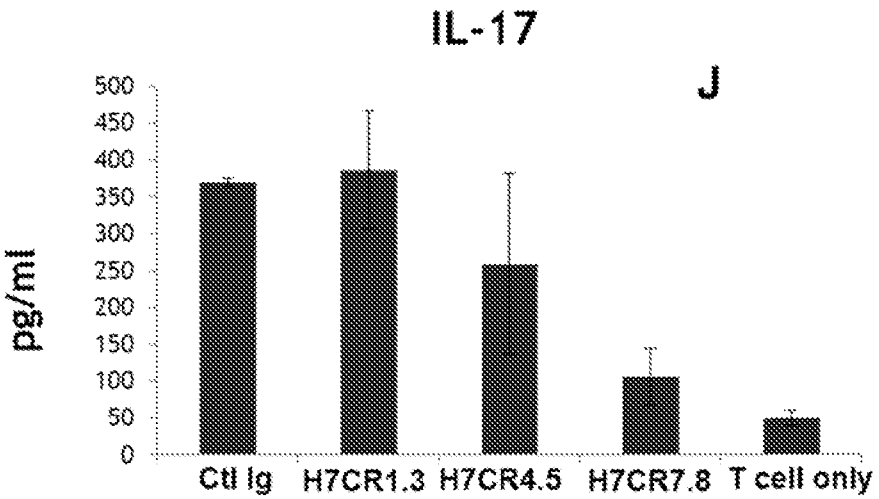


Figure 14 (continued)





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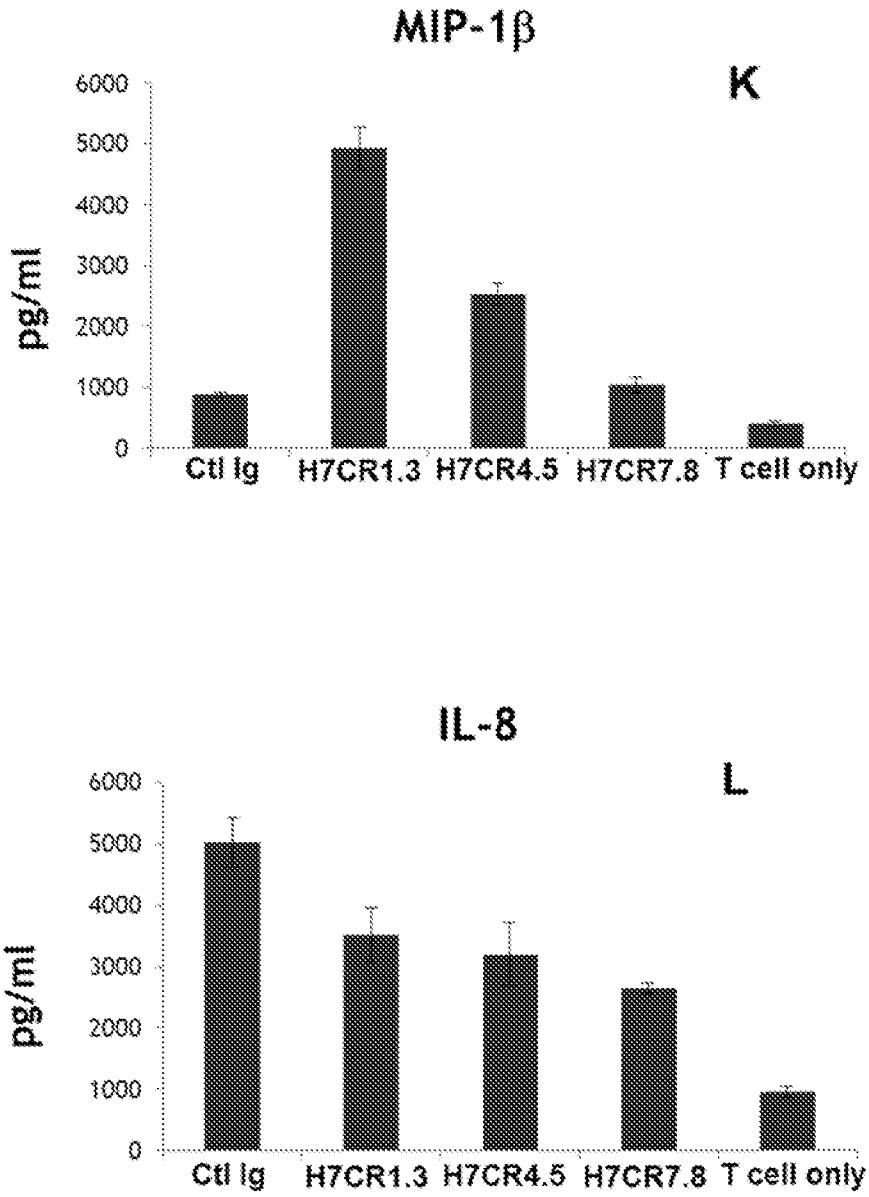


Figure 14 (continued)

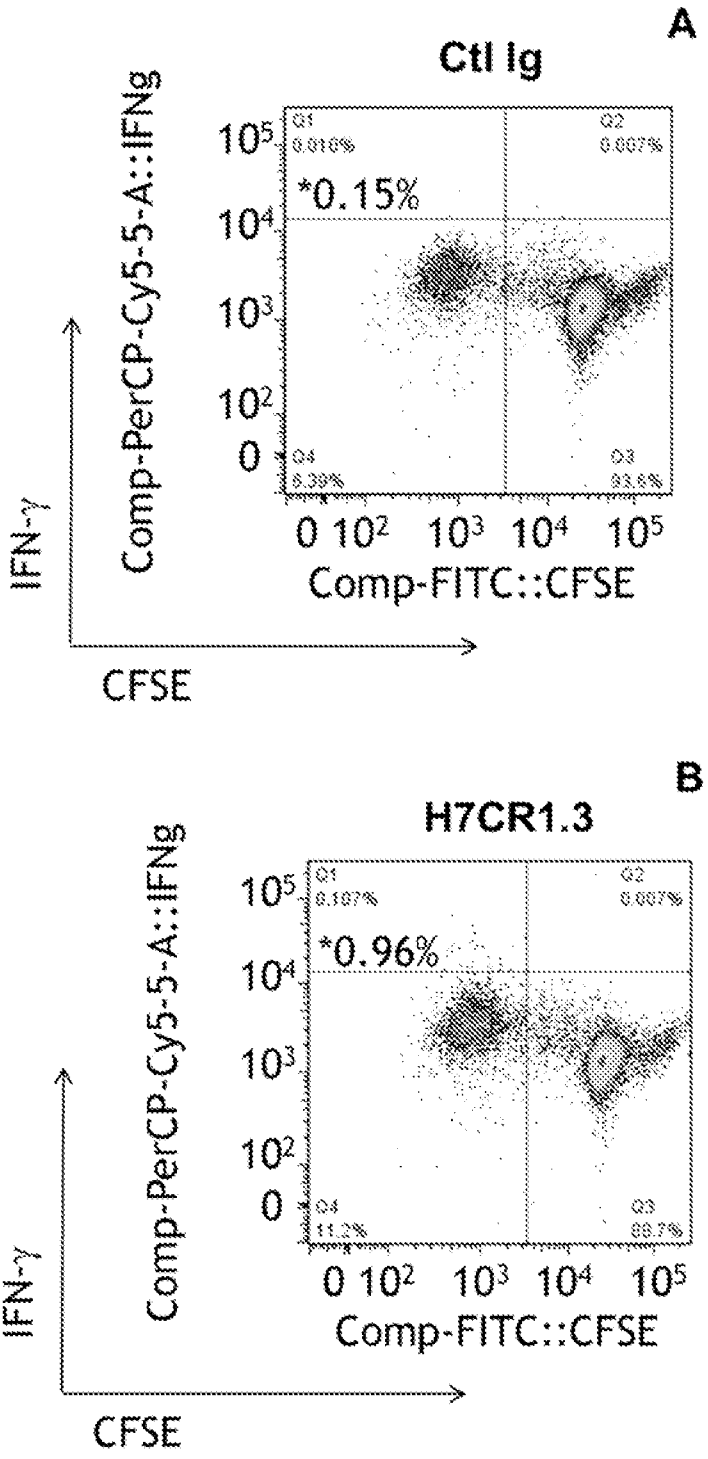

A
Ctl Ig
Comp-PerCP-Cy5-5-A::IFNg
*0.15%
Comp-FITC::CFSE
IFN-γ
CFSE
B
H7CR1.3
Comp-PerCP-Cy5-5-A::IFNg
*0.96%
Comp-FITC::CFSE
IFN-γ
CFSE

Figure 15

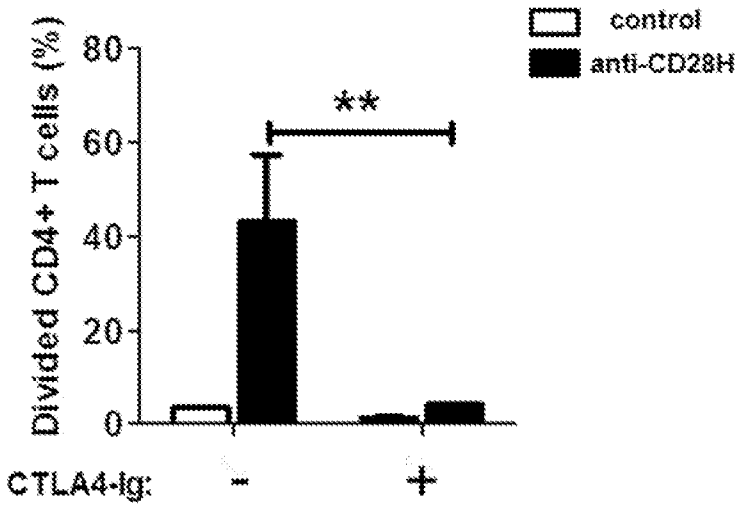
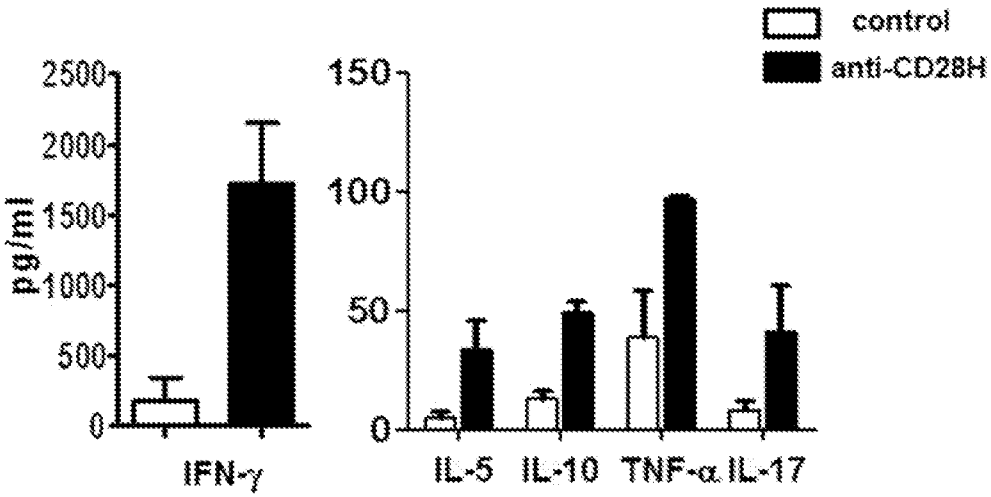


