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Described herein are compositions and methods for inhibiting an inflammatory or autoimmune response and for inducing immune tolerance in a subject in need thereof comprising administering to the subject a therapeutically effective amount of an antigen presenting cell (APC)-targeted antibody operatively linked to IL-10 or a fragment thereof. The compositions and methods described herein are useful for treating inflammatory and autoimmune disorders.

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(54) Title: METHODS AND COMPOSITIONS FOR TREATING AUTOIMMUNE AND INFLAMMATORY CONDITIONS

(57) Abstract: Described herein are compositions and methods for inhibiting an inflammatory or autoimmune response and for inducing immune tolerance in a subject in need thereof comprising administering to the subject a therapeutically effective amount of an antigen presenting cell (APC)-targeted antibody operatively linked to IL-10 or a fragment thereof. The compositions and methods described herein are useful for treating inflammatory and autoimmune disorders.



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DESCRIPTION

METHODS AND COMPOSITIONS FOR TREATING AUTOIMMUNE AND INFLAMMATORY CONDITIONS

BACKGROUND OF THE INVENTION

[0001] This application claims the benefit of priority to U.S. Provisional Patent Application Serial No. 61/994,239, filed May 16, 2014, and U.S. Provisional Patent Application Serial No. 62/014,504, filed June 19, 2014.

[0002]

1. Field of the Invention

[0003] The present invention relates generally to the field of medicine. More particularly, it concerns pharmaceutical compositions for enhancing tolerance to antigens and for treating inflammatory and autoimmune disorders.

2. Background

[0004] Autoimmune and inflammatory diseases arise from an abnormal immune response of the body against substances and tissues normally present in the body. This may be restricted to certain organs (*e.g.*, in autoimmune thyroiditis) or involve a particular tissue in different places (*e.g.*, Goodpasture's disease which may affect the basement membrane in both the lung and the kidney). Autoimmune and auto-inflammatory diseases affect up to 50 million people in America alone, and the cause of autoimmunity remains unknown.

[0005] The treatment of these diseases is typically with immunosuppression—medication that decreases the immune response. Conventional immunotherapies using immunosuppressants, such as cyclosporine, tacrolimus, methotrexate or anti-TNF α /IL-6 non-specifically suppress the function of T cell including non-pathogenic T cells in the host. Therefore, treatment with these immunosuppressants often results in the development of

severe infections and sometimes leads to the lethal consequences. There is a need in the art for therapeutics that treat autoimmune responses without global immunosuppression.

SUMMARY OF THE INVENTION

[0006] This disclosure fulfills a need in the art by providing methods and compositions for delivering the anti-inflammatory cytokine, IL-10, to antigen presenting cells (APCs) to suppress and alter the pathophysiologic functions of APCs in the subjects using APC-targeted antibody operatively linked to IL-10 or a fragment thereof. Targeted delivery of anti-inflammatory cytokines to the APCs in the patients is expected to result in more effective and pro-longed immune tolerance in the patients. Accordingly, aspects of the disclosure relate to a method for inhibiting an inflammatory or autoimmune response in a subject in need thereof comprising administering to the subject a therapeutically effective amount of an antigen presenting cell (APC)-targeted antibody operatively linked to IL-10 or a fragment thereof.

[0007] In some embodiments, the disclosure relates to a method for preventing or treating graft versus host disease in a subject in need thereof comprising administering to the subject a therapeutically effective amount of DC-ASGPR operatively linked to IL-10 or a fragment thereof.

[0008] Further aspects relate to a method of inducing immune tolerance in a subject in need thereof comprising administering to the subject a therapeutically effective amount of an APC-targeted antibody operatively linked to IL-10 or a fragment thereof. Other aspects relate to a method of suppressing a T cell response in a subject having or at risk of developing an inflammatory response by administering to the subject a therapeutically effective amount of an APC-targeted antibody operatively linked to IL -10 or a fragment thereof.

[0009] The term “operatively linked” refers to a situation where two components are combined to form the active complex prior to binding at the target site. For example, an antibody conjugated to one-half of a cohesin-dockerin complex and a cytokine (*e.g.* IL-10) or other molecule (*e.g.* antigen) complexed to the other one-half of the cohesin-dockerin complex are operatively linked through complexation of the cohesin and dockerin molecules. The term operatively linked is also intended to refer to covalent or chemical linkages that conjugate two molecules together.

[0010] Yet further aspects relate to methods and compositions for treating undesired and/or abnormal immune responses without non-specific suppression of the host immune system. In particular, an anti-DC-ASGPR antibody or antigen binding fragment thereof can be used in compositions and methods described herein for generating anti-pathogenic antigen-specific T regulatory cells and/or for decreasing pathogenic T cell responses.

[0011] The term “anti-pathogenic antigen-specific T regulatory cells” refers to T cells with beneficial and therapeutic properties. In one embodiment, the anti-pathogenic antigen-specific T regulatory cells are alloantigen-specific T regulatory cells. In another embodiment, the anti-pathogenic antigen-specific T regulatory cells is one that produces IL-10. The anti-pathogenic antigen-specific T regulatory cells may also be a CD4+ T cell.

[0012] The term pathogenic T cell responses refers to abnormal or undesired T cell responses that contribute to the pathology of autoimmune disease or to the pathology of graft versus host disease (GVHD) or graft rejection. In one embodiment, the pathogenic T cell response is an allogeneic T cell response. In a further embodiment, the pathogenic T cell response comprises allogeneic CD4+ and CD8+ T cells. In one embodiment, the pathogenic T cell response is one that comprises immune cells of the tissue graft.

[0013] A further aspect of the disclosure relates to a method for preventing or treating GVHD in a subject in need thereof comprising administering to the subject an anti-DC-ASGPR antibody or antigen binding fragment thereof.

[0014] Graft-versus-host disease (GVHD) is a common complication following an allogeneic tissue transplant. It is commonly associated with stem cell or bone marrow transplant but the term also applies to other forms of tissue graft. Immune cells (white blood cells) in the tissue (the graft) recognize the recipient (the host) as “foreign”. The transplanted immune cells then attack the host's body cells. GVHD may also occur after a blood transfusion if the blood products used have not been irradiated.

[0015] In another instance, the disclosure describes a method for preventing or treating graft rejection in a subject in need thereof comprising administering to the subject an anti-DC-ASGPR antibody or antigen binding fragment thereof.

[0016] Graft rejection occurs when transplanted tissue is rejected by the recipient's immune system, which destroys the transplanted tissue. Graft rejection may also be referred to as transplant rejection or host versus graft disease.

[0017] In certain embodiments, the antibody or antigen binding fragment specifically binds to DC-ASGPR and activates DC-ASGPR. DC-asialoglycoprotein receptor (DC-ASGPR) is a scavenger receptor carrying an immunoreceptor tyrosine-based activation motiflike motif. ASGPR may also be known as ASGR1, ASGPR1, CLEC4H1, and HL-1. In one embodiment, the antibody or antigen binding fragment thereof binds to human DC-ASGPR.

[0018] In some embodiments, the APC-targeted antibody targets one or more APCs of the group Langerhans cells, macrophages, dendritic cells, B cells, and peripheral blood mononuclear cells. In further embodiments, the APC-targeted antibody is selected from an antibody that specifically binds to MHC class I, MHC class II, CD1d, CD2, CD3, CD4, CD8, CD11b, CD14, CD15, CD16, CD19, CD20, CD29, CD31, CD40, CD43, CD44, CD45, CD54, CD56, CD57, CD58, CD83, CD86, CMRF-44, CMRF-56, DCIR, DC-ASGPR, CLEC-6, CD40, BDCA-2, MARCO, DEC-205, mannose receptor, Langerin, DECTIN-1, B7-1, B7-2, IFN- γ receptor, IL-2 receptor, ICAM-1, Fc γ receptor, LOX-1, and ASPGR.

[0019] In other embodiments, the APC-targeted antibody targets Langerhans cells. One example of an APC-targeted antibody to Langerhans cells is anti-Langerin. In further embodiments, the APC-targeted antibody targets macrophages. For example, the APC-targeted antibody may be anti-MARCO.

[0020] In yet further embodiments, the APC-targeted antibody targets one or more APCs of the group dendritic cells, B cells, and macrophages. In specific embodiments, the APC-targeted antibody targets dendritic cells. In some embodiments, the APC-targeted antibody comprises anti-CD40. In further embodiments, the anti-CD40 antibody comprises anti-CD40 clone 12E12 or fragments thereof. As shown in Example 1, anti-CD40 (12E12)-IL-10 suppressed the expression of CD86. In some embodiments, the anti-CD40 antibody comprises one or more CDRs having a sequence of SEQ ID NOS:31-33 and 37-39. In other embodiments, the anti-CD40 antibody comprises a heavy chain comprising one or more CDRs of SEQ ID NOS:31-33. In further embodiments, the anti-CD40 antibody comprises a light chain comprising one or more CDRs of SEQ ID NOS:37-39.

[0021] In specific embodiments, the anti-CD40 antibody is a humanized antibody comprising a heavy chain comprising three CDRs, wherein CDR1 comprises SEQ ID NO:31, CDR2 comprises SEQ ID NO:32, and CDR3 comprises SEQ ID NO:33. In further embodiments, the anti-CD40 antibody is a humanized antibody comprising a light chain

comprising three CDRs, wherein CDR1 comprises SEQ ID NO:37, CDR2 comprises SEQ ID NO:38, and CDR3 comprises SEQ ID NO:39.

[0022] In some embodiments, the APC-targeted antibody comprises anti-DC-ASGPR or anti-Dectin-1. The anti-DC-ASGRP or anti-Dectin-1 may be one known in the art or described herein. In some embodiments the antibody comprises a variable region comprising an amino acid sequence selected from the sequences of SEQ ID NOS: 3, 8, 62, 64, 66, or 68. In some embodiments, the antibody comprises a heavy or light chain with an amino acid sequence selected from the sequences of SEQ ID NOS: 1, 7, 61, 63, 65, 67, or 69-72. In some embodiments, the antibody comprises one or more CDRs from the variable region, heavy chain, or light chain of SEQ ID NOS: 1, 3, 7, 8, 61, 62, 63, 64, 65, 66, 67, or 68-72.

[0023] In some embodiments, the APC-targeted antibody comprises anti-DCIR. In specific embodiments, anti-DCIR antibody comprises anti-DCIR clone 9E8 or fragments thereof. In further embodiments, the anti-DCIR antibody comprises one or more CDRs having a sequence of SEQ ID NOS:18-20 or 24-26. In other embodiments, the anti-DCIR antibody comprises a heavy chain comprising one or more CDRs of SEQ ID NOS:18-20. In yet further embodiments, the anti-CD40 antibody comprises a light chain comprising one or more CDRs of SEQ ID NOS:24-26.

[0024] Certain aspects of the disclosure relate to a method for inhibiting an inflammatory or autoimmune response or for inducing tolerance in a subject in need thereof comprising administering to the subject a therapeutically effective amount of an anti-CD40 antibody operatively linked to IL-10 or a fragment thereof, wherein the anti-CD40 is a humanized antibody having three heavy chain CDRs comprising an amino acid sequence of SEQ ID NO:31 (CDR1), SEQ ID NO:32 (CDR2), and SEQ ID NO:33 (CDR3) and three light chain CDRs comprising an amino acid sequence of SEQ ID NO:37 (CDR1), SEQ ID NO:38 (CDR2), and SEQ ID NO:39 (CDR3).

[0025] Further aspects relate to a method for inhibiting an inflammatory or autoimmune response or for inducing tolerance in a subject in need thereof comprising administering to the subject a therapeutically effective amount of an anti-DCIR antibody operatively linked to IL-10 or a fragment thereof, wherein the anti-DCIR is a humanized antibody having three heavy chain CDRs from the variable region of anti-DCIR 9E8 heavy chain (SEQ ID NO:17) and three light chain CDRs from the variable region of anti-DCIR 9E8 light chain (SEQ ID NO:23).

[0026] Further aspects relate to a method for inhibiting an inflammatory or autoimmune response in a subject in need thereof comprising administering to the subject a therapeutically effective amount of an anti-DC-ASGPR antibody operatively linked to IL-10 or a fragment thereof, wherein the anti-DC-ASGPR antibody is a humanized antibody having three heavy chain CDRs and three light chain CDRs from the variable regions of an anti-DC-ASGPR heavy chain and light chain pair selected from SEQ ID NO:3 and 8; SEQ ID NO:58 and 60; SEQ ID NO:62 and 64; or SEQ ID NO:66 and 68; or is a humanized antibody having three heavy chain CDRs and three light chain CDRs from the heavy and light chains of an anti-DC-ASGPR heavy chain and light chain pair selected from SEQ ID NO:69 and 70 and SEQ ID NO:71 and 72.

[0027] In some embodiments, the APC-targeted antibody or antibody conjugate or antigen binding fragment thereof comprises an amino acid sequence that is at least or at most 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical or similar (or any derivable range therein) to an APC-targeted antibody or antigen binding fragment of any of SEQ ID NOS:1, 2, 3, 7, 8, 10, 11, 13, 15-20, 22-26, 28-33, 35-39, or 45-114 (or any range derivable therein). In further embodiments, the APC-targeted antibody conjugate or antigen binding fragment thereof comprises a variable region comprising an amino acid sequence that is at least or at most 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% (or any range derivable therein) identical or similar to the APC-targeted antibody variable region described herein as SEQ ID NOS: 3, 8, 17, 23, 30, 36, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 79, 81, 83, 85, 87, 89, 108, 110, 112, and 114. In further embodiments, the antibody comprises a CDR having an amino acid sequence corresponding to a CDR in any one of SEQ ID NOS: 2, 3, 7, 8, 11, 13, 16, 17-20, 22-26, 29-33, 35-39, or 45-114 (or any derivable range therein). In some embodiments, the antibody comprises the CDRs of SEQ ID NOS:18-20, 24-26, 31-33, or 37-39. In further embodiments, the APC-targeted antibody or antigen binding fragment thereof comprises a heavy or light chain amino acid sequence that is at least or at most 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% (or any range derivable therein) identical or similar to the APC-targeted antibody or antigen binding fragment of any of SEQ ID NOS:1, 2, 7, 10, 11, 13, 15, 16, 22, 28, 29, 35, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69-78, 80, 82, 84, 86, 88, 90-107, 109, 111, or 113. In certain embodiments, the antibody conjugate or antigen binding fragment thereof comprises CDR1, CDR2, and/or CDR3 from the heavy and/or light chain variable region of a APC-targeted antibody described herein. In certain embodiments, the antibody conjugate or antigen binding

fragment thereof comprises all three CDRs from the light chain variable region and/or all three CDRs from the heavy chain variable region of a APC-targeted antibody described herein.

[0028] In certain embodiments, the antibody or antigen binding fragment specifically binds to DC-ASGPR and activates DC-ASGPR. DC-asialoglycoprotein receptor (DC-ASGPR) is a scavenger receptor carrying an immunoreceptor tyrosine-based activation motiflike motif. ASGPR may also be known as ASGR1, ASGPR1, CLEC4H1, and HL-1. In one embodiment, the antibody or antigen binding fragment thereof binds to human DC-ASGPR.

[0029] In some embodiments, the antibody or antigen binding fragment of the methods and compositions described herein is an anti-DC-ASGPR antibody and comprises an amino acid sequence that is at least or at most 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% (or any derivable range therein) identical or similar to the DC-ASGPR antibody or antigen binding fragment of any of SEQ ID NO: 2, 3, 7, 8, and 61-72 (or any range derivable therein). In a further embodiment, the DC-ASGPR antibody or antigen binding fragment thereof may include a polypeptide, peptide, or protein that is, is at least, or is at most 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% (or any range derivable therein) identical or similar to an ASGPR binding polypeptide, such as Anti-ASGPR_49C11_7H (heavy chain), SEQ ID NO:2; Anti-ASGPR_49C11_7K (light chain), SEQ ID NO:7; anti-hASGPR_6.3H9.1D11H (heavy chain), SEQ ID NO:69; anti-hASGPR_6.3H9.1D11K (light chain), SEQ ID NO:70; anti-hASGPR_5H8.1D4H (heavy chain), SEQ ID NO:71; anti-hASGPR_5H8.1D4K (light chain), SEQ ID NO: 72; Anti-ASGPR_4G2.2_ (heavy chain), SEQ ID NO: 57; Anti-ASGPR_4G2.2_ (light chain), SEQ ID NO: 59; Anti-ASGPR—5F10H (heavy chain), SEQ ID NO:61; Anti-ASGPR—5F10H (light chain), SEQ ID NO: 63; Anti-ASGPR1H11 (heavy chain), SEQ ID NO: 65; or Anti-ASGPR1H11 (light chain). SEQ ID NO: 67. In further embodiments, the DC-ASGPR antibody or antigen binding fragment thereof comprises a variable region comprising an amino acid sequence that is at least or at most 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical or similar to the DC-ASGPR antibody or antigen binding fragment of any of SEQ ID NOs: 3, 8, 62, 64, 66, and 68. In some embodiments, the antibody comprises at least or exactly one, two, or all three CDRs of a variable region from a heavy or light chain amino acid sequence selected from SEQ ID NO:2, 7, 57, 59, 61, 63, 65, 67, and 69-72. In some embodiments, the antibody comprises at least or exactly one, two, or all three CDRs of

a variable region from a heavy or light chain variable region amino acid sequence selected from SEQ ID NO:3, 8, 58, 60, 62, 64, 66, and 68. In further embodiments, the antibody comprises at least or exactly 1, 2, 3, 4, 5, or 6 (or any derivable range therein) CDRs from a heavy and light chain antibody fragment selected from SEQ ID NOS: 2 and 7, SEQ ID NOS: 57 and 59; SEQ ID NOS: 61 and 63; SEQ ID NOS: 65 and 67; SEQ ID NOS: 69 and 70; or SEQ ID NOS: 71 and 72. In some embodiments, the antibody comprises at least or exactly 1, 2, 3, 4, 5, or 6 (or any derivable range therein) CDRs from a heavy and light chain variable region antibody fragment selected from SEQ ID NOS: 3 and 8, SEQ ID NOS: 58 and 60; SEQ ID NOS: 62 and 64; or SEQ ID NOS: 66 and 68..

[0030] The ASGPR antibody or antigen binding fragments described herein may include 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100 or more variant amino acids within at least, or at most 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, 250, 300, 400, 500, 550, 1000 or more contiguous amino acids, or any range derivable therein, of SEQ ID NO: 2, 3, 7, 8, and 61-72.

[0031] The APC-targeted antibody conjugate or antigen binding fragments described herein may include 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72,

73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100 or more variant amino acids (or any range derivable therein) within at least, or at most 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, 250, 300, 400, 500, 550, 1000 or more contiguous amino acids, or any range derivable therein, of any of SEQ ID NOS:1-5, 7-8, 10-11, 13, 15-20, 22-26, 28-33, 35-39, or 45-114..

[0032] Embodiments are provided in which the APC-targeted antibody or antigen binding fragments comprises one or more CDR domains from an antibody that specifically binds to an antigen presenting cell surface protein. In particular embodiments, the APC-targeted antibody or antigen binding fragment thereof comprises one, two, three, four, five, six, or more CDR domains from among the VH or VL domain of the monoclonal antibodies listed herein in SEQ ID NOS: 3, 8, 17, 23, 30, 36, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 79, 81, 83, 85, 87, 89, 108, 110, 112, and 114. In certain aspects, the APC-targeted antibody or antigen binding fragment thereof comprises six CDR domains from among the VH or VL domains of the monoclonal antibodies: anti-Dectin-1 clone 11B6.4, 15E2.5, or 2D8.2D4; ASGPR clone 49C11, 4G2.2, 5F10, 1H11, 6.3H9.1D11, or 5H8.1D4; anti-CD40 clone 12E12, 12B4.2C10, 24A3, or 11B6.1C3; anti-Lox-1 clone 11C8, 10F9, or 15C4; anti-DCIR clone 24A5.4A5, 24E7.3H9, 29E9.2E2, 29G10.3D9, 31A6.IF5, 3C2.2D9, 6C8.1G9, 9E8, or 2C9; or anti-Langrin clone 15B10 or 2G3. In some embodiments, the APC-targeted antibody or antigen binding fragment thereof comprises a sequence at least or at most 70%, 75%, 80%, 85%, 90%, 95%, or 99% (or any range derivable therein) identical to the VH or VL domain of the monoclonal antibodies: anti-Dectin-1 clone 11B6.4, 15E2.5, or 2D8.2D4;

ASGPR clone 49C11, 4G2.2, 5F10, 1H11, 6.3H9.1D11, or 5H8.1D4; anti-CD40 clone 12E12, 12B4.2C10, 24A3, or 11B6.1C3; anti-Lox-1 clone 11C8, 10F9, or 15C4; anti-DCIR clone 24A5.4A5, 24E7.3H9, 29E9.2E2, 29G10.3D9, 31A6.IF5, 3C2.2D9, 6C8.1G9, 9E8, or 2C9; or anti-Langrin clone 15B10 or 2G3. Embodiments are provided in which the APC-targeted antibody or antigen binding fragment thereof comprises the VH domain from the monoclonal antibodies listed herein and/or the VL domain from the monoclonal antibodies listed herein. In further embodiments, the monoclonal antibody is selected from: anti-Dectin-1 clone 11B6.4, 15E2.5, or 2D8.2D4; ASGPR clone 49C11, 4G2.2, 5F10, 1H11, 6.3H9.1D11, or 5H8.1D4; anti-CD40 clone 12E12, 12B4.2C10, 24A3, or 11B6.1C3; anti-Lox-1 clone 11C8, 10F9, or 15C4; anti-DCIR clone 24A5.4A5, 24E7.3H9, 29E9.2E2, 29G10.3D9, 31A6.IF5, 3C2.2D9, 6C8.1G9, 9E8, or 2C9; or anti-Langrin clone 15B10 or 2G3.

[0033] In certain embodiments, the APC-targeted antibody or antigen binding fragment thereof is recombinant. In certain aspects, the recombinant polypeptide comprises at least 90%, 95%, or 99% of one or more CDR domains from the VH or VL domain of the anti-Dectin-1 clone 11B6.4, 15E2.5, or 2D8.2D4; ASGPR clone 49C11, 4G2.2, 5F10, 1H11, 6.3H9.1D11, or 5H8.1D4; anti-CD40 clone 12E12, 12B4.2C10, 24A3, or 11B6.1C3; anti-Lox-1 clone 11C8, 10F9, or 15C4; anti-DCIR clone 24A5.4A5, 24E7.3H9, 29E9.2E2, 29G10.3D9, 31A6.IF5, 3C2.2D9, 6C8.1G9, 9E8, or 2C9; or anti-Langrin clone 15B10 or 2G3 monoclonal antibodies. In some embodiments, the recombinant polypeptide comprises two, three, four, five, six, or more CDR domains from the VH or VL domain of the anti-Dectin-1 clone 11B6.4, 15E2.5, or 2D8.2D4; ASGPR clone 49C11, 4G2.2, 5F10, 1H11, 6.3H9.1D11, or 5H8.1D4; anti-CD40 clone 12E12, 12B4.2C10, 24A3, or 11B6.1C3; anti-Lox-1 clone 11C8, 10F9, or 15C4; anti-DCIR clone 24A5.4A5, 24E7.3H9, 29E9.2E2, 29G10.3D9, 31A6.IF5, 3C2.2D9, 6C8.1G9, 9E8, or 2C9; or anti-Langrin clone 15B10 or 2G3 monoclonal antibodies.

[0034] In some embodiments, a recombinant polypeptide comprises i) CDR1 (SEQ ID NO:37), CDR2 (SEQ ID NO:38), and/or CDR3 (SEQ ID NO:39) from the variable light chain of anti-CD40 12E12; and/or ii) CDR1 (SEQ ID NO:31), CDR2 (SEQ ID NO:32), and/or CDR3 (SEQ ID NO:33) from the variable heavy chain of 12E12. In some embodiments, a recombinant polypeptide comprises i) CDR1, CDR2, and/or CDR3 from the variable light chain of anti-DCIR 9E8; and/or ii) CDR1, CDR2, and/or CDR3 from the variable heavy chain of 9E8.

[0035] Certain aspects are directed to methods of inhibiting an inflammatory response or inducing tolerance in a subject in need thereof comprising administering to the subject an effective amount of one or more APC-targeted antibody or antigen binding fragment thereof operatively linked to IL-10. The antibody can be a purified polyclonal antibody, a purified monoclonal antibody, a recombinant polypeptide, or a fragment thereof. In certain aspects the antibody is humanized or human. In still further aspects the antibody is a recombinant antibody segment. In certain aspects a monoclonal antibody includes one or more of anti-Dectin-1 clone 11B6.4, 15E2.5, or 2D8.2D4; ASGPR clone 49C11, 4G2.2, 5F10, 1H11, 6.3H9.1D11, or 5H8.1D4; anti-CD40 clone 12E12, 12B4.2C10, 24A3, or 11B6.1C3; anti-Lox-1 clone 11C8, 10F9, or 15C4; anti-DCIR clone 24A5.4A5, 24E7.3H9, 29E9.2E2, 29G10.3D9, 31A6.IF5, 3C2.2D9, 6C8.1G9, 9E8, or 2C9; or anti-Langrin clone 15B10 or 2G3. An antibody can be administered at a dose of 0.1, 0.5, 1, 5, 10, 50, 100 mg or $\mu\text{g/kg}$ to 5, 10, 50, 100, 500 mg or $\mu\text{g/kg}$, or any range derivable therein.

[0036] The methods described herein provide a dose sparing effect such that the targeted delivery of IL-10 requires a smaller amount or dose to achieve the same effect as a non-targeted IL-10. In certain embodiments, the therapeutically effective amount of the APC-targeted antibodies operatively linked to IL-10 is at least 5, 10, 20, 50, 100, 500, or 1000 fold less than the dose of non-targeted IL-10. In further embodiments, the therapeutically effective amount of the APC-targeted antibodies operatively linked to IL-10 is greater than 50%, greater than 75%, greater than 80%, greater than 90% or greater than 99% less than the effective amount of the dose of non-targeted IL-10. The therapeutically effective amount of non-targeted IL-10 is known in the art, and may vary depending on the disease to be treated. In certain embodiments, the effective amount of non-targeted IL-10 is 1, 5, 10, or 20 $\mu\text{g/kg}$. In one embodiment, the effective amount of non-targeted IL-10 is 5 $\mu\text{g/kg}$. In other embodiments, the therapeutically effective amount of the APC-targeted antibodies operatively linked to IL-10 is at least 5 fold less than the dose of non-targeted IL-10.

[0037] In certain embodiments, the antibody is a human antibody, humanized antibody, recombinant antibody, bi-specific antibody, chimeric antibody, a nanobody, a DARPIn, an antibody derivative, a veneered antibody, a diabody, a monoclonal antibody, or a polyclonal antibody. In a specific embodiment, the antibody is a humanized antibody.

[0038] In certain embodiments, the antibody is a non-naturally occurring antibody. In some embodiments, the antibody is non-naturally occurring since it comprises at least two

polypeptide segments from different sources. The different sources may be different mammals, such as human and mouse, for example.

[0039] In some embodiments of the methods described herein, the subject is a human subject. The term “subject,” “individual” or “patient” is used interchangeably herein and refers to a vertebrate, for example a primate, a mammal or preferably a human. Mammals include, but are not limited to equines, canines, bovines, ovines, murines, rats, simians, humans, farm animals, sport animals and pets.

[0040] In some embodiments, the subject is one that has an autoimmune disease or an inflammatory disorder. The autoimmune disease or inflammatory disorder may be one known in the art and/or described herein. In some embodiments, the autoimmune disease or inflammatory disorder is selected from rheumatoid arthritis, allergy, asthma, systemic onset juvenile arthritis, inflammatory bowel disease, systemic lupus erythematosus, multiple sclerosis, type 1 diabetes, graft rejection, graft versus host disease, colitis, and Crohn’s disease.

[0041] In some embodiments, the subject is at risk for the development of a disease mediated by a pathogenic T cell response. In further embodiments, the subject is one that is suffering from or at risk of suffering from an autoimmune disease or an auto-inflammatory disease. In a specific embodiment, the autoimmune disease or auto-inflammatory disease is selected from rheumatoid arthritis, allergy, asthma, systemic onset juvenile arthritis, inflammatory bowel disease, systemic lupus erythematosus, multiple sclerosis, type 1 diabetes, graft rejection, graft versus host disease, colitis, and Crohn’s disease.

[0042] In some embodiments, the subject is one that will receive or has received transplanted tissues. In a related embodiment, the transplanted tissue is an allograft. An allograft (also known as allotransplantation, allogeneic transplant, or homograft) is the transplantation of cells, tissues, or organs, to a recipient from a genetically non-identical donor of the same species. In a related embodiment, the subject is one that has a complication from the transplanted tissue, wherein the complication is graft rejection or GVHD.

[0043] In some embodiments, the APC-targeted antibody is administered prior to tissue transplantation. When the antibody or antigen binding fragment thereof is administered prior to tissue transplantation, the method may further comprise the prevention

of a complication relating to the transplanted tissue, wherein the complication comprises GVHD or graft rejection.

[0044] In some embodiments, the APC-targeted antibody is administered after tissue transplantation. When the antibody or antigen binding fragment thereof is administered after tissue transplantation, the method may further comprise treating a complication from the transplanted tissue, wherein the complication comprises GVHD or graft rejection.

[0045] The tissue used in transplantation may be any tissue known in the art to be therapeutically useful for transplantation. Non-limiting examples of tissue transplantations include anterior cruciate ligament (ACL); joint reconstruction in the knee and ankle; meniscal replacement; reconstruction due to cancer or trauma; ridge augmentation in dental procedures; shoulder repair; spinal fusion; urological tissues; skin transplants; corneal transplants; heart transplants; heart valves; lung transplantation; intestinal transplantation such as isolated small bowel, intestine, or multivisceral; liver transplants; kidney transplants; bone marrow transplants; bone allograft; and ligament or tendon allograft.

[0046] In one embodiment, the transplanted tissue comprises immune cells. The term immune cells includes cells of the immune system that are involved in defending the body against both infectious disease and foreign materials. Immune cells may include, for example, neutrophils, eosinophils, basophils, lymphocytes such as b cells and t cells, and monocytes. T cells may include, for example, CD4+, CD8+, T helper cells, cytotoxic T cells, $\gamma\delta$ T cells, regulatory T cells, suppressor T cells, and natural killer cells.