Figure 16A



Panel A Panel B

Figure 16B

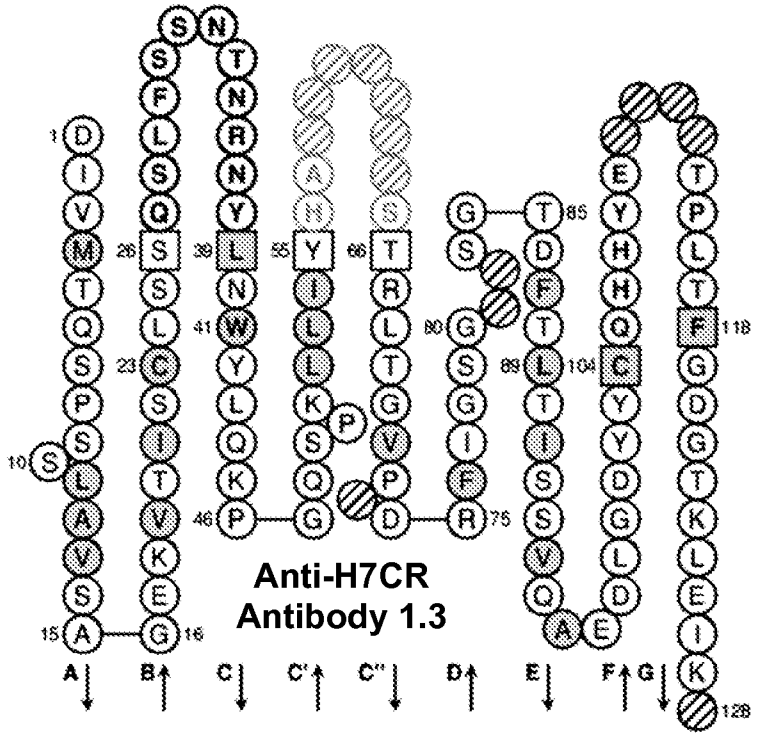


Figure 17A

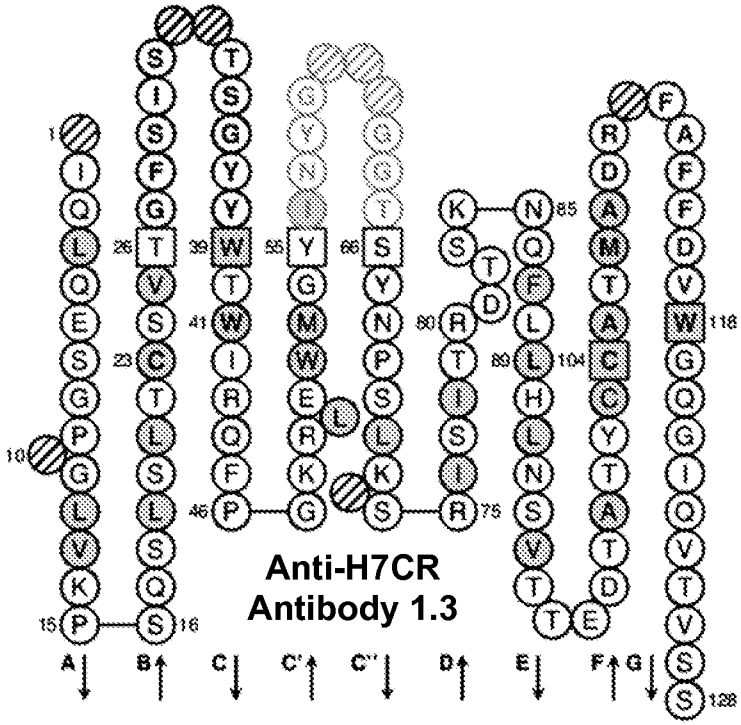
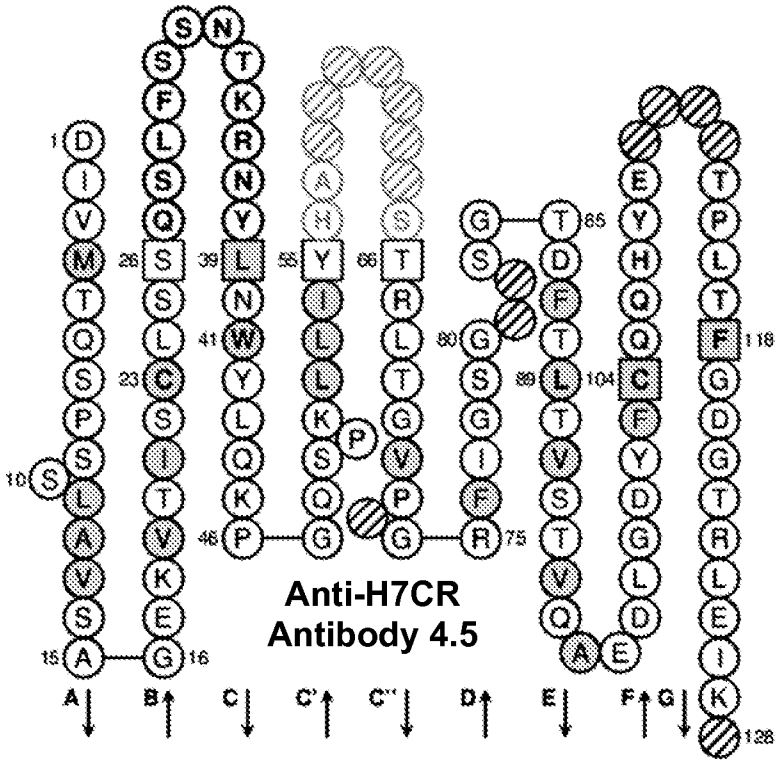


Figure 17B



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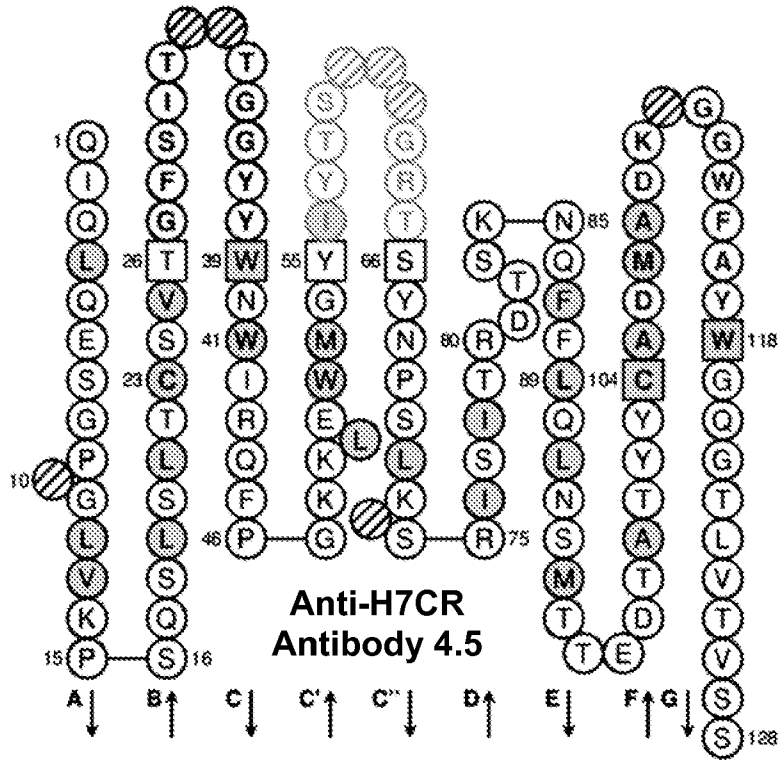