[0047] In another embodiment, the transplanted tissue comprises stem cells. Stem cell types are known in the art. Non-limiting examples of stem cells include hematopoietic stem cells, neural stem cells, and embryonic stem cells. In one embodiment, the stem cells are hematopoietic stem cells. In a further embodiment, the transplanted tissue comprises bone marrow. In a yet further embodiment, the transplanted tissue comprises blood. In another embodiment, the transplanted tissue comprises skin cells.

[0048] In some embodiments, the APC-targeted antibody operatively linked to IL-10 or a fragment thereof is administered in an amount effect for the maintenance of pathogen-specific immunity in the subject.

[0049] The IL-10 polypeptide may be a polypeptide or fragment of an IL-10 protein known in the art or described herein by accession number NP_000563.1. In some embodiments, the IL-10 polypeptide comprises SEQ ID NO:5. In some embodiments, IL-10

is covalently linked to the antibody. In some embodiments, the covalent linkage is through a peptide bond. The IL-10 polypeptide may also be linked to the antibody through binding polypeptides. In one embodiment, the binding polypeptides are dockerin and cohesin.

[0050] In some embodiments, the method further comprises administration of an antigen or allergen. The antigen or allergen may be operatively linked to the APC-targeted antibody or to IL-10. In some embodiments, the antigen or allergen is covalently linked (*i.e.* by a peptide bond) to the APC-targeted antibody, antigen binding fragment thereof, or IL-10. When the antigen or allergen is operatively linked to the APC-targeted antibody, antigen binding fragment thereof, or IL-10, it may be linked through binding polypeptides. Binding peptides include, for example, dockerin and cohesin.

[0051] In further embodiments, the compositions or methods do not comprise an antigen or allergen or the administration of an allergy or antigen. For example, an antigen or allergen is not operatively (either directly or indirectly) linked to the APC-targeted antibody. In some embodiments, the compositions consists essentially of an antigen presenting cell (APC)-targeted antibody operatively linked to IL-10 or a fragment thereof.

[0052] In further embodiments, the compositions or methods do not comprise a TLR molecule or the administration of a TLR molecule.

[0053] In some embodiments, the antibody may comprise a $\gamma 4$ constant region. In a related embodiment, the $\gamma 4$ constant region comprises a substitution of glutamic acid for leucine at residue 235. In another embodiment, $\gamma 4$ constant region comprises a substitution of proline for serine at residue 228 in the hinge region.

[0054] In certain embodiments, the methods comprises multiple administrations of the composition. The administrations may be days, weeks, months, years, or decades apart. The compositions comprising the conjugate described herein may be administered orally, intravenously, subcutaneously, intradermally, intramuscularly, intranasally, by injection, by inhalation, mucosally, and/or by using a nebulizer.

[0055] In certain embodiments of the methods described herein, the anti-DC-ASGPR antibody or antigen binding fragment is administered in a therapeutically effective amount. In certain embodiments, the antibody or antigen binding fragment is administered in an amount that increases production of IL-10 in the subject. In a further embodiment, the antibody or antigen binding fragment is administered in an amount whereby the subject

maintains pathogen-specific immunity after administration of the antibody or antigen binding fragment.

[0056] In some embodiments, the anti-DC-ASGPR antibody or antigen binding fragment thereof may be administered in a pharmaceutical composition. In some embodiments, the pharmaceutical composition does not contain an antigen or does not contain detectable amounts of an antigen. In a further embodiment, the pharmaceutical composition consists essentially of an anti-DC-ASGPR antibody. In further embodiments, the antibody or antigen binding fragment thereof is not conjugated to an antigen or is not is not conjugated to a dockerin or cohesion molecule. In yet further embodiments, the antibody is not covalently or operatively linked to an antigen.

[0057] The term “operatively linked” refers to a situation where two components are combined to form the active complex prior to binding at the target site. For example, an antibody conjugated to one-half of a cohesion-dockerin complex and an antigen complexed to the other one-half of the cohesion-dockerin complex are operatively linked through complexation of the cohesion and dockerin molecules.

[0058] Also disclosed herein are compositions comprising the antibodies and antibody conjugates as described herein.

[0059] Aspects of the disclosure relate to APC-targeted antibodies and APC-targeted antibodies conjugated to IL-10 in pharmaceutical compositions and for use in the preparation of medicaments for treating an autoimmune and/or inflammatory condition described herein.

[0060] Aspects also relate to an APC-targeted antibody or an APC-targeted antibody conjugated to IL-10 in pharmaceutical compositions and for use in the preparation of medicaments for inducing immune tolerance or suppressing a T cell response in a subject having or at risk of developing an autoimmune or inflammatory response, wherein the autoimmune or inflammatory response is caused by an autoimmune or inflammatory disease described herein.

[0061] As used herein the specification, “a” or “an” may mean one or more. As used herein in the claim(s), when used in conjunction with the word “comprising”, the words “a” or “an” may mean one or more than one. A composition with the words “consisting essentially of” is intended to exclude any active ingredients not specifically recited in the composition. Examples of active ingredients include cytokines, TLRs, antigens, adjuvants,

etc... In any of the embodiments described herein, embodiments consisting essentially of the recited elements is also contemplated.

[0062] The use of the term “or” in the claims is used to mean “and/or” unless explicitly indicated to refer to alternatives only or the alternatives are mutually exclusive, although the disclosure supports a definition that refers to only alternatives and “and/or.” As used herein “another” may mean at least a second or more.

[0063] Throughout this application, the term “about” is used to indicate that a value includes the inherent variation of error for the device, the method being employed to determine the value, or the variation that exists among the study subjects.

[0064] Other objects, features and advantages of the present invention will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples, while indicating preferred embodiments of the invention, are given by way of illustration only, since various changes and modifications within the spirit and scope of the invention will become apparent to those skilled in the art from this detailed description.

BRIEF DESCRIPTION OF THE DRAWINGS

[0065] The following drawings form part of the present specification and are included to further demonstrate certain aspects of the present invention. The invention may be better understood by reference to one or more of these drawings in combination with the detailed description of specific embodiments presented herein.

[0066] **FIG. 1** shows that recombinant fusion proteins of antibody and IL-10 target human APCs.

[0067] **FIG. 2** shows that antibody-IL-10 fusion proteins inhibit DC maturation induced by *E. coli* lipopolysaccharide.

[0068] **FIG. 3** demonstrates the dose sparing effects of the targeted IL-10 fusion proteins.

[0069] **FIG. 4** shows that treatment of PBMCs from healthy donors with anti-DC-ASGPR mAb reduces the proliferation of CD4⁺ and CD8⁺ T cells from MHC-mismatched donors. Summary of data generated with PBMCs from 6 pairs of MHC-mismatched healthy donors (Mean $\pm$ SD).

[0070] **FIG. 5** shows that blocking IL-10 partially recovers allogeneic CD4+ T cells proliferation induced by anti-DC-ASGPR-activated PBMCs.

[0071] **FIG. 6** shows that allogeneic CD4+ T cells cultured with anti-DC-ASGPR-activated PBMCs secrete decreased IFN γ but increased IL-10 during restimulation.

[0072] **FIG. 7** demonstrates the effect of anti-DC-ASGPR mAb on delay of xenogenic GVHD in NOG mice.

[0073] **FIG. 8** shows the hypothetical pathways of DC-ASGPR-induced suppression of allogeneic T cell responses.

DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS

[0074] Methods and compositions described herein can be used to treat or prevent inflammatory and/or autoimmune disorders or for inducing immune tolerance. It was discovered that delivering the anti-inflammatory cytokine, IL-10, to human antigen presenting cells (APCs) can suppress and alter the pathophysiologic functions of APCs in the patients. It is contemplated that targeted delivery of anti-inflammatory cytokines to the APCs in the patients is expected to result in more effective and pro-longed immune tolerance in the patients. Delivering IL-10 to APCs can directly suppress ongoing inflammatory reaction in a short term period and can also induce regulatory T cells which can prolong the effectiveness of the treatment. Furthermore, the methods described herein provide a dose sparing effect such that the targeted delivery of IL-10 requires a smaller amount or dose to achieve the same effect as a non-targeted IL-10.

I. Antibodies

[0075] Methods and compositions of the disclosure relate to APC-targeted antibodies and antibody binding fragments thereof. In some embodiments, the antibodies are operatively linked to IL-10. As used herein, an “antibody” includes whole antibodies and any antigen binding fragment or a single chain thereof. Thus the term “antibody” includes any protein or peptide-containing molecule that comprises at least a portion of an immunoglobulin molecule. Examples of such include, but are not limited to a complementarity determining region (CDR) of a heavy or light chain or a ligand binding portion thereof, a heavy chain or light chain variable region, a heavy chain or light chain constant region, a framework (FR) region or any portion thereof or at least one portion of a binding protein.

[0076] The antibody can be any of the various antibodies described herein, non-limiting, examples of such include a polyclonal antibody, a monoclonal antibody, a chimeric antibody, a recombinant antibody, a human antibody, a veneered antibody, a diabody, a humanized antibody, an antibody derivative, a recombinant humanized antibody, or a derivative or fragment of each thereof.

[0077] Antibodies can be generated using conventional techniques known in the art and are well-described in the literature. Several methodologies exist for production of polyclonal antibodies. For example, polyclonal antibodies are typically produced by immunization of a suitable mammal such as, but not limited to, chickens, goats, guinea pigs, hamsters, horses, mice, rats, and rabbits. An antigen is injected into the mammal, induces the B-lymphocytes to produce immunoglobulins specific for the antigen. Immunoglobulins may be purified from the mammal's serum. Common variations of this methodology include modification of adjuvants, routes and site of administration, injection volumes per site and the number of sites per animal for optimal production and humane treatment of the animal. For example, adjuvants typically are used to improve or enhance an immune response to antigens. Most adjuvants provide for an injection site antigen depot, which allows for a slow release of antigen into draining lymph nodes. Other adjuvants include surfactants which promote concentration of protein antigen molecules over a large surface area and immunostimulatory molecules. Non-limiting examples of adjuvants for polyclonal antibody generation include Freund's adjuvants, Ribi adjuvant system, and Titermax. Polyclonal antibodies can be generated using methods known in the art some of which are described in U.S. Pat. Nos. 7,279,559; 7,119,179; 7,060,800; 6,709,659; 6,656,746; 6,322,788; 5,686,073; and 5,670,153.

[0078] Unless specified otherwise, the antibodies can be polyclonal or monoclonal and can be isolated from any suitable biological source, e.g., murine, rat, sheep or canine.

[0079] In a specific embodiment, the antibody is a monoclonal antibody. As used herein, "monoclonal antibody" refers to an antibody obtained from a substantially homogeneous antibody population. Monoclonal antibodies are highly specific, as each monoclonal antibody is directed against a single determinant on the antigen. The antibodies may be detectably labeled, e.g., with a radioisotope, an enzyme which generates a detectable product, a fluorescent protein, and the like. The antibodies may be further conjugated to other moieties, such as members of specific binding pairs, e.g., biotin (member of biotin-

avidin specific binding pair), and the like. The antibodies may also be bound to a solid support, including, but not limited to, polystyrene plates or beads, and the like.

[0080] Monoclonal antibodies can be generated using conventional hybridoma techniques known in the art and well-described in the literature. For example, a hybridoma is produced by fusing a suitable immortal cell line (e.g., a myeloma cell line such as, but not limited to, Sp2/0, Sp2/0-AG14, NSO, NS1, NS2, AE-1, L.5, P3X63Ag8,653, Sp2 SA3, Sp2 MAI, Sp2 SS1, Sp2 SA5, U397, MIA 144, ACT IV, MOLT4, DA-1, JURKAT, WEHI, K-562, COS, RAJI, NIH 313, HL-60, MLA 144, NAMAIWA, NEURO 2A, CHO, PerC.6, YB2/O) or the like, or heteromyelomas, fusion products thereof, or any cell or fusion cell derived there from, or any other suitable cell line as known in the art, with antibody producing cells, such as, but not limited to, isolated or cloned spleen, peripheral blood, lymph, tonsil, or other immune or B cell containing cells, or any other cells expressing heavy or light chain constant or variable or framework or CDR sequences, either as endogenous or heterologous nucleic acid, as recombinant or endogenous, viral, bacterial, algal, prokaryotic, amphibian, insect, reptilian, fish, mammalian, rodent, equine, ovine, goat, sheep, primate, eukaryotic, genomic DNA, cDNA, rDNA, mitochondrial DNA or RNA, chloroplast DNA or RNA, hnRNA, mRNA, tRNA, single, double or triple stranded, hybridized, and the like or any combination thereof. Antibody producing cells can also be obtained from the peripheral blood or, preferably the spleen or lymph nodes, of humans or other suitable animals that have been immunized with the antigen of interest. Any other suitable host cell can also be used for expressing-heterologous or endogenous nucleic acid encoding an antibody, specified fragment or variant thereof. The fused cells (hybridomas) or recombinant cells can be isolated using selective culture conditions or other suitable known methods, and cloned by limiting dilution or cell sorting, or other known methods.

[0081] Other suitable methods of producing or isolating antibodies of the requisite specificity can be used, including, but not limited to, methods that select recombinant antibody from a peptide or protein library (e.g., but not limited to, a bacteriophage, ribosome, oligonucleotide, cDNA, or the like, display library; e.g., as available from various commercial vendors such as MorphoSys (Martinsreid/Planegg, Del.), BioInvent (Lund, Sweden), Affitech (Oslo, Norway) using methods known in the art. Art known methods are described in the patent literature some of which include U.S. Pat. Nos. 4,704,692; 5,723,323; 5,763,192; 5,814,476; 5,817,483; 5,824,514; 5,976,862. Alternative methods rely upon immunization of transgenic animals (e.g., SCID mice, Nguyen et al. (1977) Microbiol.

Immunol. 41:901-907 (1997); Sandhu et al. (1996) Crit. Rev. Biotechnol. 16:95-118; Eren et al. (1998) Mamma 93:154-161 that are capable of producing a repertoire of human antibodies, as known in the art and/or as described herein. Such techniques, include, but are not limited to, ribosome display Wanes et al. (1997) Proc. Natl. Acad. Sci. USA, 94:4937-4942; Hanes et al, (1998) Proc. Natl. Acad. Sci. USA 95:14130-14135); single cell antibody producing technologies (e.g., selected lymphocyte antibody method ("SLAM") (U.S. Pat. No. 5,627,052, Wen et al, (1987) J. Immunol 17:887-892; Babcook et al. (1996) Proc. Natl. Acad. Sci. USA 93:7843-7848); gel microdroplet and flow cytometry (Powell et al. (1990) Biotechnol. 8:333-337; One Cell Systems, (Cambridge, Mass.); Gray et al. (1995) J. Imm. Meth. 182:155-163; and Kenny et al, (1995) Bio. Technol. 13:787-790); B-cell selection (Steenbakkers et al. (1994) Molec. Biol. Reports 19:125-134).

[0082] The terms "polyclonal antibody" or "polyclonal antibody composition" as used herein refer to a preparation of antibodies that are derived from different B-cell lines. They are a mixture of immunoglobulin molecules secreted against a specific antigen, each recognizing a different epitope.