Figure 18B

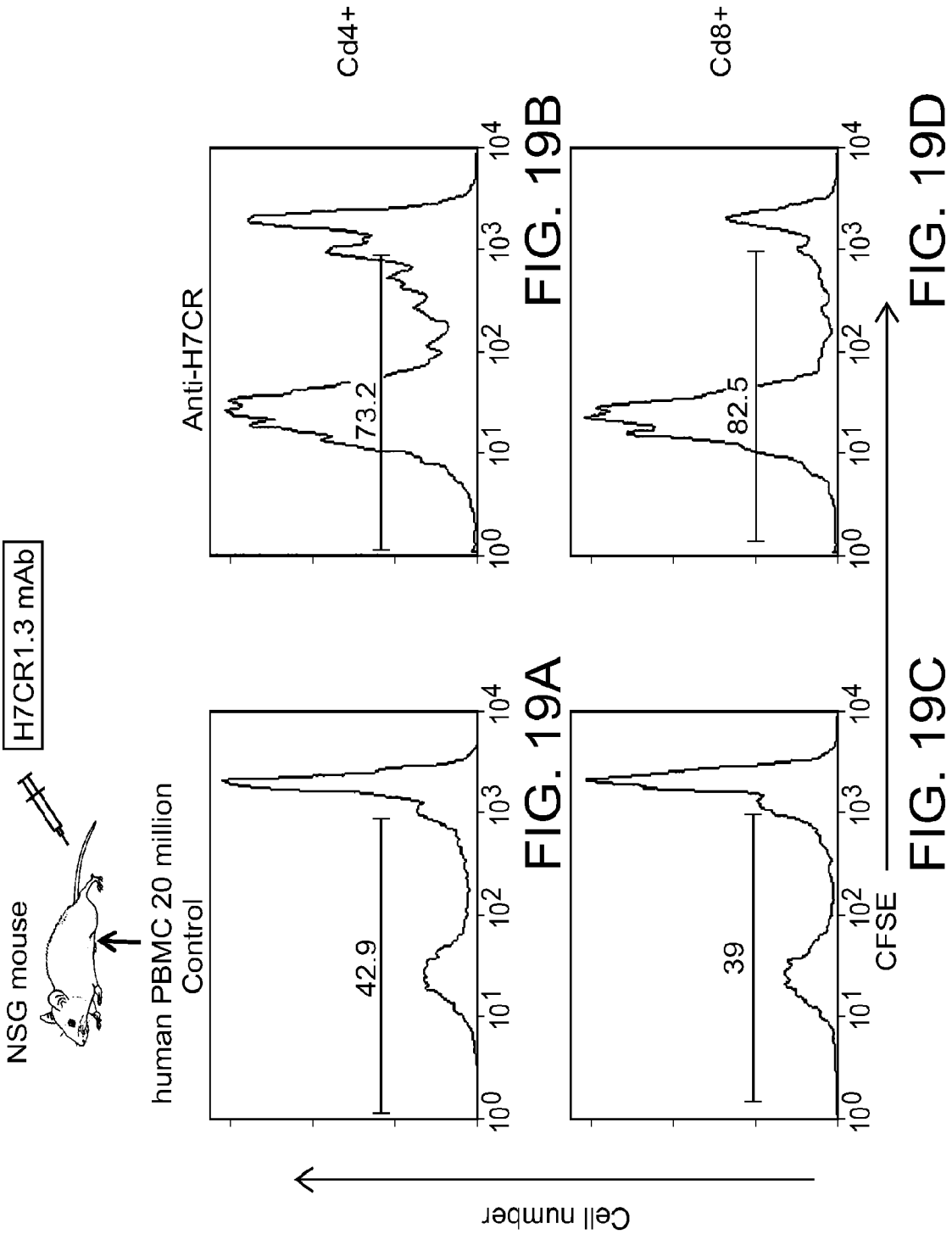

FIG. 19A

FIG. 19B

FIG. 19C

FIG. 19D

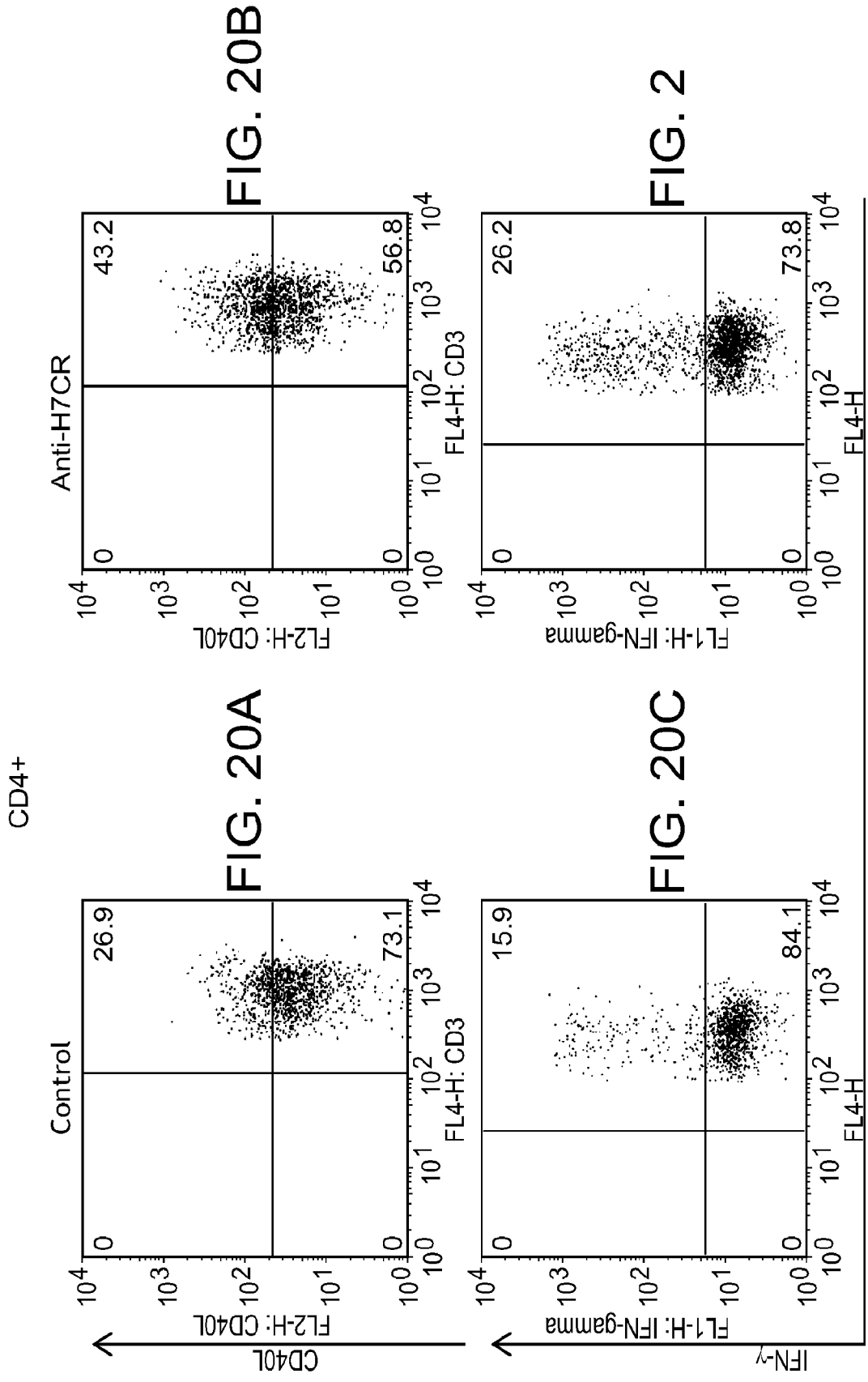

FIG. 20A

FIG. 20B

FIG. 20C

FIG. 2

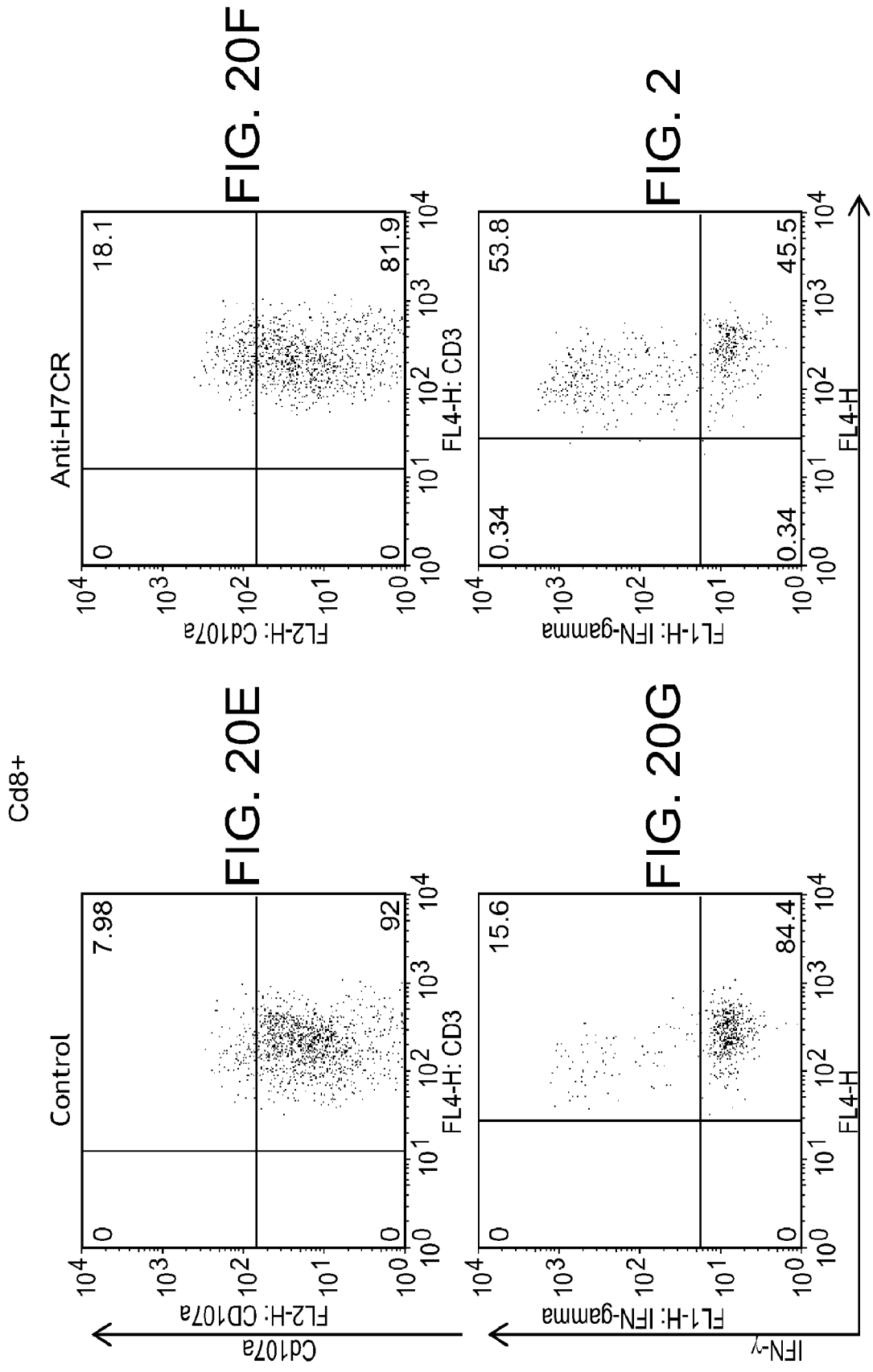

FIG. 20E

FIG. 20F

FIG. 20G

FIG. 2

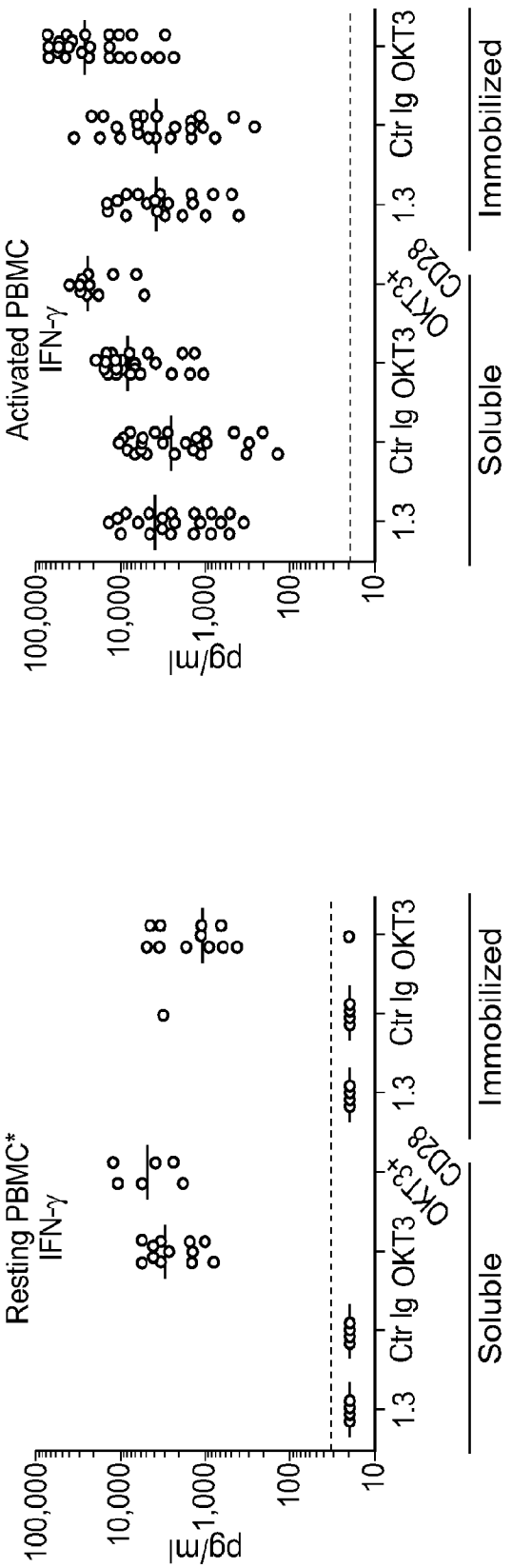

FIG. 21A

FIG. 21B

FIG. 22

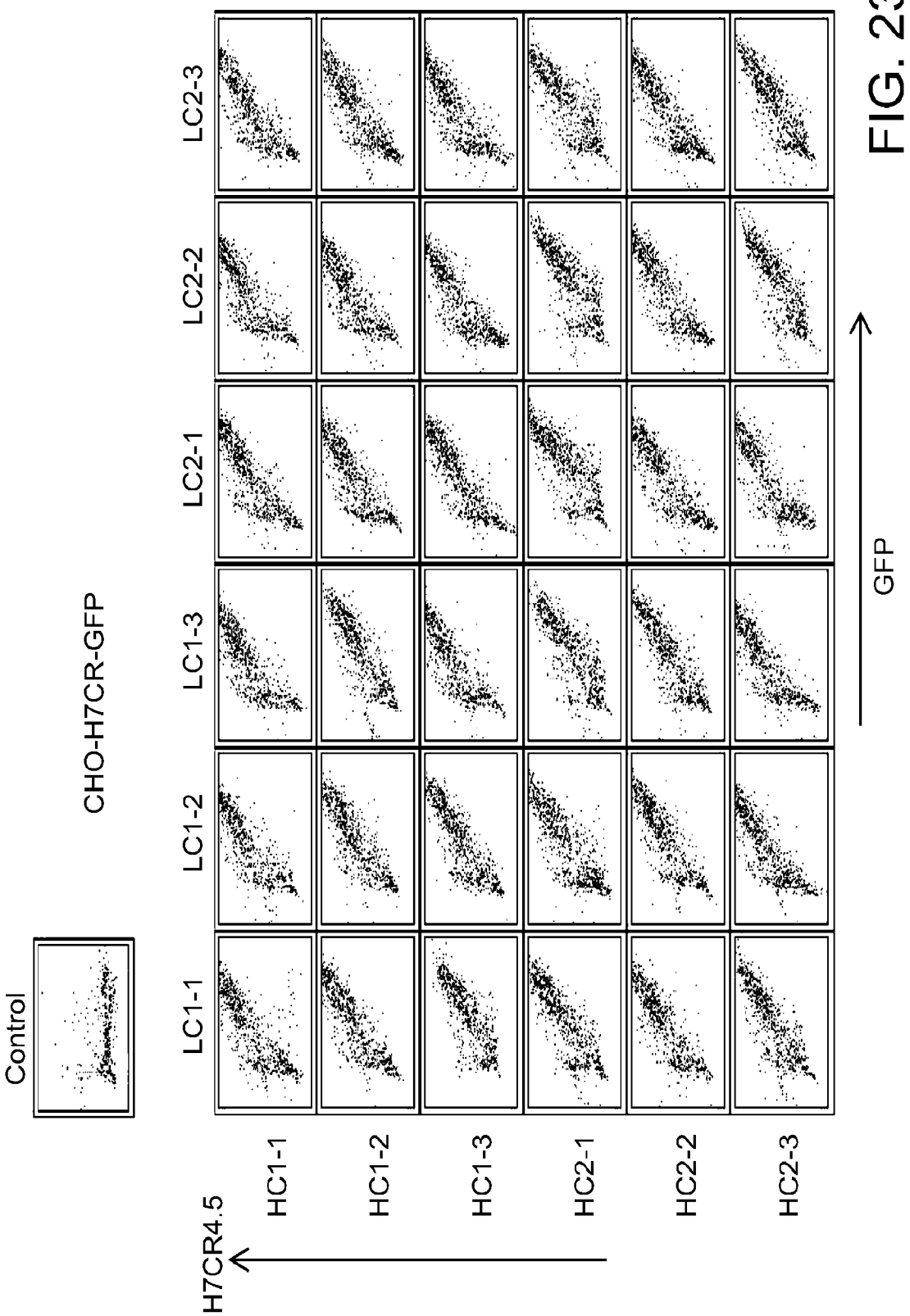
Control
CHO-H7CR-GFP
LC1-1
LC1-2
LC1-3
LC2-1
LC2-2
LC2-3
H7CR4.5
HC1-1
HC1-2
HC1-3
HC2-1
HC2-2
HC2-3
GFP