[0083] The term "mouse antibody" as used herein, is intended to include antibodies having variable and constant regions derived from mouse germline immunoglobulin sequences.

[0084] As used herein, chimeric antibodies are antibodies whose light and heavy chain genes have been constructed, typically by genetic engineering, from antibody variable and constant region genes belonging to different species. In one embodiment, the antibody is a mouse/human chimeric antibody.

[0085] In further embodiments, the antibody comprises a modification and is an "antibody derivative." The term "antibody derivative" includes post-translational modification to linear polypeptide sequence of the antibody or fragment. For example, U.S. Pat. No. 6,602,684 B1 describes a method for the generation of modified glycol-forms of antibodies, including whole antibody molecules, antibody fragments, or fusion proteins that include a region equivalent to the Fc region of an immunoglobulin, having enhanced Fe-mediated cellular toxicity, and glycoproteins so generated.

[0086] The antibodies provided herein also include derivatives that are modified by the covalent attachment of any type of molecule to the antibody such that covalent attachment does not prevent the antibody from generating an anti-idiotypic response. Antibody

derivatives include, but are not limited to, antibodies that have been modified by glycosylation, acetylation, pegylation, phosphorylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to a cellular ligand or other protein, etc. Additionally, the derivatives may contain one or more non-classical amino acids.

[0087] Antibody derivatives can also be prepared by delivering a polynucleotide encoding an antibody to a suitable host such as to provide transgenic animals or mammals, such as goats, cows, horses, sheep, and the like, that produce such antibodies in their milk. These methods are known in the art and are described for example in U.S. Pat. Nos. 5,827,690; 5,849,992; 4,873,316; 5,849,992; 5,994,616; 5,565,362; and 5,304,489.

[0088] Antibody derivatives also can be prepared by delivering a polynucleotide to provide transgenic plants and cultured plant cells (e.g., but not limited to tobacco, maize, and duckweed) that produce such antibodies, specified portions or variants in the plant parts or in cells cultured therefrom. Antibody derivatives have also been produced in large amounts from transgenic plant seeds including antibody fragments, such as single chain antibodies (scFv's), including tobacco seeds and potato tubers. See, e.g., Conrad et al. (1998) Plant Mol. Biol. 38:101-109. Thus, antibodies can also be produced using transgenic plants, according to known methods.

[0089] Antibody derivatives also can be produced, for example, by adding exogenous sequences to modify immunogenicity or reduce, enhance or modify binding, affinity, on-rate, off-rate, avidity, specificity, half-life, or any other suitable characteristic. Generally part or all of the non-human or human CDR sequences are maintained while the non-human sequences of the variable and constant regions are replaced with human or other amino acids.

[0090] The term “variable region” refers to a portion of the antibody that gives the antibody its specificity for binding antigen. The variable region is typically located at the ends of the heavy and light chains. Variable loops of β -strands, three each on the light (VL) and heavy (VH) chains are responsible for binding to the antigen. These loops are referred to as the “complementarity determining regions” (CDRs).

[0091] In general, the CDR residues are directly and most substantially involved in influencing antigen binding. Humanization or engineering of antibodies can be performed using any known method such as, but not limited to, those described in U.S. Pat. Nos. 5,723,323; 5,976,862; 5,824,514; 5,817,483; 5,814,476; 5,763,192; 5,723,323; 5,766,886;

5,714,352; 6,204,023; 6,180,370; 5,693,762; 5,530,101; 5,585,089; 5,225,539; and 4,816,567.

[0092] The term “constant region” refers to a portion of the antibody that is identical in all antibodies of the same isotype. The constant region differs in antibodies of different isotypes.

[0093] In one embodiment, the antibody is a humanized antibody. As used herein, the term “humanized antibody” or “humanized immunoglobulin” refers to a human/non-human chimeric antibody that contains a minimal sequence derived from non-human immunoglobulin. For the most part, humanized antibodies are human immunoglobulins (recipient antibody) in which residues from a variable region of the recipient are replaced by residues from a variable region of a non-human species (donor antibody) such as mouse, rat, rabbit, or non-human primate having the desired specificity, affinity and capacity. Humanized antibodies may comprise residues that are not found in the recipient antibody or in the donor antibody. The humanized antibody can optionally also comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin, a non-human antibody containing one or more amino acids in a framework region, a constant region or a CDR, that have been substituted with a correspondingly positioned amino acid from a human antibody. In general, humanized antibodies are expected to produce a reduced immune response in a human host, as compared to a non-humanized version of the same antibody. The humanized antibodies may have conservative amino acid substitutions which have substantially no effect on antigen binding or other antibody functions. Conservative substitutions groupings include: glycine-alanine, valine-leucine-isoleucine, phenylalanine-tyrosine, lysine-arginine, alanine-valine, serine-threonine and asparagine-glutamine.

[0094] Chimeric, humanized or primatized antibodies can be prepared based on the sequence of a reference monoclonal antibody prepared using standard molecular biology techniques. DNA encoding the heavy and light chain immunoglobulins can be obtained from the hybridoma of interest and engineered to contain non-reference (e.g., human) immunoglobulin sequences using standard molecular biology techniques. For example, to create a chimeric antibody, the murine variable regions can be linked to human constant regions using methods known in the art (U.S. Pat. No. 4,816,567). To create a humanized antibody, the murine CDR regions can be inserted into a human framework using methods known in the art (U.S. Pat. No. 5,225,539 and U.S. Pat. Nos. 5,530,101; 5,585,089; 5,693,762

and 6,180,370). Similarly, to create a primatized antibody the murine CDR regions can be inserted into a primate framework using methods known in the art (WO 93/02108 and WO 99/55369). Methods of determining CDRs from the sequence of a variable region are known in the art (see, for example, Zhao and Lu, "A germline knowledge based computational approach for determining antibody complementarity determining regions." *Mol. Immunol.*, (2010) 47(4):694-700).

[0095] Techniques for making partially to fully human antibodies are known in the art and any such techniques can be used. According to one embodiment, fully human antibody sequences are made in a transgenic mouse which has been engineered to express human heavy and light chain antibody genes. Multiple strains of such transgenic mice have been made which can produce different classes of antibodies. B cells from transgenic mice which are producing a desirable antibody can be fused to make hybridoma cell lines for continuous production of the desired antibody. (See for example, Russel et al. (2000) *Infection and Immunity* April 2000:1820-1826; Gallo et al. (2000) *European J. of Immun.* 30:534-540; Green (1999) *J. of Immun. Methods* 231:11-23; Yang et al. (1999A) *J. of Leukocyte Biology* 66:401-410; Yang (1999B) *Cancer Research* 59(6):1236-1243; Jakobovits (1998) *Advanced Drug Reviews* 31:33-42; Green and Jakobovits (1998) *J. Exp. Med.* 188(3):483-495; Jakobovits (1998) *Exp. Opin. Invest. Drugs* 7(4):607-614; Tsuda et al. (1997) *Genomics* 42:413-421; Sherman-Gold (1997) *Genetic Engineering News* 17(14); Mendez et al. (1997) *Nature Genetics* 15:146-156; Jakobovits (1996) *Weir's Handbook of Experimental Immunology, The Integrated Immune System Vol. IV*, 194.1-194.7; Jakobovits (1995) *Current Opinion in Biotechnology* 6:561-566; Mendez et al. (1995) *Genomics* 26:294-307; Jakobovits (1994) *Current Biology* 4(8):761-763; Arbones et al. (1994) *Immunity* 1(4):247-260; Jakobovits (1993) *Nature* 362(6417):255-258; Jakobovits et al. (1993) *Proc. Natl. Acad. Sci. USA* 90(6):2551-2555; and U.S. Pat. No. 6,075,181.)

[0096] Antibodies also can be modified to create chimeric antibodies. Chimeric antibodies are those in which the various domains of the antibodies' heavy and light chains are coded for by DNA from more than one species. See, e.g., U.S. Pat. No. 4,816,567.

[0097] Alternatively, antibodies can also be modified to create veneered antibodies. Veneered antibodies are those in which the exterior amino acid residues of the antibody of one species are judiciously replaced or "veneered" with those of a second species so that the antibodies of the first species will not be immunogenic in the second species thereby reducing the immunogenicity of the antibody. Since the antigenicity of a protein is primarily

dependent on the nature of its surface, the immunogenicity of an antibody could be reduced by replacing the exposed residues which differ from those usually found in another mammalian species antibodies. This judicious replacement of exterior residues should have little, or no, effect on the interior domains, or on the interdomain contacts. Thus, ligand binding properties should be unaffected as a consequence of alterations which are limited to the variable region framework residues. The process is referred to as “veneering” since only the outer surface or skin of the antibody is altered, the supporting residues remain undisturbed.

[0098] The procedure for “veneering” makes use of the available sequence data for human antibody variable domains compiled by Kabat et al. (1987) Sequences of Proteins of Immunological interest, 4th ed., Bethesda, Md., National Institutes of Health,. Non-limiting examples of the methods used to generate veneered antibodies include EP 519596; U.S. Pat. No. 6,797,492; and described in Padlan et al. (1991) Mol. Immunol. 28(4-5):489-498.

[0099] The term “antibody derivative” also includes “diabodies” which are small antibody fragments with two antigen-binding sites, wherein fragments comprise a heavy chain variable domain (VH) connected to a light chain variable domain (VL) in the same polypeptide chain. (See for example, EP 404,097; WO 93/11161; and Hollinger et al. (1993) Proc. Natl. Acad. Sci. USA 90:6444-6448.) By using a linker that is too short to allow pairing between the two domains on the same chain, the domains are forced to pair with the complementary domains of another chain and create two antigen-binding sites. (See also, U.S. Pat. No. 6,632,926 to Chen et al, which discloses antibody variants that have one or more amino acids inserted into a hypervariable region of the parent antibody and a binding affinity for a target antigen which is at least about two fold stronger than the binding affinity of the parent antibody for the antigen).

[00100] The term “antibody derivative” further includes engineered antibody molecules, fragments and single domains such as scFv, dAbs, nanobodies, minibodies, Unibodies, and Affibodies & Hudson (2005) Nature Biotech 23(9):1126-36; U.S. Patent Publication US 2006/0211088; PCT Publication W02007/059782; U.S. Pat. No. 5,831,012).

[00101] The term “antibody derivative” further includes “linear antibodies”. The procedure for making linear antibodies is known in the art and described in Zapata et al.

(1995) Protein Eng. 8(10):1057-1062. Briefly, these antibodies comprise a pair of tandem Ed segments (V.sub.H-C.sub.H 1-VH-C.sub.H1) which form a pair of antigen binding regions. Linear antibodies can be bispecific or monospecific.

[00102] Antibodies can be recovered and purified from recombinant cell cultures by known methods including, but not limited to, protein A purification, ammonium sulfate or ethanol precipitation, acid extraction, anion or cation exchange chromatography, phosphocellulose chromatography, hydrophobic interaction chromatography, affinity chromatography, hydroxylapatite chromatography and lectin chromatography. High performance liquid chromatography ("HPLC") can also be used for purification.

[00103] It also is possible to determine without undue experimentation, whether an antibody has the same specificity as antibodies contemplated herein by determining whether the antibody being tested prevents an antibody from binding the protein or polypeptide with which the antibody is normally reactive. If the antibody being tested competes with an antibody used in embodiments described herein as shown by a decrease in binding by the monoclonal antibody, then it is likely that the two antibodies bind to the same or a closely related epitope. Alternatively, one can pre-incubate an antibody for use in embodiments with a protein with which it is normally reactive, and determine if the antibody being tested is inhibited in its ability to bind the antigen. If the antibody being tested is inhibited then, in all likelihood, it has the same, or a closely related, epitopic specificity as the antibody for use in embodiments described herein.

[00104] The term "antibody" also is intended to include antibodies of all immunoglobulin isotypes and subclasses unless specified otherwise. An isotype refers to the genetic variations or differences in the constant regions of the heavy and light chains of an antibody. In humans, there are five heavy chain isotypes: IgA, IgD, IgG, IgE, and IgM and two light chain isotypes: kappa and lambda. The IgG class is divided into four isotypes: IgG1, IgG2, IgG3 and IgG4 in humans, and IgG1, IgG2a, IgG2b and IgG3 in mice. They share more than 95% homology in the amino acid sequences of the Fc regions but show major differences in the amino acid composition and structure of the hinge region. Particular isotypes of a monoclonal antibody can be prepared either directly by selecting from an initial fusion, or prepared secondarily, from a parental hybridoma secreting a monoclonal antibody of different isotype by using the sib selection technique to isolate class switch variants using the procedure described in Steplewski et al. (1985) Proc. Natl. Acad. Sci. USA 82:8653 or

Spira et al, (1984) J. Immunol. Methods 74:307. Alternatively, recombinant DNA techniques may be used.

[00105] The isolation of other monoclonal antibodies with the specificity of the monoclonal antibodies described herein can also be accomplished by one of ordinary skill in the art by producing anti-idiotypic antibodies. Herlyn et al. (1986) Science 232:100. An anti-idiotypic antibody is an antibody which recognizes unique determinants present on the monoclonal antibody of interest.

[00106] In some aspects, it will be useful to detectably or therapeutically label the antibody. Methods for conjugating antibodies to these agents are known in the art. For the purpose of illustration only, antibodies can be labeled with a detectable moiety such as a radioactive atom, a chromophore, a fluorophore, or the like. Such labeled antibodies can be used for diagnostic techniques, either in vivo, or in an isolated test sample.

[00107] In certain embodiments, the antibody or antigen binding fragment further comprises a modification. The modification may be a conservative amino acid mutation within the VH and/or VL CDR 1, CDR 2 and/or CDR 3 regions, of conservative amino acid mutations in the Fc hinge region, pegylation, conjugation to a serum protein, conjugation to human serum albumin, conjugation to a detectable label, conjugation to a diagnostic agent, conjugation to an enzyme, conjugation to a fluorescent, luminescent, or bioluminescent material, conjugation to a radioactive material, or conjugation to a therapeutic agent.

[00108] As used herein, the term “label” intends a directly or indirectly detectable compound or composition that is conjugated directly or indirectly to the composition to be detected, e.g., polynucleotide or protein such as an antibody so as to generate a “labeled” composition. The term also includes sequences conjugated to the polynucleotide that will provide a signal upon expression of the inserted sequences, such as green fluorescent protein (GFP) and the like. The label may be detectable by itself (e.g. radioisotope labels or fluorescent labels) or, in the case of an enzymatic label, may catalyze chemical alteration of a substrate compound or composition which is detectable. The labels can be suitable for small scale detection or more suitable for high-throughput screening. As such, suitable labels include, but are not limited to radioisotopes, fluorochromes, chemiluminescent compounds, dyes, and proteins, including enzymes. The label may be simply detected or it may be quantified. A response that is simply detected generally comprises a response whose existence merely is confirmed, whereas a response that is quantified generally comprises a

response having a quantifiable (e.g., numerically reportable) value such as an intensity, polarization, and/or other property. In luminescence or fluorescence assays, the detectable response may be generated directly using a luminophore or fluorophore associated with an assay component actually involved in binding, or indirectly using a luminophore or fluorophore associated with another (e.g., reporter or indicator) component.

[00109] Examples of luminescent labels that produce signals include, but are not limited to bioluminescence and chemiluminescence. Detectable luminescence response generally comprises a change in, or an occurrence of, a luminescence signal. Suitable methods and luminophores for luminescently labeling assay components are known in the art and described for example in Haugland, Richard P. (1996) Handbook of Fluorescent Probes and Research Chemicals (6.sup.th ed.). Examples of luminescent probes include, but are not limited to, aequorin and luciferases.

[00110] Examples of suitable fluorescent labels include, but are not limited to, fluorescein, rhodamine, tetramethylrhodamine, eosin, erythrosin, coumarin, methylcoumarins, pyrene, Malacite green, stilbene, Lucifer Yellow, Cascade Blue.TM., and Texas Red. Other suitable optical dyes are described in the Haugland, Richard P. (1996) Handbook of Fluorescent Probes and Research Chemicals (6.sup.th ed.).

[00111] In another aspect, the fluorescent label is functionalized to facilitate covalent attachment to a cellular component present in or on the surface of the cell or tissue such as a cell surface marker. Suitable functional groups, including, but not are limited to, isothiocyanate groups, amino groups, haloacetyl groups, maleimides, succinimidyl esters, and sulfonyl halides, all of which may be used to attach the fluorescent label to a second molecule. The choice of the functional group of the fluorescent label will depend on the site of attachment to either a linker, the agent, the marker, or the second labeling agent.

[00112] Attachment of the fluorescent label may be either directly to the cellular component or compound or alternatively, can be via a linker. Suitable binding pairs for use in indirectly linking the fluorescent label to the intermediate include, but are not limited to, antigens/antibodies, e.g., rhodamine/anti-rhodamine, biotin/avidin and biotin/streptavidin.

[00113] The coupling of antibodies to low molecular weight haptens can increase the sensitivity of the antibody in an assay. The haptens can then be specifically detected by means of a second reaction. For example, it is common to use haptens such as biotin, which

reacts avidin, or dinitrophenol, pyridoxal, and fluorescein, which can react with specific anti-hapten antibodies.

[00114] The variable region of an antibody can be modified by mutating amino acid residues within the VH and/or VL CDR 1, CDR 2 and/or CDR 3 regions to improve one or more binding properties (e.g., affinity) of the antibody. Mutations may be introduced by site-directed mutagenesis or PCR-mediated mutagenesis and the effect on antibody binding, or other functional property of interest, can be evaluated in appropriate in vitro or in vivo assays. Preferably conservative modifications are introduced and typically no more than one, two, three, four or five residues within a CDR region are altered. The mutations may be amino acid substitutions, additions or deletions.

[00115] Framework modifications can be made to the antibodies to decrease immunogenicity, for example, by “backmutating” one or more framework residues to the corresponding germline sequence.

[00116] In addition, an antibody may be engineered to include modifications within the Fc region to alter one or more functional properties of the antibody, such as serum half-life, complement fixation, Fc receptor binding, and/or antigen-dependent cellular cytotoxicity. Such modifications include, but are not limited to, alterations of the number of cysteine residues in the hinge region to facilitate assembly of the light and heavy chains or to increase or decrease the stability of the antibody (U.S. Pat. No. 5,677,425) and amino acid mutations in the Fc hinge region to decrease the biological half life of the antibody (U.S. Pat. No. 6,165,745).

[00117] Additionally, one or more antibodies may be chemically modified. Glycosylation of an antibody can be altered, for example, by modifying one or more sites of glycosylation within the antibody sequence to increase the affinity of the antibody for antigen (U.S. Pat. Nos. 5,714,350 and 6,350,861). Alternatively, to increase antibody-dependent cell-mediated cytotoxicity, a hypofucosylated antibody having reduced amounts of fucosyl residues or an antibody having increased bisecting GlcNAc structures can be obtained by expressing the antibody in a host cell sub.-- with altered glycosylation mechanism (Shields, R. L. et al., 2002 J. Biol. Chem. 277:26733-26740; Umana et al., 1999 Nat. Biotech. 17:176-180).

[00118] Antibodies can be pegylated to increase biological half-life by reacting the antibody or fragment thereof with polyethylene glycol (PEG) or a reactive ester or aldehyde

derivative of PEG, under conditions in which one or more PEG groups become attached to the antibody or antibody fragment. Antibody pegylation may be carried out by an acylation reaction or an alkylation reaction with a reactive PEG molecule (or an analogous reactive watersoluble polymer). As used herein, the term "polyethylene glycol" is intended to encompass any of the forms of PEG that have been used to derivatize other proteins, such as mono (C1-C10) alkoxy- or aryloxy-polyethylene glycol or polyethylene glycol-maleimide. The antibody to be pegylated can be an aglycosylated antibody. Methods for pegylating proteins are known in the art and can be applied to one or more antibodies (EP 0 154 316 and EP 0 401 384).

[00119] Additionally, antibodies may be chemically modified by conjugating or fusing the antigen-binding region of the antibody to serum protein, such as human serum albumin, to increase half-life of the resulting molecule. Such approach is for example described in EP 0322094 and EP 0 486 525.

[00120] The antibodies or fragments thereof may be conjugated to a diagnostic agent and used diagnostically, for example, to monitor the development or progression of a disease and determine the efficacy of a given treatment regimen. Examples of diagnostic agents include enzymes, prosthetic groups, fluorescent materials, luminescent materials, bioluminescent materials, radioactive materials, positron emitting metals using various positron emission tomographies, and nonradioactive paramagnetic metal ions. The detectable substance may be coupled or conjugated either directly to the antibody or fragment thereof, or indirectly, through a linker using techniques known in the art. Examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase, beta-galactosidase, or acetylcholinesterase. Examples of suitable prosthetic group complexes include streptavidin/biotin and avidin/biotin. Examples of suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin. An example of a luminescent material includes luminol. Examples of bioluminescent materials include luciferase, luciferin, and aequorin. Examples of suitable radioactive material include Indium-111, Lutetium-171, Bismuth-212, Bismuth-213, Astatine-211, Copper-62, Copper-64, Copper-67, Yttrium-90, Iodine-125, Iodine-131, Phosphorus-32, Phosphorus-33, Scandium-47, Silver-111, Gallium-67, Praseodymium-142, Samarium-153, Terbium-161, Dysprosium-166, Holmium-166, Rhenium-186, Ithium-188, Rhenium-189, Lead-212, Radium-223, Actinium-225, Iron-59, Selenium-75, Arsenic-77, Strontium-89, Molybdenum-99, Rhodium-

1105, Palladium-109, Praseodymium-143, Promethium-149, Erbium-169, Iridium-194, Gold-198, Gold-199, and Lead-211. Monoclonal antibodies may be indirectly conjugated with radiometal ions through the use of bifunctional chelating agents that are covalently linked to the antibodies. Chelating agents may be attached through amities (Meares et al., 1984 Anal. Biochem. 142: 68-78); sulfhydryl groups (Koyama 1994 Chem. Abstr. 120: 217262t) of amino acid residues and carbohydrate groups (Rodwell et al. 1986 PNAS USA 83: 2632-2636; Quadri et al. 1993 Nucl. Med. Biol. 20: 559-570).

[00121] Additional suitable conjugated molecules include ribonuclease (RNase), DNase I, an antisense nucleic acid, an inhibitory RNA molecule such as a siRNA molecule, an immunostimulatory nucleic acid, aptamers, ribozymes, triplex forming molecules, and external guide sequences. Aptamers are small nucleic acids ranging from 15-50 bases in length that fold into defined secondary and tertiary structures, such as stem-loops or G-quartets, and can bind small molecules, such as ATP (U.S. Pat. No. 5,631,146) and theophiline (U.S. Pat. No. 5,580,737), as well as large molecules, such as reverse transcriptase (U.S. Pat. No. 5,786,462) and thrombin (U.S. Pat. No. 5,543,293). Ribozymes are nucleic acid molecules that are capable of catalyzing a chemical reaction, either intramolecularly or intermolecularly. Ribozymes typically cleave nucleic acid substrates through recognition and binding of the target substrate with subsequent cleavage. Triplex forming function nucleic acid molecules can interact with double-stranded or single-stranded nucleic acid by forming a triplex, in which three strands of DNA form a complex dependant on both Watson-Crick and Hoogsteen base-pairing. Triplex molecules can bind target regions with high affinity and specificity.

[00122] The functional nucleic acid molecules may act as effectors, inhibitors, modulators, and stimulators of a specific activity possessed by a target molecule, or the functional nucleic acid molecules may possess a de novo activity independent of any other molecules. In one embodiment, the antibody is a stimulator of dendritic cells

[00123] The conjugated agents can be linked to the antibody directly or indirectly, using any of a large number of available methods. For example, an agent can be attached at the hinge region of the reduced antibody component via disulfide bond formation, using cross-linkers such as N-succinyl 3-(2-pyridyldithio)propionate (SPDP), or via a carbohydrate moiety in the Fc region of the antibody (Yu et al. 1994 Int. J. Cancer 56: 244; Upeslakis et al., "Modification of Antibodies by Chemical Methods," in Monoclonal antibodies: principles and applications, Birch et al. (eds.), pages 187-230 (Wiley-Liss, Inc. 1995); Price,

“Production and Characterization of Synthetic Peptide-Derived Antibodies,” in *Monoclonal antibodies: Production, engineering and clinical application*, Ritter et al. (eds.), pages 60-84 (Cambridge University Press 1995)).

[00124] Techniques for conjugating agents to antibodies are well known (Amon et al., “Monoclonal Antibodies For Immunotargeting Of Drugs In Cancer Therapy”, in *Monoclonal Antibodies And Cancer Therapy*, Reisfeld et al. (eds.), pp. 243-56 (Alan R. Liss, Inc. 1985); Hellstrom et al., “Antibodies For Drug Delivery”, in *Controlled Drug Delivery* (2nd Ed.), Robinson et al. (eds.), pp. 623-53 (Marcel Dekker, Inc. 1987); Thorpe, “Antibody Carriers Of Cytotoxic Agents In Cancer Therapy: A Review”, in *Monoclonal Antibodies '84: Biological And Clinical Applications*, Pinchera et al. (eds.), pp. 475-506 (1985); “Analysis, Results, And Future Prospective Of The Therapeutic Use Of Radiolabeled Antibody in Cancer Therapy”, in *Monoclonal Antibodies For Cancer Detection And Therapy*, Baldwin et al. (eds.), pp. 303-16 (Academic Press 1985), and Thorpe et al., *The Preparation And Cytotoxic Properties Of Antibody-Toxin Conjugates*” 1982 *Immunol. Rev.* 62:119-58),

[00125] Antibodies or antigen-binding regions thereof can be linked to another functional molecule such as another antibody or ligand for a receptor to generate a bi-specific or multi-specific molecule that binds to at least two or more different binding sites or target molecules. Linking of the antibody to one or more other binding molecules, such as another antibody, antibody fragment, peptide or binding mimetic, can be done, for example, by chemical coupling, genetic fusion, or noncovalent association. Multi-specific molecules can further include a third binding specificity, in addition to the first and second target epitope.

[00126] Bi-specific and multi-specific molecules can be prepared using methods known in the art. For example, each binding unit of the bi-specific molecule can be generated separately and then conjugated to one another. When the binding molecules are proteins or peptides, a variety of coupling or cross-linking agents can be used for covalent conjugation. Examples of cross-linking agents include protein A, carbodiimide, N-succinimidyl-S-acetyl-thioacetate (SATA), 5,5'-dithiobis(2-nitrobenzoic acid) (DTNB), o-phenylenedimaleimide (oRDM), N-succinimidyl-3-(2-pyridyldithio)propionate (SPDP), and sulfosuccinimidyl 4-(N-maleimidomethyl)cyclohexane-1-carboxylate (sulfo-SMCC) (Karpovsky et al., 1984 *J. Exp. Med.* 160:1686; Liu et al., 1985 *Proc. Natl. Acad. Sci. USA* 82:8648). When the binding molecules are antibodies, they can be conjugated by sulfhydryl bonding of the C-terminus hinge regions of the two heavy chains.

[00127] The antibodies or fragments thereof may be linked to a moiety that is toxic to a cell to which the antibody is bound to form “depleting” antibodies. These antibodies are particularly useful in applications where it is desired to deplete an NK cell.

[00128] The antibodies may also be attached to solid supports, which are particularly useful for immunoassays or purification of the target antigen. Such solid supports include, but are not limited to, glass, cellulose, polyacrylamide, nylon, polystyrene, polyvinyl chloride or polypropylene.

[00129] The antibodies also can be bound to many different carriers. Thus, compositions are also provided containing the antibodies and another substance, active or inert. Examples of well-known carriers include glass, polystyrene, polypropylene, polyethylene, dextran, nylon, amylase, natural and modified cellulose, polyacrylamide, agarose, and magnetite. The nature of the carrier can be either soluble or insoluble for purposes of embodiments described herein. Those skilled in the art will know of other suitable carriers for binding monoclonal antibodies, or will be able to ascertain such, using routine experimentation.

II. Constructs

[00130] All examples of H chain constructs are typically used in co-transfection of CHO cells with matching L chain vectors. Also, in some embodiments immunotherapeutics will have humanized variable regions.

[00131] The following depicts APC-targeted antibodies and antibody-IL10 fusion proteins useful in the methods and compositions described herein.

Anti-ASGPR-49C11-hIL-10

[00132] SEQ ID NO:1 shows a fusion protein of the heavy chain of the anti-ASGPR 49C11 antibody fused through a linker to human IL-10. The linker is underlined and the IL-10 amino acid sequence is in bold italics.

[00133] mAnti-ASGPR_49C11_7H-LV-hIgG4H-C-Flex-v1-***hIL-10***]antibody, SEQ ID NO:1:

VQLQESGPDLVKPSQSLTCTVTGYSITSGYSWHWIRQFPGNKLEWMGYILFSGST
 NYNPSLKSRISITRDTSKNQFFLQLNSVTTEDTATYFCARSNYGSFASWGQGTLVTVS
 AAKTTGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL
 QSSGLYSLSSVVTVPSSSLGKTYTCNVDPHKPSNTKVDKRVESKYGPCCPPCPAPEFE

GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKP
 REEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQV
 YTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFF
 LYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLGLGKASQTPTNTISVTPTN
NSTPTNNSNPKNP***ASPGQGTQSENSCTHFPGNLPNMLRDLRDAFSRVKTFFQMKD***
QLDNLLLKESLLEDFKGYLGCAQALSEMIQFYLEEVMPPQAENQDPDIKAHVNSLGEN
LKTLRLRLRRCHRFLPCENKSKAVEQVKNAFNKLQEKGIYKAMSEFDIFINYIEAYM
TMKIRN (SEQ ID NO:1).

[00134] The heavy chain of the anti-ASGPR 49C11 antibody from above is SEQ ID NO:2:

VQLQESGPDLVKPSQSLSLTCTVTGYSITSGYSWHWIRQFPGNKLEWMGYILFSGST
 NYNPSLKSRISITRDTSKNQFFLQLNSVTTEDTATYFCARSNYGSFASWGQGTTLTVTS
 AAKTTGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL
 QSSGLYSLSSVTVPPSSSLGKTYTCNVDPHKPSNTKVDKRVESKYGPPCPPCPAPEFE
 GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKP
 REEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQV
 YTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFF
 LYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLGLGKAS (SEQ ID NO:2).