FIG. 23

SEQUENCE LISTING

<110> Amplimmune, Inc.
Langermann, Solomon
Liu, Linda
Yao, Sheng
Chen, Lieping

<120> ANTI-H7CR ANTIBODIES AND THEIR USES

<130> AMP h932 PCT

<150> US 61/745,296
<151> 2012-12-21

<150> US 61/745,312
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<170> PatentIn version 3.5

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<213> Homo sapiens

<400> 1

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1 5 10 15

Leu Ser Gly Ser Gln Gly Ile Phe Pro Leu Ala Phe Phe Ile Tyr Val
20 25 30

Pro Met Asn Glu Gln Ile Val Ile Gly Arg Leu Asp Glu Asp Ile Ile
35 40 45

Leu Pro Ser Ser Phe Glu Arg Gly Ser Glu Val Val Ile His Trp Lys
50 55 60

Tyr Gln Asp Ser Tyr Lys Val His Ser Tyr Tyr Lys Gly Ser Asp His
65 70 75 80

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

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

Leu Leu Asp Glu Gly Ile Tyr Thr Cys Tyr Val Gly Thr Ala Ile Gln
115 120 125

Val Ile Thr Asn Lys Val Val Leu Lys Val Gly Val Phe Leu Thr Pro

130 135 140

Val Met Lys Tyr Glu Lys Arg Asn Thr Asn Ser Phe Leu Ile Cys Ser
145 150 155 160

Val Leu Ser Val Tyr Pro Arg Pro Ile Ile Thr Trp Lys Met Asp Asn
165 170 175

Thr Pro Ile Ser Glu Asn Asn Met Glu Glu Thr Gly Ser Leu Asp Ser
180 185 190

Phe Ser Ile Asn Ser Pro Leu Asn Ile Thr Gly Ser Asn Ser Ser Tyr
195 200 205

Glu Cys Thr Ile Glu Asn Ser Leu Leu Lys Gln Thr Trp Thr Gly Arg
210 215 220

Trp Thr Met Lys Asp Gly Leu His Lys Met Gln Ser Glu His Val Ser
225 230 235 240

Leu Ser Cys Gln Pro Val Asn Asp Tyr Phe Ser Pro Asn Gln Asp Phe
245 250 255

Lys Val Thr Trp Ser Arg Met Lys Ser Gly Thr Phe Ser Val Leu Ala
260 265 270

Tyr Tyr Leu Ser Ser Ser Gln Asn Thr Ile Ile Asn Glu Ser Arg Phe
275 280 285

Ser Trp Asn Lys Glu Leu Ile Asn Gln Ser Asp Phe Ser Met Asn Leu
290 295 300

Met Asp Leu Asn Leu Ser Asp Ser Gly Glu Tyr Leu Cys Asn Ile Ser
305 310 315 320

Ser Asp Glu Tyr Thr Leu Leu Thr Ile His Thr Val His Val Glu Pro
325 330 335

Ser Gln Glu Thr Ala Ser His Asn Lys Gly Leu Trp Ile Leu Val Pro
340 345 350

Ser Ala Ile Leu Ala Ala Phe Leu Leu Ile Trp Ser Val Lys Cys Cys
355 360 365

Arg Ala Gln Leu Glu Ala Arg Arg Ser Arg His Pro Ala Asp Gly Ala
370 375 380

Gln Gln Glu Arg Cys Cys Val Pro Pro Gly Glu Arg Cys Pro Ser Ala
385 390 395 400

Pro Asp Asn Gly Glu Glu Asn Val Pro Leu Ser Gly Lys Val

405 410

<210> 2
<211> 1242
<212> DNA
<213> Homo sapiens

<400> 2
atgaaggcac agacagcact gtctttcttc ctcattctca taacatctct gagtggatct 60

caaggcatat tccctttggc tttcttcatt tatgttccta tgaatgaaca aatcgtcatt 120

ggaagacttg atgaagatat aattctccct tcttcatttg agaggggatc cgaagtcgta 180

atacactgga agtatcaaga tagctataag gttcatagtt actacaaagg cagtgaccat 240

ttggaaagcc aagatcccag atatgcaaac aggacatccc ttttctataa tgagattcaa 300

aatgggaatg cgtcactatt tttcagaaga gtaagccttc tggacgaagg aatttacacc 360

tgctatgtag gaacagcaat tcaagtgatt acaaacaaag tggtgctaaa ggtgggagtt 420

tttctcacac ccgtgatgaa gtatgaaaag aggaacacaa acagcttctt aatatgcagc 480

gtgttaagtg tttatcctcg tccaattatc acgtggaaaa tggacaacac acctatctct 540

gaaaacaaca tggaagaaac agggtctttg gattcttttt ctattaacag cccactgaat 600

attacaggat caaattcatc ttatgaatgt acaattgaaa attcactgct gaagcaaaca 660

tggacagggc gctggacgat gaaagatggc cttcataaaa tgcaaagtga acacgtttca 720

ctctcatgtc aacctgtaaa tgattatttt tcaccaaacc aagacttcaa agttacttgg 780

tccagaatga aaagtgggac tttctctgtc ctggcttact atctgagctc ctcacaaaat 840

acaattatca atgaatcccg attctcatgg aacaaagagc tgataaacca gagtgacttc 900

tctatgaatt tgatggatct taatctttca gacagtgggg aatatttatg caatatttct 960

tcggatgaat atactttact taccatccac acagtgcatg tagaaccgag ccaagaaaca 1020

gcttcccata acaaaggctt atggattttg gtgccctctg cgattttggc agcttttctg 1080

ctgatttgga gcgtaaaatg ttgcagagcc cagctagaag ccaggaggag cagacaccct 1140

gctgatggag cccaacaaga aagatgttgt gtccctcctg gtgagcgctg tcccagtgca 1200

cccgataatg gcgaagaaaa tgtgcctctt tcaggaaaag ta 1242

<210> 3
<211> 282
<212> PRT
<213> Homo sapiens

<400> 3

Met Gly Ser Pro Gly Met Val Leu Gly Leu Leu Val Gln Ile Trp Ala
1 5 10 15

Leu Gln Glu Ala Ser Ser Leu Ser Val Gln Gln Gly Pro Asn Leu Leu
20 25 30

Gln Val Arg Gln Gly Ser Gln Ala Thr Leu Val Cys Gln Val Asp Gln

35 40 45

Ala Thr Ala Trp Glu Arg Leu Arg Val Lys Trp Thr Lys Asp Gly Ala
50 55 60

Ile Leu Cys Gln Pro Tyr Ile Thr Asn Gly Ser Leu Ser Leu Gly Val
65 70 75 80

Cys Gly Pro Gln Gly Arg Leu Ser Trp Gln Ala Pro Ser His Leu Thr
85 90 95

Leu Gln Leu Asp Pro Val Ser Leu Asn His Ser Gly Ala Tyr Val Cys
100 105 110

Trp Ala Ala Val Glu Ile Pro Glu Leu Glu Glu Ala Glu Gly Asn Ile
115 120 125

Thr Arg Leu Phe Val Asp Pro Asp Asp Pro Thr Gln Asn Arg Asn Arg
130 135 140

Ile Ala Ser Phe Pro Gly Phe Leu Phe Val Leu Leu Gly Val Gly Ser
145 150 155 160

Met Gly Val Ala Ala Ile Val Trp Gly Ala Trp Phe Trp Gly Arg Arg
165 170 175

Ser Cys Gln Gln Arg Asp Ser Gly Asn Ser Pro Gly Asn Ala Phe Tyr
180 185 190

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

Cys Ser Gly Glu Gly Lys Asp Gln Arg Gly Gln Ser Ile Tyr Ser Thr
210 215 220

Ser Phe Pro Gln Pro Ala Pro Arg Gln Pro His Leu Ala Ser Arg Pro
225 230 235 240

Cys Pro Ser Pro Arg Pro Cys Pro Ser Pro Arg Pro Gly His Pro Val
245 250 255

Ser Met Val Arg Val Ser Pro Arg Pro Ser Pro Thr Gln Gln Pro Arg
260 265 270

Pro Lys Gly Phe Pro Lys Val Gly Glu Glu
275 280

<210> 4
<211> 846
<212> DNA
<213> Homo sapiens

<400> 4
atggggtccc cgggcatggt gctgggcctc ctggtgcaga tctgggccct gcaagaagcc 60

tcaagcctga gcgtgcagca ggggcccaac ttgctgcagg tgaggcaggg cagtcaggcg 120

accctggtct gccaggtgga ccaggccaca gcctgggaac ggctccgtgt taagtggaca 180

aaggatgggg ccatcctgtg tcaaccgtac atcaccaacg gcagcctcag cctgggggtc 240

tgcgggcccc agggacggct ctcctggcag gcacccagcc atctcaccct gcagctggac 300

cctgtgagcc tcaaccacag cggggcgtac gtgtgctggg cggccgtaga gattcctgag 360

ttggaggagg ctgagggcaa cataacaagg ctctttgtgg acccagatga ccccacacag 420

aacagaaacc ggatcgcaag cttcccagga ttcctcttcg tgctgctggg ggtgggaagc 480

atgggtgtgg ctgcgatcgt gtggggtgcc tggttctggg gccgccgcag ctgccagcaa 540

agggactcag gtaacagccc aggaaatgca ttctacagca acgtcctata ccggccccgg 600

ggggccccaa agaagagtga ggactgctct ggagagggga aggaccagag gggccagagc 660

atttattcaa cctccttccc gcaaccggcc ccccgccagc cgcacctggc gtcaagaccc 720

tgccccagcc cgagaccctg ccccagcccc aggcccggcc accccgtctc tatggtcagg 780

gtctctccta gaccaagccc cacccagcag ccgaggccaa aagggttccc caaagtggga 840

gaggag 846

<210> 5
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Anti-Human H7CR Antibody

<400> 5

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

Glu Lys Val Thr Ile Ser Cys Leu Ser Ser Gln Ser Leu Phe Ser Ser
20 25 30

Asn Thr Asn Arg Asn Tyr Leu Asn Trp Tyr Leu Gln Lys Pro Gly Gln
35 40 45

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

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

Ile Ser Ser Val Gln Ala Glu Asp Leu Gly Asp Tyr Tyr Cys Gln His
85 90 95

His Tyr Glu Thr Pro Leu Thr Phe Gly Asp Gly Thr Lys Leu Glu Ile
100 105 110

Lys

<210> 6
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> Anti-Human H7CR Antibody

<400> 6

Gln Ile Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1 5 10 15

Ser Leu Ser Leu Thr Cys Ser Val Thr Gly Phe Ser Ile Ser Thr Ser
20 25 30

Gly Tyr Tyr Trp Thr Trp Ile Arg Gln Phe Pro Gly Lys Arg Leu Glu
35 40 45

Trp Met Gly Tyr Ile Asn Tyr Gly Gly Gly Thr Ser Tyr Asn Pro Ser
50 55 60

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

Leu Leu His Leu Asn Ser Val Thr Thr Glu Asp Thr Ala Thr Tyr Cys
85 90 95

Cys Ala Thr Met Ala Asp Arg Phe Ala Phe Phe Asp Val Trp Gly Gln
100 105 110

Gly Ile Gln Val Thr Val Ser Ser
115 120

<210> 7
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Anti-Human H7CR Antibody

<400> 7

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

Glu Lys Val Thr Ile Ser Cys Leu Ser Ser Gln Ser Leu Phe Ser Ser
20 25 30

Asn Thr Lys Arg Asn Tyr Leu Asn Trp Tyr Leu Gln Lys Pro Gly Gln
35 40 45

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

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

Val Ser Thr Val Gln Ala Glu Asp Leu Gly Asp Tyr Phe Cys Gln Gln
85 90 95

His Tyr Glu Thr Pro Leu Thr Phe Gly Asp Gly Thr Arg Leu Glu Ile
100 105 110

Lys

<210> 8
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> Anti-Human H7CR Antibody

<400> 8

Gln Ile Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1 5 10 15

Ser Leu Ser Leu Thr Cys Ser Val Thr Gly Phe Ser Ile Thr Thr Gly
20 25 30

Gly Tyr Tyr Trp Asn Trp Ile Arg Gln Phe Pro Gly Lys Lys Leu Glu
35 40 45

Trp Met Gly Tyr Ile Tyr Thr Ser Gly Arg Thr Ser Tyr Asn Pro Ser
50 55 60

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

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

Cys Ala Asp Met Ala Asp Lys Gly Gly Trp Phe Ala Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 9
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Anti-Human H7CR Antibody

<400> 9

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

Glu Lys Val Thr Ile Ser Cys Leu Ser Ser Gln Ser Leu Phe Ser Ser
20 25 30

Asn Thr Asn Arg Asn Tyr Leu Ser Trp Tyr Leu Gln Arg Pro Gly Gln
35 40 45

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

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

Val Ser Thr Val Gln Ala Gly Asp Leu Gly Asp Tyr Phe Cys Gln Gln
85 90 95

His Tyr Val Thr Pro Leu Thr Phe Gly Asp Gly Thr Arg Leu Glu Ile
100 105 110

Lys

<210> 10
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> Anti-Human H7CR Antibody

<400> 10

Gln Ile Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1 5 10 15

Ser Leu Ser Leu Thr Cys Ser Val Thr Gly Phe Ser Ile Thr Thr Gly
20 25 30

Gly Tyr Tyr Trp Asn Trp Ile Arg Gln Phe Pro Gly Lys Lys Leu Glu
35 40 45

Trp Met Gly Tyr Ile Tyr Ser Ser Gly Arg Thr Ser Tyr Asn Pro Ser
50 55 60

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

```
Phe Leu Gln Leu Asn Ser Val Thr Thr Glu Asp Thr Ala Thr Tyr Tyr
                85                  90                  95


Cys Ala Asp Met Ala Asp Lys Gly Gly Trp Phe Asp Tyr Trp Gly Gln
            100                 105                 110


Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210>  11
<211>  465
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Humanized antibody

<400>  11

Met Glu Trp Ser Trp Val Phe Leu Phe Phe Leu Ser Val Thr Thr Gly
1               5                   10                  15


Val His Ser Gln Ile Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys
            20                  25                  30


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


Ser Thr Ser Gly Tyr Tyr Trp Thr Trp Ile Arg Gln Phe Pro Gly Lys
    50                  55                  60


Arg Leu Glu Trp Met Gly Tyr Ile Asn Tyr Gly Gly Gly Thr Ser Tyr
65                  70                  75                  80


Asn Pro Ser Leu Lys Ser Arg Ile Ser Ile Thr Arg Asp Thr Ser Lys
                85                  90                  95


Asn Gln Phe Leu Leu His Leu Asn Ser Val Thr Thr Glu Asp Thr Ala
            100                 105                 110


Thr Tyr Cys Cys Ala Thr Met Ala Asp Arg Phe Ala Phe Phe Asp Val
        115                 120                 125


Trp Gly Gln Gly Ile Gln Val Thr Val Ser Ser Ala Ser Thr Lys Gly
    130                 135                 140


Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser
145                 150                 155                 160


Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val
                165                 170                 175


Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe
            180                 185                 190
```

```
Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val
        195                 200                 205

Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val
    210                 215                 220

Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys
225                 230                 235                 240

Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly
                245                 250                 255

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
            260                 265                 270

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu
        275                 280                 285

Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
    290                 295                 300

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg
305                 310                 315                 320

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
                325                 330                 335

Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu
            340                 345                 350

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
        355                 360                 365

Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu
    370                 375                 380

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
385                 390                 395                 400

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
                405                 410                 415

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp
            420                 425                 430

Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His
        435                 440                 445

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
    450                 455                 460
```

Gly
465

<210> 12
<211> 240
<212> PRT
<213> Artificial Sequence

<220>
<223> Humanized antibody

<400> 12

Met Ser Val Pro Thr Gln Val Leu Gly Leu Leu Leu Leu Trp Leu Thr
1 5 10 15

Asp Ala Arg Cys Asp Ile Val Met Thr Gln Ser Pro Ser Ser Leu Ala
20 25 30

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

Leu Phe Ser Ser Asn Thr Asn Arg Asn Tyr Leu Asn Trp Tyr Leu Gln
50 55 60

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

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

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

Tyr Cys Gln His His Tyr Glu Thr Pro Leu Thr Phe Gly Asp Gly Thr
115 120 125

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

Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys
145 150 155 160

Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val
165 170 175

Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln
180 185 190

Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser
195 200 205

Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His
210 215 220

Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225 230 235 240

<210> 13
<211> 1401
<212> DNA
<213> Artificial Sequence

<220>
<223> Chimeric antibody coding sequence

<400> 13
atggaatggt cctgggtgtt cctgttcttc ctgtccgtga ccaccggcgt gcactcccag 60

atccagctgc aggaatctgg ccctggcctc gtgaagcctt cccagtccct gtccctgacc 120

tgcagcgtga ccggcttctc tatcacaacc ggcggctact actggaactg gatccggcag 180

ttccccggca agaaactgga atggatgggc tacatctata ccagcggccg gacctcctac 240

aaccccagcc tgaagtcccg gatctccatc acccgggaca cctccaagaa ccagttcttt 300

ctgcagctga actccatgac caccgaggac accgccacct actactgcgc cgacatggcc 360

gataagggcg gatggttcgc ttactggggc cagggcacac tcgtgaccgt gtcctctgct 420

tccaccaagg gcccctccgt gtttcctctg gcccccttgct ccagatccac ctccgagtct 480

accgccgctc tgggctgcct cgtgaaagac tacttccccg agcccgtgac agtgtcttgg 540

aactctggcg ccctgacctc tggcgtgcac acctttccag ctgtgctgca gtcctccggc 600

ctgtactccc tgtcctccgt cgtgactgtg ccctccagct ctctgggcac caagacctac 660

acctgtaacg tggaccacaa gccctccaac accaaggtgg acaagcgggt ggaatctaag 720

tacggccctc cctgccctcc ttgcccagcc cctgaatttc tgggcggacc ttctgtgttt 780

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gtggtggtgg atgtgtccca ggaagatccc gaggtgcagt tcaattggta cgtggacggc 900

gtggaagtgc acaacgccaa gaccaagcct agagaggaac agttcaactc cacctaccgg 960

gtggtgtccg tgctgaccgt gctgcaccag gattggctga acggcaaaga gtacaagtgc 1020

aaggtgtcca acaagggcct gcccagctcc atcgaaaaga ccatctccaa ggctaagggc 1080

cagccccgcg agccccaggt gtacacactg cctccaagcc aggaagagat gaccaagaat 1140

caggtgtcac tgacctgtct cgtgaagggc ttctaccct ccgatatcgc cgtggaatgg 1200

gagtccaacg gccagcccga gaacaactac aagaccaccc cccctgtgct ggactccgac 1260

ggctccttct ttctgtactc tcgcctgacc gtggacaagt cccggtggca ggaaggcaac 1320

gtgttctcct gctctgtgat gcacgaggcc ctgcacaacc actacaccca gaagtccctg 1380

agcctgtccc ccggctgatg a 1401

<210> 14
<211> 726

<212> DNA
<213> Artificial Sequence

<220>
<223> Chimeric antibody coding sequence

<400> 14
atgtccgtgc ccacccaggt gctgggattg ctgctgctgt ggctgaccga cgccagatgc 60

gacatcgtga tgacccagtc cccctcctcc ctggctgtgt ctgctggcga gaaagtgacc 120

atctcctgcc tgtcctccca gtccctgttc tccagcaaca ccaagcggaa ctacctgaac 180

tggtatctgc agaagcccgg ccagtcccct aagctgctga tctaccacgc ctccaccaga 240

ctgaccggcg tgcccggaag attcatcggc tctggctctg gcaccgactt caccctgacc 300

gtgtctaccg tgcaggccga ggacctgggc gactacttct gccagcagca ctacgagaca 360

cccctgacct ttggcgacgg cacccggctg gaaatcaaga gaaccgtggc cgctccctcc 420

gtgttcatct tcccaccttc cgacgagcag ctgaagtccg gcaccgcttc tgtcgtgtgc 480

ctgctgaaca acttctaccc ccgcgaggcc aaggtgcagt ggaaggtgga caacgccctg 540

cagtccggca actcccagga atccgtgacc gagcaggact ccaaggacag cacctactcc 600

ctgtcctcta ccctgaccct gagcaaggcc gactacgaga agcacaaggt gtacgcctgc 660

gaagtgaccc accagggcct gtctagcccc gtgaccaagt ctttcaaccg gggcgagtgc 720

tgatga 726

<210> 15
<211> 465
<212> PRT
<213> Artificial Sequence

<220>
<223> Chimeric antibody heavy chain sequence

<400> 15

Met Glu Trp Ser Trp Val Phe Leu Phe Phe Leu Ser Val Thr Thr Gly
1 5 10 15

Val His Ser Gln Ile Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys
20 25 30

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

Thr Thr Gly Gly Tyr Tyr Trp Asn Trp Ile Arg Gln Phe Pro Gly Lys
50 55 60

Lys Leu Glu Trp Met Gly Tyr Ile Tyr Thr Ser Gly Arg Thr Ser Tyr
65 70 75 80

Asn Pro Ser Leu Lys Ser Arg Ile Ser Ile Thr Arg Asp Thr Ser Lys
85 90 95

```
Asn Gln Phe Phe Leu Gln Leu Asn Ser Met Thr Thr Glu Asp Thr Ala
            100                 105                 110

Thr Tyr Tyr Cys Ala Asp Met Ala Asp Lys Gly Gly Trp Phe Ala Tyr
        115                 120                 125

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

Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser
145                 150                 155                 160

Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val
                165                 170                 175

Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe
            180                 185                 190

Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val
        195                 200                 205

Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val
    210                 215                 220

Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys
225                 230                 235                 240

Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly
                245                 250                 255

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
            260                 265                 270

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu
        275                 280                 285

Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
    290                 295                 300

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg
305                 310                 315                 320

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
                325                 330                 335

Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu
            340                 345                 350

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
        355                 360                 365
```

```
Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu
    370                 375                 380

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
385                 390                 395                 400

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
                405                 410                 415

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp
            420                 425                 430

Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His
        435                 440                 445

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
    450                 455                 460

Gly
465
```

<210> 16
<211> 240
<212> PRT
<213> Artificial Sequence

<220>
<223> Chimeric antibiody light chain

<400> 16

```
Met Ser Val Pro Thr Gln Val Leu Gly Leu Leu Leu Leu Trp Leu Thr
1               5                   10                  15

Asp Ala Arg Cys Asp Ile Val Met Thr Gln Ser Pro Ser Ser Leu Ala
            20                  25                  30

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

Leu Phe Ser Ser Asn Thr Lys Arg Asn Tyr Leu Asn Trp Tyr Leu Gln
    50                  55                  60

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

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

Phe Thr Leu Thr Val Ser Thr Val Gln Ala Glu Asp Leu Gly Asp Tyr
            100                 105                 110

Phe Cys Gln Gln His Tyr Glu Thr Pro Leu Thr Phe Gly Asp Gly Thr
        115                 120                 125
```

```
Arg Leu Glu Ile Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe
    130                 135                 140

Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys
145                 150                 155                 160

Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val
                165                 170                 175

Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln
            180                 185                 190

Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser
        195                 200                 205

Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His
    210                 215                 220

Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225                 230                 235                 240
```

<210> 17
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Variant of humanized anti-human H7CR Antibody

<400> 17

```
Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
1               5                   10                  15

Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Leu Phe Ser Ser
            20                  25                  30

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

Pro Pro Lys Leu Leu Ile Tyr His Ala Ser Thr Arg Glu Ser Gly Val
    50                  55                  60

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65                  70                  75                  80

Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln His
                85                  90                  95

His Tyr Glu Thr Pro Leu Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile
            100                 105                 110
```

Lys

<210> 18
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Variant of humanized anti-human H7CR Antibody

<400> 18

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

Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Leu Phe Ser Ser
20 25 30

Asn Thr Asn Arg Asn Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln
35 40 45

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

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Asp Tyr Tyr Cys Gln His
85 90 95

His Tyr Glu Thr Pro Leu Thr Phe Gly Asp Gly Thr Lys Leu Glu Ile
100 105 110

Lys

<210> 19
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Variant of humanized anti-human H7CR Antibody