[00135] The H chain variable region of anti-ASGPR 49C11 is shown in SEQ ID NO.:3:

QLQESGPDLVKPSQSLSLTCTVTGYSITSGYSWHWIRQFPGNKLEWMGYILFSGSTN
 YNPSLKSRISITRDTSKNQFFLQLNSVTTEDTATYFCARSNYGSFASWGQGTTLTVSA
 AKTT (SEQ ID NO:3).

[00136] The linker shown above is SEQ ID NO:4:
 QTPTNTISVTPTNNSPTNNSNPKNP (SEQ ID NO:4).

[00137] The hIL-10 amino acid sequence from the Anti-ASGPR-49C11-hIL-10 is shown in SEQ ID NO:5:

ASPGQGTQSENSCTHFPGNLPNMLRDLRDAFSRVKTFFQMKDQLDNLLLKESLLEDF
 KGYLGCAQALSEMIQFYLEEVMPPQAENQDPDIKAHVNSLGENLKTLRLRLRRCHRFLP
 CENKSKAVEQVKNAFNKLQEKGIYKAMSEFDIFINYIEAYMTMKIRN (SEQ ID NO:5).

[00138] The DNA sequence of the mAnti-ASGPR_49C11_7H-LV-hIgG4H-C-Flex-v1-hIL-10 antibody is shown in SEQ ID NO:6:

ATGAGAGCGCTGATTCTTTTGTGCCTGTTACAGCCTTTCCTGGTATCCTGTCTGA
TGTGCAGCTTCAGGAGTCAGGACCTGACCTGGTGAAACCTTCTCAGTCACTTTCA
CTCACCTGCACTGTCACTGGCTACTCCATCACCAGTGGTTATAGCTGGCACTGGA
TCCGGCAGTTTCCAGGAAACAACTGGAATGGATGGGCTACATACTCTTCAGTGG
TAGCACTAACTACAACCCATCTCTGAAAAGTCGAATCTCTATCACTCGAGACACA
TCCAAGAACCAGTTCTTCCTGCAGTTGAATTCTGTGACTACTGAGGACACAGCCA
CATATTTCTGTGCAAGATCTAACTATGGTTCCTTTGCTTCCTGGGGCCAAGGGACT
CTGGTCACTGTCTCTGCAGCCAAAACAACGGGGCCATCCGTCTTCCCCCTGGCGC
CCTGCTCCAGGAGCACCTCCGAGAGCACAGCCGCCCTGGGCTGCCTGGTCAAGG
ACTACTTCCCCGAACCGGTGACGGTGTCTGTGGAACCTCAGGCGCCCTGACCAGCG
GCGTGACACCTTCCCGGCTGTCTACAGTCCTCAGGACTCTACTCCCTCAGCAG
CGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACGAAGACCTACACCTGCAACGT
AGATCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTTGAGTCCAAATATGG
TCCCCCATGCCCACCCTGCCCAGCACCTGAGTTCGAAGGGGGACCATCAGTCTTC
CTGTTCCCCC AAAACCCAAGGACACTCTCATGATCTCCCGGACCCCTGAGGTCA
CGTGCGTGGTGGTGGACGTGAGCCAGGAAGACCCCGAGGTCCAGTTCAACTGGT
ACGTGGATGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAG
TTCAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGC
TGAACGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGGCCTCCCGTCCTCCA
TCGAGAAAACCATCTCCAAGCCAAAGGGCAGCCCCGAGAGCCACAGGTGTACA
CCCTGCCCCCATCCCAGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCC
TGGTCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGC
AGCCGGAGAACA ACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCT
TCTTCCTCTACAGCAGGCTAACCGTGGACAAGAGCAGGTGGCAGGAGGGGAATG
TCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACACAGAAGAG
CCTCTCCCTGTCTCTGGGTAAAGCTAGTCAGACCCCCACCAACACCATCAGCGTG
ACCCCCACCAACAACAGCACCCCCACCAACAACAGCAACCCCAAGCCCAACCCC
GCTAGCCCAGGCCAGGGCACCCAGTCTGAGAACAGCTGCACCCACTTCCCAGGC
AACCTGCCTAACATGCTTCGAGATCTCCGAGATGCCTTCAGCAGAGTGAAGACTT
TCTTTCAAATGAAGGATCAGCTGGACA ACTTGTGTGTTAAAGGAGTCCTTGCTGGA
GGACTTTAAGGGTTACCTGGGTTGCCAAGCCTTGTCTGAGATGATCCAGTTTTAC
CTGGAGGAGGTGATGCCCCAAGCTGAGAACCAAGACCCAGACATCAAGGCGCAT
GTGAACTCCCTGGGGGAGAACCTGAAGACCCTCAGGCTGAGGCTACGGCGCTGT
CATCGATTTCTTCCCTGTGAAAACAAGAGCAAGGCCGTGGAGCAGGTGAAGAAT

GCCTTTAATAAGCTCCAAGAGAAAGGCATCTACAAAGCCATGAGTGAGTTTGAC
ATCTTCATCAACTACATAGAAGCCTACATGACAATGAAGATACGAAACTGA (SEQ
ID NO:6).

[00139] The corresponding light chain amino acid sequence, mAnti-
ASGPR_49C11_7K-LV-hIgGK-C, is shown in SEQ ID NO:7:

QIVLTQSPAIMASAPGEKVTMTCSASSSVSHMHWYQQKSGTSPKRWIYDTSRLASGV
PARFSGSGSGTSYSLTISSMEAEDAATYYCQQWSSHPWSFGGGTKLEIKRTVAAPSVF
IFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTY
SLSSTLTLSKADYEEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO:7).

[00140] The L chain variable region of anti-ASGPR 49C11 is shown in SEQ ID
NO.:8:

QIVLTQSPAIMASAPGEKVTMTCSASSSVSHMHWYQQKSGTSPKRWIYDTSRLASGV
PARFSGSGSGTSYSLTISSMEAEDAATYYCQQWSSHPWSFGGGTKLE (SEQ ID NO:8)

[00141] The DNA sequence of mAnti-ASGPR_49C11_7K-LV-hIgGK-C is shown in
SEQ ID NO:9:

ATGGATTTTCAAGTGCAGATTTTCAGCTTCCTGCTAATCAGTGCCTCAGTCATAAT
ATCCAGAGGACAAATTGTTCTCACCCAGTCTCCAGCAATCATGTCTGCATCTCCA
GGGGAGAAGGTCACCATGACCTGCAGTGCCAGCTCAAGTGTAAGTCACATGCAC
TGGTACCAGCAGAAGTCAGGCACTTCCCCCAAAGATGGATTTATGACACATCC
AGACTGGCTTCTGGAGTCCCTGCTCGCTTCAGTGGCAGTGGGTCTGGGACCTCTT
ACTCTCTCACAATCAGCAGCATGGAGGCTGAAGATGCTGCCACTTATTACTGCCA
GCAGTGGAGTAGTCACCCATGGTCGTTCCGGTGGAGGCACCAAACCTCGAGATCAA
ACGAACTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTG
AAATCTGGAAGTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGG
CCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGA
GTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCTGA
CGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTATGCCTGCGAAGTCACCC
ATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAG
(SEQ ID NO:9).

Anti-CD40-24A3-hIL-10

[00142] SEQ ID NO:10 shows a fusion protein of the heavy chain of the anti-CD40 24A3 antibody fused through a linker to human IL-10. The linker is underlined and the IL-10 amino acid sequence is in bold italics.

[00143] manti-hCD40_24A3.3F1_H-LV-hIgG4H-C-Flex-v1-***hIL-10*** antibody, SEQ ID NO:10:

VQLQESGPDLVKPSQSLSLTCTVTGYSITSDYSWHWIRQFPGNKLEWMGYIYYSGST
 NYNPSLKSRISITRDTSKNQFFLQLNSVTTEDSATYFCARFYYGYSFFDYWGQGTTLT
 VSSAKTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPA
 VLQSSGLYSLSSVTVPSSSLGKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPE
 FEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKT
 KPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREP
 QVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGS
 FFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGKASQTPTNTISVTP
TNNSTPTNNSNPKNP***ASPGQGTQSENSCTHFPGNLPNMLRDLRDAFSRVKTFQMKDQLDNLLLKESLLEDFKGYLGCA***
ALSEMIQFYLEEVMPPQAENQDPDIKAHVNSLG
ENLKTLLRLRRCHRFLPCENKSKAVEQVKNAFNKLQEKGIYKAMSEFDIFINYIEAY
MTMKIRN (SEQ ID NO:10).

[00144] The heavy chain of the anti-CD40 24A3 antibody from above is SEQ ID NO:11:

VQLQESGPDLVKPSQSLSLTCTVTGYSITSDYSWHWIRQFPGNKLEWMGYIYYSGST
 NYNPSLKSRISITRDTSKNQFFLQLNSVTTEDSATYFCARFYYGYSFFDYWGQGTTLT
 VSSAKTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPA
 VLQSSGLYSLSSVTVPSSSLGKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPE
 FEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKT
 KPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREP
 QVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGS
 FFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGKAS (SEQ ID NO:11).

[00145] The linker shown above is SEQ ID NO:4 and the IL-10 amino acid sequence is shown as SEQ ID NO:5.

[00146] The DNA sequence of the manti-hCD40_24A3.3F1_H-LV-hIgG4H-C-Flex-v1-***hIL-10*** antibody is shown in SEQ ID NO:12:

ATGAGAGTGCTGATTCTTTTGTGCCTGTTACAGCCTTTCCTGGTATCCTGTCTGA
TGTGCAGCTTCAGGAGTCAGGACCTGACCTGGTGAAACCTTCTCAGTCACTTTCA
CTCACCTGCACTGTCCTGGCTACTCCATCACCAGTGATTATAGCTGGCACTGGA
TCCGGCAGTTCCCAGGAAACAACTGGAATGGATGGGCTACATATATTACAGTG
GTAGCACTAACTACAACCCATCTCTCAAAAGTCGAATCTCTATCACTCGAGACAC
ATCCAAGAACCAGTTCTTCCTGCAGTTGAATTCTGTGACTACTGAGGACTCAGCC
ACATATTTCTGTGCAAGATTTTACTACGGTTATAGCTTCTTTGACTACTGGGGCCA
AGGCACCACTCTCACAGTCTCCTCAGCCAAAACAAAGGGCCCATCCGTCTTCCCC
CTGGCGCCCTGCTCCAGGAGCACCTCCGAGAGCACAGCCGCCCTGGGCTGCCTG
GTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACCTCAGGCGCCCTG
ACCAGCGGCGTGACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCC
TCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACGAAGACCTACACCT
GCAACGTAGATCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTTGAGTCCA
AATATGGTCCCCCATGCCCACCCTGCCCAGCACCTGAGTTCGAAGGGGGACCATC
AGTCTTCCTGTTCCCCCAAAACCCAAGGACACTCTCATGATCTCCCGGACCCCT
GAGGTCACGTGCGTGGTGGTGGACGTGAGCCAGGAAGACCCCGAGGTCCAGTTC
AACTGGTACGTGGATGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAG
GAGCAGTTCAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGG
ACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGGCCTCCCGT
CCTCCATCGAGAAAACCATCTCCAAGGCCAAAGGGCAGCCCCGAGAGCCACAGG
TGTACACCCTGCCCCCATCCCAGGAGGAGATGACCAAGAACCAGGTCAGCCTGA
CCTGCCTGGTCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAGAGCA
ATGGGCAGCCGGAGAACAACACTACAAGACCACGCCTCCCGTGCTGGACTCCGACG
GCTCCTTCTTCTCTACAGCAGGCTAACCGTGGACAAGAGCAGGTGGCAGGAGG
GGAATGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACACA
GAAGAGCCTCTCCCTGTCTCTGGGTAAAGCTAGTCAGACCCCCACCAACACCATC
AGCGTGACCCCCACCAACAACAGCACCCCCACCAACAACAGCAACCCCCAAGCCC
AACCCCGCTAGCCCAGGCCAGGGCACCCAGTCTGAGAACAGCTGCACCCACTTC
CCAGGCAACCTGCCTAACATGCTTCGAGATCTCCGAGATGCCTTCAGCAGAGTGA
AGACTTTCTTTCAAATGAAGGATCAGCTGGACAACCTTGTTGTTAAAGGAGTCCTT
GCTGGAGGACTTTAAGGGTTACCTGGGTTGCCAAGCCTTGTCTGAGATGATCCAG
TTTTACCTGGAGGAGGTGATGCCCCAAGCTGAGAACCAAGACCCAGACATCAAG
GCGCATGTGAACTCCCTGGGGGAGAACCTGAAGACCCCTCAGGCTGAGGCTACGG
CGCTGTCATCGATTTCTTCCCTGTGAAAACAAGAGCAAGGCCGTGGAGCAGGTG

AAGAATGCCTTTAATAAGCTCCAAGAGAAAGGCATCTACAAAGCCATGAGTGAG
TTTGACATCTTCATCAACTACATAGAAGCCTACATGACAATGAAGATACGAAACT
GA (SEQ ID NO:12).

[00147] The corresponding light chain amino acid sequence, manti-
hCD40_24A3.3F1_K-LV-hIgGK-C, is shown in SEQ ID NO:13:

QIVLTQSPAFMSASPGEKVTMTCSASSSVSYMHWYQQKSGTSPKRWIYDTSKLASG
VPAFSGSGSGTSYSLTISSMEAEDAATYYCQQWSSNPLTFGAGTKLEIKRTVAAPSV
FIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDST
YLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGECAS (SEQ ID NO:13).

[00148] The DNA sequence of manti-hCD40_24A3.3F1_K-LV-hIgGK-C is shown in
SEQ ID NO:14:

ATGGATTTTCAAGTGCAGATTTTCAGCTTCCTGCTAATCAGTGCCTCAGTCATAGT
ATCCAGAGGACAAATTGTTCTCACCCAGTCTCCAGCATTTCATGTCTGCATCTCCA
GGGGAGAAGGTCACCATGACCTGCAGTGCCAGCTCAAGTGTGAGTTACATGCAC
TGGTACCAGCAGAAGTCAGGCACCTCCCCCAAAGATGGATTTATGACACATCC
AAACTGGCTTCTGGAGTCCCTGCTCGCTTCAGTGGCAGTGGGTCTGGGACCTCTT
ACTCTCTCACAATCAGCAGCATGGAGGCTGAAGATGCTGCCACTTATTACTGCCA
GCAGTGGAGTAGTAACCCACTCACGTTTCGGTGCTGGGACCAAGCTCGAGATCAA
ACGAACTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTG
AAATCTGGAAGTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGG
CCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGA
GTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCTGA
CGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTATGCCTGCGAAGTCACCC
ATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTGCTA
GCTAG (SEQ ID NO:14).

Anti-DCIR-9E8-hIL-10

[00149] SEQ ID NO:15 shows a fusion protein of the heavy chain of the anti-DCIR
9E8 antibody fused through a linker to human IL-10. The linker is underlined and the IL-10
amino acid sequence is in bold italics.

[00150] mAnti-DCIR_9E8_H-LV-hIgG4H-C-Flex-v1-***hIL-10*** antibody, SEQ ID
NO:15:

QVTLKESGPGILQPSQTLSTCSFSGFSLSTSGMGLSWIRQPSGKGLEWLAHIYWDDD

KRYNPSLKSRLTISKDTSSNQVFLKITIVDTADAATYYCARSSHYGYGYGGYFDVW
 GAGTTVTVSSAKTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTS
 GVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKYTCNVDHKPSNTKVDKRVESKYGPP
 CPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSDQEDPEVQFNWYVDGVE
 VHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAK
 GQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPV
 LDDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLGLKASQTPTN
TISVTPTNNSPTNNSNPKNP***ASPGQGTQSENSCTHFPGNLPNMLRDLRDAFSRVKT***
FFQMKDQLDNLLLKESLLEDFKGYLGCQALSEMIQFYLEEVMPPQAENQDPDIKAHV
NSLGENLKTLLRLRLRRCHRLFPCENKSKAVEQVKNAFNKLQEKGIYKAMSEFDIFIN
YIEAYMTMKIRN (SEQ ID NO:15).

[00151] The heavy chain of the anti-DCIR 9E8 antibody from above is SEQ ID
 NO:16:

QVTLKESGPGILQPSQTLSTCSFSGFSLSTSGMGLSWIRQPSGKGLEWLAHIYWDDD
 KRYNPSLKSRLTISKDTSSNQVFLKITIVDTADAATYYCARSSHYGYGYGGYFDVW
 GAGTTVTVSSAKTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTS
 GVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKYTCNVDHKPSNTKVDKRVESKYGPP
 CPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSDQEDPEVQFNWYVDGVE
 VHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAK
 GQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPV
 LDDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLGLKAS (SEQ
 ID NO:16).

[00152] The H chain variable region of anti-DCIR 9E8 is shown in SEQ ID NO.:17:
 QVTLKESGPGILQPSQTLSTCSFSGFSLSTSGMGLSWIRQPSGKGLEWLAHIYWDDD
 KRYNPSLKSRLTISKDTSSNQVFLKITIVDTADAATYYCARSSHYGYGYGGYFDVW
 GAGTTVTVS.

[00153] The linker shown above is SEQ ID NO:18:
 QTPTNTISVTPTNNSPTNNSNPKNP (SEQ ID NO:18).

[00154] The IL-10 amino acid sequence is shown as SEQ ID NO:19:
 ASPGQGTQSENSCTHFPGNLPNMLRDLRDAFSRVKTFFQMKDQLDNLLLKESLLEDF
 KGYLGCQALSEMIQFYLEEVMPPQAENQDPDIKAHVNSLGENLKTLLRLRLRRCHRLF

CENKSKAVEQVKNAFNKLQEKGIIYKAMSEFDIFINYIEAYMTMKIRN (SEQ ID NO:19).

[00155] The corresponding DNA sequence for the IL-10 gene is shown as SEQ ID NO:20:

CGCTAGCCCAGGCCAGGGCACCCAGTCTGAGAACAGCTGCACCCACTTCCCAGG
CAACCTGCCTAACATGCTTCGAGATCTCCGAGATGCCTTCAGCAGAGTGAAGACT
TTCTTTCAAATGAAGGATCAGCTGGACAACCTTGTTGTTAAAGGAGTCCTTGCTGG
AGGACTTTAAGGGTTACCTGGGTTGCCAAGCCTTGTCTGAGATGATCCAGTTTTA
CCTGGAGGAGGTGATGCCCCAAGCTGAGAACCAAGACCCAGACATCAAGGCGCA
TGTGAACTCCCTGGGGGAGAACCTGAAGACCCTCAGGCTGAGGCTACGGCGCTG
TCATCGATTTCTTCCCTGTGAAAACAAGAGCAAGGCCGTGGAGCAGGTGAAGAA
TGCCTTTAATAAGCTCCAAGAGAAAGGCATCTACAAAGCCATGAGTGAGTTTGA
CATCTTCATCAACTACATAGAAGCCTACATGACAATGAAGATACGAAACTGA
(SEQ ID NO:20).

[00156] The DNA sequence of mAnti-DCIR_9E8_H-LV-hIgG4H-C-Flex-v1-*hIL-10* antibody is shown in SEQ ID NO:21:

ATGAACAGGCTTACTTCCTCATTGCTGCTGCTGATTGTCCCTGCATATGTCCTGTC
CCAGGTTACTCTGAAAGAGTCTGGCCCTGGGATATTGCAGCCCTCCCAGACCCCTC
AGTCTGACTTGTTCTTTCTCTGGGTTTTCACTGAGCACTTCTGGTATGGGTCTGAG
CTGGATTTCGTCAGCCTTCAGGAAAGGGTCTGGAGTGGCTGGCACACATTTACTGG
GATGATGACAAGCGCTATAACCCATCCCTGAAGAGCCGGCTCACAATCTCCAAG
GATACCTCCAGCAACCAGGTTTTCTCAAGATCACCATTGTGGACACTGCAGATG
CTGCCACATACTACTGTGCTCGAAGCTCCCATTACTACGGTTATGGCTACGGGGG
ATACTTCGATGTCTGGGGCGCAGGGACCACGGTCACCGTCTCCTCAGCCAAAACG
AAGGGCCCATCCGTCTTCCCCCTGGCGCCCTGCTCCAGGAGCACCTCCGAGAGCA
CAGCCGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTC
GTGGAACCTCAGGCGCCCTGACCAGCGGCGTGACACCTTCCCGGCTGTCCTACAG
TCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCAGCAGCTTGG
GCACGAAGACCTACACCTGCAACGTAGATCACAAGCCCAGCAACACCAAGGTGG
ACAAGAGAGTTGAGTCCAAATATGGTCCCCCATGCCACCCCTGCCAGCACCTGA
GTTCTGAAGGGGGACCATCAGTCTTCCCTGTTCCCCCAAAACCCAAGGACACTCTC
ATGATCTCCCGGACCCCTGAGGTCACGTGCGTGGTGGTGGACGTGAGCCAGGAA
GACCCCGAGGTCCAGTTCAACTGGTACGTGGATGGCGTGGAGGTGCATAATGCC

AAGACAAAGCCGCGGGAGGAGCAGTTCAACAGCACGTACCGTGTGGTCAGCGTC
 CTCACCGTCCTGCACCAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTC
 TCCAACAAAGGCCTCCCGTCCTCCATCGAGAAAACCATCTCCAAAGCCAAAGGG
 CAGCCCCGAGAGCCACAGGTGTACACCTGCCCCCATCCCAGGAGGAGATGACC
 AAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTACCCCAGCGACATC
 GCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACACTACAAGACCACGCC
 TCCCGTGCTGGACTCCGACGGCTCCTTCTTCTCTACAGCAGGCTAACCGTGGAC
 AAGAGCAGGTGGCAGGAGGGGAATGTCTTCTCATGCTCCGTGATGCATGAGGCT
 CTGCACAACCACTACACACAGAAGAGCCTCTCCCTGTCTCTGGGTAAAGCTAGTC
 AGACCCCCACCAACACCATCAGCGTGACCCCCACCAACAACAGCACCCCCACCA
 ACAACAGCAACCCCCAAGCCCAACCCCGCTAGCCCAGGCCAGGGCACCCAGTCTG
 AGAACAGCTGCACCCACTTCCCAGGCAACCTGCCTAACATGCTTCGAGATCTCCG
 AGATGCCTTCAGCAGAGTGAAGACTTTCTTTCAAATGAAGGATCAGCTGGACAA
 CTTGTTGTAAAGGAGTCCTTGCTGGAGGACTTTAAGGGTTACCTGGGTTGCCAA
 GCCTTGCTCTGAGATGATCCAGTTTTACCTGGAGGAGGTGATGCCCAAGCTGAGA
 ACCAAGACCCAGACATCAAGGCGCATGTGAACTCCCTGGGGGAGAACCTGAAGA
 CCCTCAGGCTGAGGCTACGGCGCTGTCATCGATTTCTTCCCTGTGAAAACAAGAG
 CAAGGCCGTGGAGCAGGTGAAGAATGCCTTTAATAAGCTCCAAGAGAAAGGCAT
 CTACAAAGCCATGAGTGAGTTTGACATCTTCATCAACTACATAGAAGCCTACATG
 ACAATGAAGATACGAAACTGA (SEQ ID NO:21).

[00157] The corresponding light chain amino acid sequence, mAnti-DCIR_9E8_K-LV-hIgGK-C, is shown in SEQ ID NO:22:

NIVLTQSPASLAVSLGQRATISCRASESIHSYGNSFLHWYQQKPGQPPKLLIYLASNLE
 SGVPARFSGSGSRTDFTLTIDPVEADDAATYYCQQNNEDPWTFGGGTKLEIKRTVAA
 PSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSK
 DSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO:22).

[00158] The L chain variable region of anti-DCIR 9E8 is shown in SEQ ID NO.:23:

NIVLTQSPASLAVSLGQRATISCRASESIHSYGNSFLHWYQQKPGQPPKLLIYLASNLE
 SGVPARFSGSGSRTDFTLTIDPVEADDAATYYCQQNNEDPWTFGGGTKLEIK.

[00159] The DNA sequence of the L chain variable region of the anti-DCIR 9E8 is shown in SEQ ID NO:24:

AACATTGTGCTGACCCAATCTCCAGCTTCTTTGGCTGTGTCTCTAGGGCAGAGGG
 CCACCATATCCTGCAGAGCCAGTGAAAGTATTCATAGTTATGGCAATAGTTTTCT

GCCTGGTACCAGCAGAAACCAGGACAGCCACCCAAACTCCTCATCTATCTTGCA
TCCAACCTAGAATCTGGGGTCCCTGCCAGGTTTCAGCGGCAGTGGGTCTAGGACA
GACTTCACCCTCACCATTGATCCTGTGGAGGCTGATGATGCTGCAACCTATTACT
GTCAGCAAAATAATGAGGATCCGTGGACGTTTCGGTGGAGGCACCAAGCTCGAGA
TCAAA (SEQ ID NO:24).

[00160] The leader sequence prior to the light chain amino acid sequence comprises:
METDTLLLWVLLLWVPGSTG (SEQ ID NO:25).

[00161] The corresponding DNA sequence of the leader sequence comprises:
ATGGAGACAGACACACTCCTGCTATGGGTGCTGCTGCTCTGGGTTCCAGGTTCCA
CAGGT (SEQ ID NO:26).

[00162] The DNA sequence of mAnti-DCIR_9E8_K-LV-hIgGK-C is shown in SEQ
ID NO:27:

ATGGAGACAGACACACTCCTGCTATGGGTGCTGCTGCTCTGGGTTCCAGGTTCCA
CAGGTAACATTGTGCTGACCCAATCTCCAGCTTCTTTGGCTGTGTCTCTAGGGCA
GAGGGCCACCATATCCTGCAGAGCCAGTGAAAGTATTCATAGTTATGGCAATAG
TTTTCTGCACTGGTACCAGCAGAAACCAGGACAGCCACCCAAACTCCTCATCTAT
CTTGCATCCAACCTAGAATCTGGGGTCCCTGCCAGGTTTCAGCGGCAGTGGGTCTA
GGACAGACTTCACCCTCACCATTGATCCTGTGGAGGCTGATGATGCTGCAACCTA
TACTGTGTCAGCAAAATAATGAGGATCCGTGGACGTTTCGGTGGAGGCACCAAGCT
CGAGATCAAACGAACTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGAT
GAGCAGTTGAAATCTGGAAGTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATC
CCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACT
CCCAGGAGAGTGTACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCA
GCACCCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTATGCCTGCG
AAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAG
AGTGTTAG (SEQ ID NO:27).

Anti-CD40-12E12-hIL-10

[00163] SEQ ID NO:28 shows a fusion protein of the heavy chain of the anti-DCIR
9E8 antibody fused through a linker to human IL-10. The linker is underlined and the IL-10
amino acid sequence is in bold italics.

[00164] mAnti- CD40_12E12.3F3_H-LV-hIgG4H-C-Flex-v1-***hIL-10*** antibody, SEQ
ID NO:28:

EVKLVESGGGLVQPGGSLKLSCATSGFTFSDYYMYWVRQTPEKRLEWVAYINSGGG
 STYYPD TVKGRFTISRDN AKNTLYLQMSRLKSEDTAMYYCARRGLPFHAMDYWGQ
 GTSVTVSSAKTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGV
 HTFPAVLQSSGLYSLSSVTVPSSSLGKTYTCNV DHKPSNTKVDKRVESKYGPCCPP
 CPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVDVVSQEDPEVQFNWYVDGVEVH
 NAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQ
 PREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLD
 SDGSFFLYSRLTVDKSRWQEGNVFSCSV MHEALHNHYTQKSLSLGLKASQTPTNTI
SVTPTNNSPTNNSNPKNPASPQGQTQSENSCTHFPGNLPNMLRDLRDAFSRVKTF
FQMKDQLDNL LKESLLEDFKGYLGCA LSEMIQFYLEEVMPQAENQDPDIKAHVN
SLGENLKT LRLRLRRCHRFLPCENKSKAVEQVKNAFNKLQEKGIYKAMSEFDIFINYI
EAYMTMKIRN (SEQ ID NO:28).

[00165] The heavy chain of the anti-CD40 12E12 antibody from above is SEQ ID NO:29:

EVKLVESGGGLVQPGGSLKLSCATSGFTFSDYYMYWVRQTPEKRLEWVAYINSGGG
 STYYPD TVKGRFTISRDN AKNTLYLQMSRLKSEDTAMYYCARRGLPFHAMDYWGQ
 GTSVTVSSAKTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGV
 HTFPAVLQSSGLYSLSSVTVPSSSLGKTYTCNV DHKPSNTKVDKRVESKYGPCCPP
 CPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVDVVSQEDPEVQFNWYVDGVEVH
 NAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQ
 PREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLD
 SDGSFFLYSRLTVDKSRWQEGNVFSCSV MHEALHNHYTQKSLSLGLKAS (SEQ ID NO:29).

[00166] The H chain variable region of anti-CD40 12E12 is shown in SEQ ID NO.:30:
 EVKLVESGGGLVQPGGSLKLSCATSGFTFSDYYMYWVRQTPEKRLEWVAYINSGGG
 STYYPD TVKGRFTISRDN AKNTLYLQMSRLKSEDTAMYYCARRGLPFHAMDYWGQ
 GTSVTVS.

[00167] The CDRs of the The H chain variable of anti-CD40 12E12 are CDR1:
 SASQGISNYLN (SEQ ID NO:31), CDR2: AYINSGGGSTYYPD TVK (SEQ ID NO:32),
 and CDR3: RRGLPFHAMD (SEQ ID NO:33).

[00168] The linker shown above is SEQ ID NO:4 and the IL-10 amino acid sequence
 is shown as SEQ ID NO:5.