<400> 19

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

Glu Arg Ala Thr Ile Asn Cys Leu Ser Ser Gln Ser Leu Phe Ser Ser
20 25 30

Asn Thr Asn Arg Asn Tyr Leu Asn Trp Tyr Leu Gln Lys Pro Gly Gln
35 40 45

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

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

Ile Ser Ser Leu Gln Ala Glu Asp Val Gly Asp Tyr Tyr Cys Gln His
85 90 95

His Tyr Glu Thr Pro Leu Thr Phe Gly Asp Gly Thr Lys Leu Glu Ile
100 105 110

Lys

<210> 20
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Variant of humanized anti-human H7CR Antibody

<400> 20

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Phe Ser Ser
20 25 30

Asn Thr Asn Arg Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln
35 40 45

Ser Pro Gln Leu Leu Ile Tyr His Ala Ser Asn Arg Ala Ser Gly Val
50 55 60

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys
65 70 75 80

Ile Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gln His
85 90 95

His Tyr Glu Thr Pro Leu Thr Phe Gly Asp Gly Thr Lys Leu Glu Ile
100 105 110

Lys

<210> 21
<211> 113
<212> PRT
<213> Artificial Sequence

<220>

<223> Variant of humanized anti-human H7CR Antibody

<400> 21

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Phe Ser Ser
20 25 30

Asn Thr Asn Arg Asn Tyr Leu Asn Trp Tyr Leu Gln Lys Pro Gly Gln
35 40 45

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

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys
65 70 75 80

Ile Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gln His
85 90 95

His Tyr Glu Thr Pro Leu Thr Phe Gly Asp Gly Thr Lys Leu Glu Ile
100 105 110

Lys

<210> 22
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Variant of humanized anti-human H7CR Antibody

<400> 22

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Leu Ser Ser Gln Ser Leu Phe Ser Ser
20 25 30

Asn Thr Asn Arg Asn Tyr Leu Asn Trp Tyr Leu Gln Lys Pro Gly Gln
35 40 45

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

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys
65 70 75 80

Ile Ser Arg Val Glu Ala Glu Asp Val Gly Asp Tyr Tyr Cys Gln His
85 90 95

His Tyr Glu Thr Pro Leu Thr Phe Gly Asp Gly Thr Lys Leu Glu Ile
100 105 110

Lys

<210> 23
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> Variant of humanized anti-human H7CR Antibody

<400> 23

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1 5 10 15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Phe Ser Ile Ser Thr Ser
20 25 30

Gly Tyr Tyr Trp Ser Trp Ile Arg Gln His Pro Gly Lys Gly Leu Glu
35 40 45

Trp Ile Gly Tyr Ile Asn Tyr Gly Gly Gly Thr Tyr Tyr Asn Pro Ser
50 55 60

Leu Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe
65 70 75 80

Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
85 90 95

Cys Ala Thr Met Ala Asp Arg Phe Ala Phe Phe Asp Val Trp Gly Gln
100 105 110

Gly Thr Met Val Thr Val Ser Ser
115 120

<210> 24
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> Variant of humanized anti-human H7CR Antibody

<400> 24

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1 5 10 15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Phe Ser Ile Ser Thr Ser
20 25 30

```
Gly Tyr Tyr Trp Ser Trp Ile Arg Gln His Pro Gly Lys Arg Leu Glu
        35                  40                  45

Trp Ile Gly Tyr Ile Asn Tyr Gly Gly Gly Thr Ser Tyr Asn Pro Ser
    50                  55                  60

Leu Lys Ser Arg Val Thr Ile Ser Arg Asp Thr Ser Lys Asn Gln Phe
65                  70                  75                  80

Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Cys
                85                  90                  95

Cys Ala Thr Met Ala Asp Arg Phe Ala Phe Phe Asp Val Trp Gly Gln
            100                 105                 110

Gly Thr Met Val Thr Val Ser Ser
        115                 120


<210>  25
<211>  120
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Variant of humanized anti-human H7CR Antibody

<400>  25

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1               5                   10                  15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Phe Ser Ile Ser Thr Ser
            20                  25                  30

Gly Tyr Tyr Trp Ser Trp Ile Arg Gln Phe Pro Gly Lys Arg Leu Glu
        35                  40                  45

Trp Met Gly Tyr Ile Asn Tyr Gly Gly Gly Thr Ser Tyr Asn Pro Ser
    50                  55                  60

Leu Lys Ser Arg Val Thr Ile Ser Arg Asp Thr Ser Lys Asn Gln Phe
65                  70                  75                  80

Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Thr Tyr Cys
                85                  90                  95

Cys Ala Thr Met Ala Asp Arg Phe Ala Phe Phe Asp Val Trp Gly Gln
            100                 105                 110

Gly Thr Met Val Thr Val Ser Ser
        115                 120
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<210> 26
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> Variant of humanized anti-human H7CR Antibody

<400> 26

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ala Gln
1 5 10 15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Phe Ser Ile Ser Thr Ser
20 25 30

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

Trp Ile Gly Tyr Ile Asn Tyr Gly Gly Gly Thr Tyr Tyr Asn Pro Ser
50 55 60

Leu Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe
65 70 75 80

Ser Leu Lys Leu Thr Ser Val Thr Ala Ala Asp Thr Ala Val Tyr His
85 90 95

Cys Ala Thr Met Ala Asp Arg Phe Ala Phe Phe Asp Val Trp Gly Gln
100 105 110

Gly Thr Met Val Thr Val Ser Ser
115 120

<210> 27
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> Variant of humanized anti-human H7CR Antibody

<400> 27

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ala Gln
1 5 10 15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Phe Ser Ile Ser Thr Ser
20 25 30

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

Trp Ile Gly Tyr Ile Asn Tyr Gly Gly Gly Thr Ser Tyr Asn Pro Ser
50 55 60

Leu Lys Ser Arg Val Thr Ile Ser Arg Asp Thr Ser Lys Asn Gln Phe
65 70 75 80

Ser Leu Lys Leu Thr Ser Val Thr Ala Ala Asp Thr Ala Thr Tyr Cys
85 90 95

Cys Ala Thr Met Ala Asp Arg Phe Ala Phe Phe Asp Val Trp Gly Gln
100 105 110

Gly Thr Met Val Thr Val Ser Ser
115 120

<210> 28
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> Variant of humanized anti-human H7CR Antibody

<400> 28

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ala Gln
1 5 10 15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Phe Ser Ile Ser Thr Ser
20 25 30

Gly Tyr Tyr Trp Ser Trp Ile Arg Gln Phe Pro Gly Lys Arg Leu Glu
35 40 45

Trp Met Gly Tyr Ile Asn Tyr Gly Gly Gly Thr Ser Tyr Asn Pro Ser
50 55 60

Leu Lys Ser Arg Val Thr Ile Ser Arg Asp Thr Ser Lys Asn Gln Phe
65 70 75 80

Ser Leu Lys Leu Thr Ser Val Thr Ala Ala Asp Thr Ala Thr Tyr Cys
85 90 95

Cys Ala Thr Met Ala Asp Arg Phe Ala Phe Phe Asp Val Trp Gly Gln
100 105 110

Gly Thr Met Val Thr Val Ser Ser
115 120

<210> 29
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Anti-Human H7CR Antibody

<400> 29

Gln Ser Leu Phe Ser Ser Asn Thr Asn Arg Asn Tyr
1 5 10

<210> 30
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Anti-Human H7CR Antibody

<400> 30

Gln Ser Leu Phe Ser Ser Asn Thr Lys Arg Asn Tyr
1 5 10

<210> 31
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> LC CDR1 Consensus sequence

<220>
<221> MISC_FEATURE
<222> (9)..(9)
<223> Xaa = N or K or a substitution having an equal or greater substitution score

<400> 31

Gln Ser Leu Phe Ser Ser Asn Thr Xaa Arg Asn Tyr
1 5 10

<210> 32
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> LC CDR2 Consensus Sequence:

<400> 32

His Ala Ser
1

<210> 33
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Variant of humanized anti-human H7CR Antibody

<400> 33

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

Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Leu Phe Ser Ser

20 25 30

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

Pro Pro Lys Leu Leu Ile Tyr His Ala Ser Thr Arg Glu Ser Gly Val
50 55 60

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln
85 90 95

His Tyr Glu Thr Pro Leu Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile
100 105 110

Lys

<210> 34
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Variant of humanized anti-human H7CR Antibody

<400> 34

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

Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Leu Phe Ser Ser
20 25 30

Asn Thr Lys Arg Asn Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln
35 40 45

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

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Asp Tyr Phe Cys Gln Gln
85 90 95

His Tyr Glu Thr Pro Leu Thr Phe Gly Asp Gly Thr Arg Leu Glu Ile
100 105 110

Lys

<210> 35
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Variant of humanized anti-human H7CR Antibody

<400> 35

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

Glu Arg Ala Thr Ile Asn Cys Leu Ser Ser Gln Ser Leu Phe Ser Ser
20 25 30

Asn Thr Lys Arg Asn Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln
35 40 45

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

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Asp Tyr Phe Cys Gln Gln
85 90 95

His Tyr Glu Thr Pro Leu Thr Phe Gly Asp Gly Thr Arg Leu Glu Ile
100 105 110

Lys

<210> 36
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Variant of humanized anti-human H7CR Antibody

<400> 36

Asp Ile Val Met Thr Gln Thr Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Phe Ser Ser
20 25 30

Asn Thr Lys Arg Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln
35 40 45

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

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys
65 70 75 80

Ile Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gln Gln
85 90 95

His Tyr Glu Thr Pro Leu Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile
100 105 110

Lys

<210> 37
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Variant of humanized anti-human H7CR Antibody

<400> 37

Asp Ile Val Met Thr Gln Thr Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Phe Ser Ser
20 25 30

Asn Thr Lys Arg Asn Tyr Leu Asn Trp Tyr Leu Gln Lys Pro Gly Gln
35 40 45

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

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys
65 70 75 80

Ile Ser Arg Val Glu Ala Glu Asp Val Gly Asp Tyr Phe Cys Gln Gln
85 90 95

His Tyr Glu Thr Pro Leu Thr Phe Gly Asp Gly Thr Arg Leu Glu Ile
100 105 110

Lys

<210> 38
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Variant of humanized anti-human H7CR Antibody

<400> 38

```
Asp Ile Val Met Thr Gln Thr Pro Ser Ser Leu Pro Val Thr Pro Gly
1               5                  10                  15

Glu Pro Ala Ser Ile Ser Cys Leu Ser Ser Gln Ser Leu Phe Ser Ser
            20                  25                  30

Asn Thr Lys Arg Asn Tyr Leu Asn Trp Tyr Leu Gln Lys Pro Gly Gln
        35                  40                  45

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

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys
65                  70                  75                  80

Ile Ser Arg Val Glu Ala Glu Asp Val Gly Asp Tyr Phe Cys Gln Gln
                85                  90                  95

His Tyr Glu Thr Pro Leu Thr Phe Gly Asp Gly Thr Arg Leu Glu Ile
            100                 105                 110

Lys
```

<210> 39
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> Variant of humanized anti-human H7CR Antibody

<400> 39

```
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1               5                  10                  15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Phe Ser Ile Thr Thr Gly
            20                  25                  30

Gly Tyr Tyr Trp Ser Trp Ile Arg Gln His Pro Gly Lys Gly Leu Glu
        35                  40                  45

Trp Ile Gly Tyr Ile Tyr Thr Ser Gly Arg Thr Tyr Tyr Asn Pro Ser
    50                  55                  60

Leu Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe
65                  70                  75                  80

Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
                85                  90                  95

Cys Ala Asp Met Ala Asp Lys Gly Gly Trp Phe Ala Tyr Trp Gly Gln
```

100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 40
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> Variant of humanized anti-human H7CR Antibody

<400> 40

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1 5 10 15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Phe Ser Ile Thr Thr Gly
20 25 30

Gly Tyr Tyr Trp Asn Trp Ile Arg Gln His Pro Gly Lys Lys Leu Glu
35 40 45

Trp Ile Gly Tyr Ile Tyr Thr Ser Gly Arg Thr Ser Tyr Asn Pro Ser
50 55 60

Leu Lys Ser Arg Val Thr Ile Ser Arg Asp Thr Ser Lys Asn Gln Phe
65 70 75 80

Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
85 90 95

Cys Ala Asp Met Ala Asp Lys Gly Gly Trp Phe Ala Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 41
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> Variant of humanized anti-human H7CR Antibody

<400> 41

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1 5 10 15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Phe Ser Ile Thr Thr Gly
20 25 30

Gly Tyr Tyr Trp Asn Trp Ile Arg Gln Phe Pro Gly Lys Lys Leu Glu

35 40 45

Trp Met Gly Tyr Ile Tyr Thr Ser Gly Arg Thr Ser Tyr Asn Pro Ser
50 55 60

Leu Lys Ser Arg Val Thr Ile Ser Arg Asp Thr Ser Lys Asn Gln Phe
65 70 75 80

Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
85 90 95

Cys Ala Asp Met Ala Asp Lys Gly Gly Trp Phe Ala Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 42
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> Variant of humanized anti-human H7CR Antibody

<400> 42

Gln Ile Thr Leu Lys Glu Ser Gly Pro Thr Leu Val Lys Pro Thr Gln
1 5 10 15

Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Ile Thr Thr Gly
20 25 30

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

Trp Leu Ala Leu Ile Tyr Thr Ser Gly Arg Thr Arg Tyr Ser Pro Ser
50 55 60

Leu Lys Ser Arg Leu Thr Ile Thr Lys Asp Thr Ser Lys Asn Gln Val
65 70 75 80

Val Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr
85 90 95

Cys Ala Asp Met Ala Asp Lys Gly Gly Trp Phe Ala Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 43
<211> 120
<212> PRT

<213> Artificial Sequence

<220>
<223> Variant of humanized anti-human H7CR Antibody

<400> 43

```
Gln Ile Thr Leu Lys Glu Ser Gly Pro Thr Leu Val Lys Pro Thr Gln
1               5                  10                  15

Thr Leu Thr Leu Thr Cys Thr Val Ser Gly Phe Ser Ile Thr Thr Gly
            20                  25                  30

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

Trp Leu Ala Leu Ile Tyr Thr Ser Gly Arg Thr Ser Tyr Asn Pro Ser
    50                  55                  60

Leu Lys Ser Arg Leu Thr Ile Thr Lys Asp Thr Ser Lys Asn Gln Val
65                  70                  75                  80

Val Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr
                85                  90                  95

Cys Ala Asp Met Ala Asp Lys Gly Gly Trp Phe Ala Tyr Trp Gly Gln
            100                 105                 110

Gly Thr Leu Val Thr Val Ser Ser
        115                 120
```

<210> 44
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> Variant of humanized anti-human H7CR Antibody

<400> 44

```
Gln Ile Gln Leu Lys Glu Ser Gly Pro Thr Leu Val Lys Pro Thr Gln
1               5                  10                  15

Thr Leu Thr Leu Thr Cys Thr Val Ser Gly Phe Ser Ile Thr Thr Gly
            20                  25                  30

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

Trp Met Ala Leu Ile Tyr Thr Ser Gly Arg Thr Ser Tyr Asn Pro Ser
    50                  55                  60

Leu Lys Ser Arg Leu Thr Ile Thr Lys Asp Thr Ser Lys Asn Gln Val
65                  70                  75                  80
```

Val Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr
85 90 95

Cys Ala Asp Met Ala Asp Lys Gly Gly Trp Phe Ala Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 45
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Anti-Human H7CR Antibody

<400> 45

Gln His His Tyr Glu Thr Pro Leu Thr
1 5

<210> 46
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Anti-Human H7CR Antibody

<400> 46

Gln Gln His Tyr Glu Thr Pro Leu Thr
1 5

<210> 47
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Anti-Human H7CR Antibody

<400> 47

Gln Gln His Tyr Val Thr Pro Leu Thr
1 5

<210> 48
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> LC CDR3 Consensus Sequence

<220>
<221> MISC_FEATURE
<222> (2)..(2)
<223> Xaa is H or Q or a substitution having an equal or greater

substitution score (i.e., greater than or equal 0): R, N, Q, E, or H

<220>
<221> MISC_FEATURE
<222> (5)..(5)
<223> Xaa is E or V or a substitution having an equal or greater substitution score (i.e., greater than or equal to -2): A, Q, E, K, M, P, S, T, Y, or V

<400> 48

Gln Xaa His Tyr Xaa Thr Pro Leu Thr
1 5

<210> 49
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Anti-Human H7CR Antibody

<400> 49

Gly Phe Ser Ile Ser Thr Ser Gly
1 5

<210> 50
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Anti-Human H7CR Antibody

<400> 50

Gly Phe Ser Ile Thr Thr Gly Gly
1 5

<210> 51
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Heavy chain CDR1 consensus sequence

<220>
<221> MISC_FEATURE
<222> (5)..(5)
<223> Xaa is S or T or a substitution having an equal or greater substitution score (i.e., greater than/equal to +1): S or T

<220>
<221> MISC_FEATURE
<222> (7)..(7)
<223> Xaa is S or G or a substitution having an equal or greater substitution score (i.e., greater than/equal to 0): A, N, G, or S

<400> 51

Gly Phe Asp Ile Xaa Thr Xaa Gly

1 5

<210> 52
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Anti-Human H7CR Antibody

<400> 52

Ile Asn Tyr Gly Gly Gly Thr
1 5

<210> 53
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Anti-Human H7CR Antibody

<400> 53

Ile Tyr Thr Ser Gly Arg Thr
1 5

<210> 54
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Anti-Human H7CR Antibody

<400> 54

Ile Tyr Ser Ser Gly Arg Thr
1 5

<210> 55
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Heavy chain CDR2 Consensus Sequence

<220>
<221> MISC_FEATURE
<222> (2)..(2)
<223> Xaa is N or Y or a substitution having an equal or greater substitution score (i.e., greater than/equal to -2): A, R, N, Q, E, H, K, M, S, T, Y

<220>
<221> MISC_FEATURE
<222> (3)..(3)
<223> Xaa is Y, T or S or a substitution having an equal or greater substitution score (i.e., greater than/equal to -2): A, R, N, C, Q, E, H, I, L, K, M, F, S, T, Y, or V

<220>
<221> MISC_FEATURE
<222> (4)..(4)
<223> Xaa is S or G or a substitution having an equal or greater substitution score (i.e., greater than/equal to 0): A, N, G, or S

<220>
<221> MISC_FEATURE
<222> (6)..(6)
<223> Xaa is G or R or a substitution having an equal or greater substitution score (i.e., greater than/equal to -2): A, R, N, D, Q, E, G, H, K, P, S, or T

<400> 55

Ile Xaa Xaa Xaa Gly Xaa Thr
1 5

<210> 56
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Anti-Human H7CR Antibody

<400> 56

Ala Thr Met Ala Asp Arg Phe Ala Phe Phe Asp Val
1 5 10

<210> 57
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Anti-Human H7CR Antibody

<400> 57

Ala Asp Met Ala Asp Lys Gly Gly Trp Phe Ala Tyr
1 5 10

<210> 58
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Anti-Human H7CR Antibody

<400> 58

Ala Asp Met Ala Asp Lys Gly Gly Trp Phe Asp Tyr
1 5 10

<210> 59
<211> 12
<212> PRT
<213> Artificial Sequence

<220>

<223> Heavy chain CDR3 Consensus Sequence:

<220>
<221> MISC_FEATURE
<222> (2)..(2)
<223> Xaa is T or D or a substitution having an equal or greater substitution score (i.e., greater than/equal to -1): N, D, Q, E, K, P, S, or T

<220>
<221> MISC_FEATURE
<222> (6)..(6)
<223> Xaa is R or K or a substitution having an equal or greater substitution score (i.e., greater than/equal to +2): R, or K

<220>
<221> MISC_FEATURE
<222> (7)..(7)
<223> Xaa is F or G or a substitution having an equal or greater substitution score (i.e., greater than/equal to -3): A, R, N, D, C, Q, E, G, H, K, M, F, S, T, W, Y, or V

<220>
<221> MISC_FEATURE
<222> (8)..(8)
<223> Xaa is A or G or a substitution having an equal or greater substitution score (i.e., greater than/equal to 0): A, G, or S

<220>
<221> MISC_FEATURE
<222> (9)..(9)
<223> Xaa is F or W or a substitution having an equal or greater substitution score (i.e., greater than/equal to +1): F, W, or Y

<220>
<221> MISC_FEATURE
<222> (11)..(11)
<223> Xaa is A or D or a substitution having an equal or greater substitution score (i.e., greater than/equal to): A, R, N, D, C, Q, E, G, H, I, L, K, M, F, P, S, T, W, Y, or V

<220>
<221> MISC_FEATURE
<222> (11)..(11)
<223> Xaa is A or D or a substitution having an equal or greater substitution score : A, R, N, D, C, Q, E, G, H, I, L, K, M, F, P, S, T, W, Y, or V

<220>
<221> MISC_FEATURE
<222> (12)..(12)
<223> Xaa is V or Y or a substitution having an equal or greater substitution score (i.e., greater than/equal to -2): A, R, N, D, C, Q, E, G, H, I, L, K, M, F, P, S, T, W, Y, or V

<400> 59

Ala Xaa Met Ala Asp Xaa Xaa Xaa Xaa Phe Xaa Xaa
1 5 10

<210> 60
<211> 40
<212> PRT
<213> Artificial Sequence

<220>

<223> Humanized Antibody

<400> 60

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


Glu Lys Val Thr Ile Ser Cys Leu Ser Ser Gln Ser Leu Phe Ser Ser
            20                  25                  30


Asn Thr Asn Arg Asn Tyr Leu Asn
        35                  40
```

<210> 61
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Variant of humanized anti-human H7CR Antibody

<400> 61

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


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


Ser Asn Asn Lys Asn Tyr Leu Ala
        35                  40
```

<210> 62
<211> 39
<212> PRT
<213> Artificial Sequence

<220>
<223> Variant of humanized anti-human H7CR Antibody

<400> 62

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Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1               5                  10                  15


Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
            20                  25                  30


Asn Gly Tyr Asn Tyr Leu Asp
        35
```

<210> 63
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Humanized antibody

<400> 63

Trp Tyr Leu Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile Tyr His
1 5 10 15

Ala Ser Thr Arg Leu Thr Gly Val Pro Asp Arg Phe Ile Gly Ser Gly
20 25 30

Ser Gly Thr Asp Phe Thr Leu Thr
35 40

<210> 64
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Variant of humanized anti-human H7CR Antibody

<400> 64

Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Trp
1 5 10 15

Ala Ser Thr Arg Glu Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly
20 25 30

Ser Gly Thr Asp Phe Thr Leu Thr
35 40

<210> 65
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Variant of humanized anti-human H7CR Antibody

<400> 65

Trp Tyr Leu Gln Lys Pro Gly Gln Ser Pro Gln Leu Leu Ile Tyr Leu
1 5 10 15

Gly Ser Asn Arg Ala Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly
20 25 30

Ser Gly Thr Asp Phe Thr Leu Lys
35 40

<210> 66
<211> 33
<212> PRT
<213> Artificial Sequence

<220>
<223> Variant of humanized anti-human H7CR Antibody

<400> 66

Ile Ser Ser Val Gln Ala Glu Asp Leu Gly Asp Tyr Tyr Cys Gln His
1 5 10 15

His Tyr Glu Thr Pro Leu Thr Phe Gly Asp Gly Thr Lys Leu Glu Ile
20 25 30

Lys

<210> 67
<211> 23
<212> PRT
<213> Artificial Sequence

<220>
<223> Variant of humanized anti-human H7CR Antibody

<400> 67

Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln
1 5 10 15

Tyr Tyr Ser Thr Pro Tyr Thr
20

<210> 68
<211> 23
<212> PRT
<213> Artificial Sequence

<220>
<223> Variant of humanized anti-human H7CR Antibody

<400> 68

Ile Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln
1 5 10 15

Ala Leu Gln Thr Pro Tyr Thr
20

<210> 69
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Humanized antibody

<400> 69

Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
1 5 10

<210> 70
<211> 40
<212> PRT
<213> Artificial Sequence

<220>

<223> Humanized antibody

<400> 70

Gln Ile Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1 5 10 15

Ser Leu Ser Leu Thr Cys Ser Val Thr Gly Phe Ser Ile Ser Thr Ser
20 25 30

Gly Tyr Tyr Trp Thr Trp Ile Arg
35 40

<210> 71
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Variant of humanized anti-human H7CR Antibody

<400> 71

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1 5 10 15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Gly
20 25 30

Gly Tyr Tyr Trp Ser Trp Ile Arg
35 40

<210> 72
<211> 40
<212> PRT
<213> Homo sapiens

<400> 72

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ala Gln
1 5 10 15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Val
20 25 30

Asn Tyr Tyr Trp Ser Trp Ile Arg
35 40

<210> 73
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Variant of humanized anti-human H7CR Antibody

<400> 73

Gln Phe Pro Gly Lys Arg Leu Glu Trp Met Gly Tyr Ile Asn Tyr Gly

1 5 10 15

Gly Gly Thr Ser Tyr Asn Pro Ser Leu Lys Ser Arg Ile Ser Ile Thr
20 25 30

Arg Asp Thr Ser Lys Asn Gln Phe
35 40

<210> 74
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Variant of humanized anti-human H7CR Antibody

<400> 74

Gln His Pro Gly Lys Gly Leu Glu Trp Ile Gly Tyr Ile Tyr Tyr Ser
1 5 10 15

Gly Ser Thr Tyr Tyr Asn Pro Ser Leu Lys Ser Arg Val Thr Ile Ser
20 25 30

Val Asp Thr Ser Lys Asn Gln Phe
35 40

<210> 75
<211> 40
<212> PRT
<213> Homo sapiens

<400> 75

Gln Tyr Pro Gly Lys Gly Leu Glu Trp Ile Gly Tyr Ile Tyr Tyr Arg
1 5 10 15

Gly Ser Thr Tyr Tyr Asn Pro Ser Leu Lys Ser Arg Val Thr Ile Ser
20 25 30

Val Asp Thr Ser Lys Asn Gln Phe
35 40

<210> 76
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Humanized antibody

<400> 76

Leu Leu His Leu Asn Ser Val Thr Thr Glu Asp Thr Ala Thr Tyr Cys
1 5 10 15

Cys Ala Thr Met Ala Asp Arg Phe Ala Phe Phe Asp Val Trp Gly Gln
20 25 30

Gly Ile Gln Val Thr Val Ser Ser
35 40

<210> 77
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> Variant of humanized anti-human H7CR Antibody

<400> 77

Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
1 5 10 15

Cys Ala Arg

<210> 78
<211> 40
<212> PRT
<213> Homo sapiens

<400> 78

Ser Leu Lys Leu Thr Ser Val Thr Ala Ala Asp Thr Ala Val Tyr His
1 5 10 15

Cys Ala Arg Glu Arg Thr Met Thr Gly Ala Phe Asp Ile Trp Gly Gln
20 25 30

Gly Thr Met Val Thr Val Ser Ser
35 40

<210> 79
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Humanized antibody

<400> 79

Asp Ala Phe Asp Val Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser
1 5 10 15

<210> 80
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Humanized antibody

<400> 80

Asp Ile Val Met Thr Gln Ser Pro Ser Ser Leu Ala Val Ser Ala Gly

1 5 10 15

Glu Lys Val Thr Ile Ser Cys Leu Ser Ser Gln Ser Leu Phe Ser Ser
20 25 30

Asn Thr Lys Arg Asn Tyr Leu Asn
35 40

<210> 81
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Variant of humanized anti-human H7CR Antibody

<400> 81

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

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

Ser Asn Asn Lys Asn Tyr Leu Ala
35 40

<210> 82
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Variant of humanized anti-human H7CR Antibody

<400> 82

Asp Ile Val Met Thr Gln Thr Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu Asp Ser
20 25 30

Asp Asp Gly Asn Thr Tyr Leu Asp
35 40

<210> 83
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Humanized antibody

<400> 83

Trp Tyr Leu Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile Tyr His
1 5 10 15

Ala Ser Thr Arg Leu Thr Gly Val Pro Gly Arg Phe Ile Gly Ser Gly
20 25 30

Ser Gly Thr Asp Phe Thr Leu Thr
35 40

<210> 84
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Variant of humanized anti-human H7CR Antibody

<400> 84

Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Trp
1 5 10 15

Ala Ser Thr Arg Glu Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly
20 25 30

Ser Gly Thr Asp Phe Thr Leu Thr
35 40

<210> 85
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Variant of humanized anti-human H7CR Antibody

<400> 85

Trp Tyr Leu Gln Lys Pro Gly Gln Ser Pro Gln Leu Leu Ile Tyr Thr
1 5 10 15

Leu Ser Tyr Arg Ala Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly
20 25 30

Ser Gly Thr Asp Phe Thr Leu Lys
35 40

<210> 86
<211> 33
<212> PRT
<213> Artificial Sequence

<220>
<223> Humanized antibody

<400> 86

Val Ser Thr Val Gln Ala Glu Asp Leu Gly Asp Tyr Phe Cys Gln Gln
1 5 10 15

His Tyr Glu Thr Pro Leu Thr Phe Gly Asp Gly Thr Arg Leu Glu Ile

20 25 30

Lys

<210> 87
<211> 23
<212> PRT
<213> Artificial Sequence

<220>
<223> Variant of humanized anti-human H7CR Antibody

<400> 87

Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln
1 5 10 15

Tyr Tyr Ser Thr Pro Tyr Thr
20

<210> 88
<211> 21
<212> PRT
<213> Artificial Sequence

<220>
<223> Variant of humanized anti-human H7CR Antibody

<400> 88

Ile Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln
1 5 10 15

Arg Ile Glu Phe Pro
20

<210> 89
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Humanized antibody

<400> 89

Ile Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
1 5 10

<210> 90
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Humanized antibody

<400> 90

Gln Ile Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln

1 5 10 15

Ser Leu Ser Leu Thr Cys Ser Val Thr Gly Phe Ser Ile Thr Thr Gly
20 25 30

Gly Tyr Tyr Trp Asn Trp Ile Arg
35 40

<210> 91
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Variant of humanized anti-human H7CR Antibody

<400> 91

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1 5 10 15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Gly
20 25 30

Gly Tyr Tyr Trp Ser Trp Ile Arg
35 40

<210> 92
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Variant of humanized anti-human H7CR Antibody

<400> 92

Gln Ile Thr Leu Lys Glu Ser Gly Pro Thr Leu Val Lys Pro Thr Gln
1 5 10 15

Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Ser
20 25 30

Gly Val Gly Val Gly Trp Ile Arg
35 40

<210> 93
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Humanized antibody

<400> 93

Gln Phe Pro Gly Lys Lys Leu Glu Trp Met Gly Tyr Ile Tyr Thr Ser
1 5 10 15

Gly Arg Thr Ser Tyr Asn Pro Ser Leu Lys Ser Arg Ile Ser Ile Thr
            20   25   30

Arg Asp Thr Ser Lys Asn Gln Phe
        35   40

<210> 94
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Variant of humanized anti-human H7CR Antibody

<400> 94

Gln His Pro Gly Lys Gly Leu Glu Trp Ile Gly Tyr Ile Tyr Tyr Ser
1   5   10   15

Gly Ser Thr Tyr Tyr Asn Pro Ser Leu Lys Ser Arg Val Thr Ile Ser
            20   25   30

Val Asp Thr Ser Lys Asn Gln Phe
        35   40

<210> 95
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Variant of humanized anti-human H7CR Antibody

<400> 95

Gln Pro Pro Gly Lys Ala Leu Glu Trp Leu Ala Leu Ile Tyr Trp Asn
1   5   10   15

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

Lys Asp Thr Ser Lys Asn Gln Val
        35   40

<210> 96
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Humanized antibody

<400> 96

Phe Leu Gln Leu Asn Ser Met Thr Thr Glu Asp Thr Ala Thr Tyr Tyr
1   5   10   15

Cys Ala Asp Met Ala Asp Lys Gly Gly Trp Phe Ala Tyr Trp Gly Gln

20 25 30

Gly Thr Leu Val Thr Val Ser Ser
35 40

<210> 97
<211> 23
<212> PRT
<213> Artificial Sequence

<220>
<223> Variant of humanized anti-human H7CR Antibody

<220>
<221> UNSURE
<222> (19)..(22)

<400> 97

Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
1 5 10 15

Cys Ala Xaa Xaa Xaa Xaa Arg
20

<210> 98
<211> 24
<212> PRT
<213> Artificial Sequence

<220>
<223> Variant of humanized anti-human H7CR Antibody

<220>
<221> UNSURE
<222> (19)..(22)

<400> 98

Val Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr
1 5 10 15

Cys Ala Xaa Xaa Xaa Xaa His Arg
20

<210> 99
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Humanized antibody

<400> 99

Asn Trp Phe Asp Ser Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
1 5 10 15

<210> 100

<211> 1401
<212> DNA
<213> Artificial Sequence

<220>
<223> Chimeric antibody chain coding sequence

<400> 100
atggaatggt cctgggtgtt cctgttcttc ctgtccgtga ccaccggcgt gcactcccag 60

atccagctgc aggaatctgg ccctggcctc gtgaagcctt cccagtccct gtccctgacc 120

tgcagcgtga ccggcttctc catctccacc tccggctact actggacctg gatccggcag 180

ttccctggca agcggctgga atggatgggc tacatcaact acggcggagg cacctcctac 240

aaccccagcc tgaagtcccg gatctccatc acccgggata cctccaagaa ccagttcctg 300

ctgcacctga actccgtgac aaccgaggac accgccacct actgctgcgc taccatggcc 360

gacagattcg ccttcttcga cgtgtggggc cagggcatcc aagtgaccgt gtcctccgct 420

tccaccaagg gcccctctgt gtttcctctg gcccctgct cccggtccac ctctgagtct 480

acagccgctc tgggctgcct cgtgaaagac tacttccccg agcccgtgac agtgtcctgg 540

aactctggcg ctctgacctc tggcgtgcac accttccctg ctgtgctgca gtctagcggc 600

ctgtactccc tgtcctccgt cgtgaccgtg ccttccagct ctctgggcac caagacctac 660

acctgtaacg tggaccacaa gccctccaac accaaggtgg acaagagagt ggaatctaag 720

tacggccctc cctgcccccc ttgtcctgcc cctgaatttc tgggcggacc ctccgtgttt 780

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gtggtggtgg atgtgtccca ggaagatccc gaggtgcagt tcaattggta cgtggacggc 900

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gtggtgtccg tgctgaccgt gctgcaccag gattggctga acggcaaaga gtacaagtgc 1020

aaggtgtcca acaagggcct gccctccagc atcgaaaaga ccatctccaa ggctaagggc 1080

cagccccgcg agccccaggt gtacacactg cctccaagcc aggaagagat gaccaagaat 1140

caggtgtcac tgacctgtct cgtgaagggc ttctaccct ccgatatcgc cgtggaatgg 1200

gagtccaacg gccagcccga gaacaactac aagaccaccc cccctgtgct ggactccgac 1260

ggctccttct ttctgtactc tcgcctgacc gtggacaagt cccggtggca ggaaggcaac 1320

gtgttctcct gctctgtgat gcacgaggcc ctgcacaacc actacaccca gaagtccctg 1380

agcctgtccc ccggctgatg a 1401

<210> 101
<211> 726
<212> DNA
<213> Artificial Sequence

<220>
<223> Chimeric antibody chain coding sequence

<400> 101
atgtccgtgc ccacccaggt gctgggattg ctgctgctgt ggctgaccga cgccagatgc 60

gacatcgtga tgacccagtc cccctcctcc ctggctgtgt ctgctggcga gaaagtgacc 120

atctcctgcc tgtcctccca gtccctgttc tcctccaaca ccaaccggaa ctacctgaac 180

tggtatctgc agaagcccgg ccagtcccct aagctgctga tctaccacgc ctccaccaga 240

ctgaccggcg tgcccgatag attcatcggc tctggctccg gcaccgactt taccctgacc 300

atcagctccg tgcaggccga ggacctgggc gactactact gccagcacca ctacgagaca 360

cccctgacct ttggcgacgg caccaagctg gaaatcaagc ggaccgtggc cgctccctcc 420

gtgttcatct tcccaccttc cgacgagcag ctgaagtctg gcaccgcctc tgtcgtgtgc 480

ctgctgaaca acttctaccc ccgcgaggcc aaggtgcagt ggaaggtgga caacgccctg 540

cagtccggca actcccagga atccgtgacc gagcaggact ccaaggacag cacctactcc 600

ctgtccagca ccctgaccct gtccaaggcc gactacgaga agcacaaggt gtacgcctgc 660

gaagtgaccc accagggcct gtctagcccc gtgaccaagt ctttcaaccg gggcgagtgc 720

tgatga 726