[00169] The DNA sequence of mAnti- CD40_12E12.3F3_H-LV-hIgG4H-C-Flex-v1-hIL-10 antibody is shown in SEQ ID NO:34:

ATGAACTTGGGGCTCAGCTTGATTTTCCTTGTCTTGTGTTTAAAAGGTGTCCAGTG
TGAAGTGAAGCTGGTGGAGTCTGGGGGAGGCTTAGTGCAGCCCGGAGGGTCCCT
GAAACTCTCCTGTGCAACCTCTGGATTCACTTTCAGTGACTATTACATGTATTGGG
TTCGCCAGACTCCAGAGAAGAGGCTGGAGTGGGTCCCATACATTAATTCTGGTG
GTGGTAGCACCTATTATCCAGACACTGTAAAGGGCCGATTCACCATCTCCAGAGA
CAATGCCAAGAACACCCTGTACCTGCAAATGAGCCGGCTGAAGTCTGAGGACAC
AGCCATGTATTACTGTGCAAGACGGGGGTACCGTTCCATGCTATGGACTATTGG
GGTCAAGGAACCTCAGTCACCGTCTCCTCAGCCAAAACGAAGGGCCCATCCGTCT
TCCCCCTGGCGCCCTGCTCCAGGAGCACCTCCGAGAGCACAGCCGCCCTGGGCTG
CCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCTGGAAGTCAAGGCGCC
CTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACT
CCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACGAAGACCTACA
CCTGCAACGTAGATCACAAAGCCCAGCAACACCAAGGTGGACAAGAGAGTTGAGT
CCAAATATGGTCCCCCATGCCACCCCTGCCCAGCACCTGAGTTCGAAGGGGGACC
ATCAGTCTTCCTGTTCCCCCAAAAACCCAAGGACACTCTCATGATCTCCCGGACC
CCTGAGGTCACGTGCGTGGTGGTGGACGTGAGCCAGGAAGACCCCGAGGTCCAG
TTCAACTGGTACGTGGATGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGG
GAGGAGCAGTTCAACAGCACGTACCGTGTGGTCAAGCTCCTCACCCTCCTGCACC
AGGACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGGCCTCC
CGTCTCCATCGAGAAAACCATCTCCAAGCCAAAGGGCAGCCCCGAGAGCCAC
AGGTGTACACCCTGCCCCCATCCCAGGAGGAGATGACCAAGAACCAGGTACGCC
TGACCTGCCTGGTCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAGA
GCAATGGGCAGCCGGAGAACAACACTACAAGACCACGCCTCCCGTGCTGGACTCCG
ACGGCTCCTTCTTCTCTACAGCAGGCTAACCGTGGACAAGAGCAGGTGGCAGG
AGGGGAATGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACAC
ACAGAAGAGCCTCTCCCTGTCTCTGGGTAAAGCTAGTCAGACCCCCACCAACACC
ATCAGCGTGACCCCCACCAACAACAGCACCCCCACCAACAACAGCAACCCCCAAG
CCCAACCCCGCTAGCCCAGGCCAGGGCACCCAGTCTGAGAACAGCTGCACCCAC
TTCCCAGGCAACCTGCCTAACATGCTTCGAGATCTCCGAGATGCCTTCAGCAGAG
TGAAGACTTTCTTTCAAATGAAGGATCAGCTGGACAACCTTGTTGTTAAAGGAGTC
CTTGCTGGAGGACTTTAAGGGTTACCTGGGTTGCCAAGCCTTGCTCTGAGATGATC
CAGTTTTACCTGGAGGAGGTGATGCCCCAAGCTGAGAACCAAGACCCAGACATC

AAGGCGCATGTGAACTCCCTGGGGGAGAACCTGAAGACCCTCAGGCTGAGGCTA
CGGCGCTGTCATCGATTTCTTCCCTGTGAAAACAAGAGCAAGGCCGTGGAGCAG
GTGAAGAATGCCTTTAATAAGCTCCAAGAGAAAGGCATCTACAAAGCCATGAGT
GAGTTTGACATCTTCATCAACTACATAGAAGCCTACATGACAATGAAGATACGA
AACTGA (SEQ ID NO:34).

[00170] The corresponding light chain amino acid sequence, mAnti-
CD40_12E12.3F3_K-V-hIgGK-C, is shown in SEQ ID NO:35:

DIQMTQTTSSLSASLGDRVTISCSASQGISNYLNWYQQKPDGTVKLLIYYTSILHSGVP
SRFSGSGSGTDYSLTIGNLEPEDIATYYCQQFNKLPPTFGGGKLEIKRTVAAPSVFIFP
PSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSL
SSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO:35).

[00171] The L chain variable region of anti-CD40 12E12 is shown in SEQ ID NO.:36:
DIQMTQTTSSLSASLGDRVTISCSASQGISNYLNWYQQKPDGTVKLLIYYTSILHSGVP
SRFSGSGSGTDYSLTIGNLEPEDIATYYCQQFNKLPPTFGGGKLEIK (SEQ ID NO:36).

[00172] The CDRs of the L chain variable of anti-CD40 12E12 are CDR1:
SASQGISNYLN (SEQ ID NO:37), CDR2: YTSILHS (SEQ ID NO:38), and CDR3:
QQFNKLPP (SEQ ID NO:39).

[00173] The DNA sequence of mAnti-CD40_12E12.3F3_K-V-hIgGK-C is shown in
SEQ ID NO:40:

ATGATGTCCTCTGCTCAGTTCCTTGGTCTCCTGTTGCTCTGTTTTCAAGGTACCAG
ATGTGATATCCAGATGACACAGACTACATCCTCCCTGTCTGCCTCTCTAGGAGAC
AGAGTCACCATCAGTTGCAGTGCAAGTCAGGGCATTAGCAATTATTTAACTGGT
ATCAGCAGAAACCAGATGGAAGTGTAAACTCCTGATCTATTACACATCAATTTT
ACACTCAGGAGTCCCATCAAGGTTCAAGTGGCAGTGGGTCTGGGACAGATTATTCT
CTCACCATCGGCAACCTGGAACCTGAAGATATTGCCACTTACTATTGTCAGCAGT
TTAATAAGCTTCCTCCGACGTTCCGTGGAGGCACCAAACCTCGAGATCAAACGAA
CTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCT
GGAAGTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAG
TACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCA
CAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCCTGACGCTGA
GCAAAGCAGACTACGAGAAACACAAAGTCTATGCCTGCGAAGTCACCCATCAGG

GCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAG (SEQ ID NO:40).

IgG-hIL10 Control

[00174] SEQ ID NO:41 shows a fusion protein of the heavy chain of the IgG control antibody fused through a linker to human IL-10. The linker is underlined and the IL-10 amino acid sequence is in bold italics.

[00175] hIgG4H-Flex-v1-***hIL-10*** antibody, SEQ ID NO:41:

RLQLQESGPGLLKPSVTLSLTCTVSGDSVASSSYWGWVRQPPGKGLEWIGTINFSG
 NMYYSPLRSRVTMSADMSSENSFYCLKDSVTAADTAVYYCAAGHLVMGFGAHWG
 QGKLVSVSPASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSG
 VHTFPAVLQSSGLYSLSSVVTVPSSSLGKTYTCNVDPHKPSNTKVDKRVESKYGPPC
 PPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVE
 VHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAK
 GQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPV
 LDDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLGLKASQTPTN
TISVTPTNNSPTNNSNPKNP***ASPGQGTQSENSCTHFPGNLPNMLRDLRDAFSRVKT***
FFQMKDQLDNLKESLLEDFKGYLGCQALSEMIQFYLEEVMPPQAENQDPDIKAHV
NSLGENLKTLLRLRLRRCHRFLPCENKSKAVEQVKNAFNKLQEKGIYKAMSEFDIFIN
YIEAYMTMKIRN (SEQ ID NO:41).

[00176] The linker shown above is SEQ ID NO:4 and the IL-10 amino acid sequence is shown as SEQ ID NO:5.

[00177] The DNA sequence of hIgG4H-Flex-v1-***hIL-10*** antibody antibody is shown in SEQ ID NO:42:

ATGGACCTCCTGTGCAAGAACATGAAGCACCTGTGGTTCTTCCTCCTGCTGGTGG
 CGGCTCCCAGATGGGTCCTGTCCCGGCTGCAGCTGCAGGAGTCGGGCCCAGGCCT
 GCTGAAGCCTTCGGTGACCCTGTCCCTCACCTGCACTGTCTCGGGTGACTCCGTC
 GCCAGTAGTTCTTATTACTGGGGCTGGGTCCGTCAGCCCCCAGGGAAGGGACTCG
 AGTGGATAGGGACTATCAATTTTAGTGGCAATATGTATTATAGTCCGTCCCTCAG
 GAGTCGAGTGACCATGTCCGGCAGACATGTCCGAGAACTCCTTCTATCTGAAATTG
 GACTCTGTGACCGCAGCAGACACGGCCGTCTATTATTGTGCGGCAGGACACCTCG
 TTATGGGATTTGGGGCCCCACTGGGGACAGGGAAAACCTGGTCTCCGTCTCTCCAGC
 TTCCACCAAGGGCCCATCCGTCTTCCCCCTGGCGCCCTGCTCCAGGAGCACCTCC

GAGAGCACAGCCGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTG
ACGGTGTCTGTGGA^{ACT}CAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTG
TCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAG
CAGCTTGGGCACGAAGACCTACACCTGCAACGTAGATCACAAGCCCAGCAACAC
CAAGGTGGACAAGAGAGTTGAGTCCAAATATGGTCCCCCATGCCCACCCTGCCC
AGCACCTGAGTTCGAAGGGGGACCATCAGTCTTCCCTGTTCCCCCAAAACCCAAG
GACACTCTCATGATCTCCCGGACCCCTGAGGTACGTGCGTGGTGGTGGACGTGA
GCCAGGAAGACCCCGAGGTCCAGTTCAACTGGTACGTGGATGGCGTGGAGGTGC
ATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTTCAACAGCACGTACCGTGTGG
TCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAACGGCAAGGAGTACAAGT
GCAAGGTCTCCAACAAAGGCCTCCCGTCCTCCATCGAGAAAACCATCTCCAAAG
CCAAAGGGCAGCCCCGAGAGCCACAGGTGTACACCCTGCCCCCATCCCAGGAGG
AGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTACCCCA
GCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACA^{ACT}TACAAG
ACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCTCTACAGCAGGCTAA
CCGTGGACAAGAGCAGGTGGCAGGAGGGGAATGTCTTCTCATGCTCCGTGATGC
ATGAGGCTCTGCACAACCACTACACACAGAAGAGCCTCTCCCTGTCTCTGGGTAA
AGCTAGTCAGACCCCCACCAACACCATCAGCGTGACCCCCACCAACAACAGCAC
CCCCACCAACAACAGCAACCCCAAGCCCAACCCCGCTAGCCCAGGCCAGGGCAC
CCAGTCTGAGAACAGCTGCACCCACTTCCCAGGCAACCTGCCTAACATGCTTCGA
GATCTCCGAGATGCCTTCAGCAGAGTGAAGACTTTCTTTCAAATGAAGGATCAGC
TGGACA^{ACT}TGTTGTTAAAGGAGTCCTTGCTGGAGGACTTTAAGGGTTACCTGGG
TTGCCAAGCCTTGCTGAGATGATCCAGTTTACCTGGAGGAGGTGATGCCCCAA
GCTGAGAACCAAGACCCAGACATCAAGGCGCATGTGAACTCCCTGGGGGAGAAC
CTGAAGACCCTCAGGCTGAGGCTACGGCGCTGTCATCGATTCTTCCCTGTGAAA
ACAAGAGCAAGGCCGTGGAGCAGGTGAAGAATGCCTTTAATAAGCTCCAAGAGA
AAGGCATCTACAAAGCCATGAGTGAGTTTGACATCTTCATCAACTACATAGAAGC
CTACATGACAATGAAGATACGAAACTGA (SEQ ID NO:42).

[00178] The corresponding light chain amino acid sequence hIgGK, is shown in SEQ ID NO:43:

DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGV
PSRFSGSGSGTDFTLTISLQPEDFATYYCQQSYSTPYTFGQGTKLEIKRTVAAPSVFIF

PPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYS
LSSTLTLSKADYEHKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO:43).

[00179] The DNA sequence of hIgGK is shown in SEQ ID NO:44:

ATGAGGGTCCCCGCTCAGCTCCTGGGGCTCCTGCTACTCTGGCTCCGAGGTGCCA
GATGTGACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGA
CAGAGTCACCATCACTTGCCGGGCAAGTCAGAGCATTAGCAGCTATTTAAATTGG
TATCAGCAGAAACCAGGGAAAGCCCCCTAAGCTCCTGATCTATGCTGCATCCAGTT
TGCAAAGTGGGGTCCCATCAAGGTTCAAGTGGCAGTGGATCTGGGACAGATTTCA
CTCTCACCATCAGCAGTCTCCAACCTGAAGATTTTGCAACTTACTACTGTCAACA
GAGTTACAGTACCCCGTACACTTTTGGCCAGGGGACCAAGCTGGAGATCAAACG
AACTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAA
TCTGGAAGTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCA
AAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTG
TCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCTGACGC
TGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATC
AGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAG (SEQ
ID NO:44).

[00180] Shown below are further examples of antibodies and antibody fragments
useful in the methods and compositions described herein.

Anti-Dectin-1 mAbs

[00181] manti-Dectin-1-11B6.4-H-V-hIgG4H-C]; SEQ ID NO:45:

QVQLKESGPGLVAPSQSL SITCSVSGFSLSNYDISWIRQPPGKGLEWLGMWMTGGGA
NYNSAFMSRLSINKDNSKSQVFLKMNNLQTDDTAIYYCVRDAVRYWNFDVWGAGT
TVTVSSAKTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHT
FPAVLQSSGLYSLSSVTVPSSSLGTKTYTCNV DHKPSNTKVDKR VESKYGPPCPPCP
APEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVDVVSQEDPEVQFNWYVDGVEVHNA
KTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPR
EPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSD
GSFFLYSRLTVDKSRWQEGNVFSCSV MHEALHNHYTQKSLSLSLGKAS (SEQ ID
NO:45).

[00182] The above sequence is a chimera between the H chain variable region of the
mAb 11B6.4 and the C region of hIgG4.

[00183] The H chain variable region of the mAb 11B6.4 is shown in SEQ ID NO:46:
 QVQLKESGPGLVAPSQSL SITCSVSGFSLSNYDISWIRQPPGKGLEWLGVMWTGGGA
 NYNSAFMSRLSINKDNSKSQVFLKMNNLQTDDTAIYYCVRDAVRYWNFDVWGAGT
 TVTVSSAKTK (SEQ ID NO:46).

[00184] [manti-Dectin-1-11B6.4-K-LV-hIgGK-C] is the corresponding L chain chimera; SEQ ID NO:47:
 QIVLSQSPAILSASPGEKVTMTCRASSSVSYIHWYQQKPGSSPKPWIYATSHLASGVP
 ARFSGSGSGTSYSLTISRVEAEDTATYYCQQWSSNPFTFGSGTKLEIKRTVAAPS VFIF
 PPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYS
 LSSTLTLSKADYEEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO:47).

[00185] The L chain variable region of the manti-Dectin-1-11B6.4-K-LV-hIgGK-C is shown in SEQ ID NO:48:
 QIVLSQSPAILSASPGEKVTMTCRASSSVSYIHWYQQKPGSSPKPWIYATSHLASGVP
 ARFSGSGSGTSYSLTISRVEAEDTATYYCQQWSSNPFTFGSGTK (SEQ ID NO:48).

[00186] manti-Dectin-1-15E2.5-H-V-hIgG4H-C]; SEQ ID NO:49:
 QVQLQQSGAELARPGASVKMSCKASGYTFTTYTMHWVKQRPGQGLEWIGYINPSSG
 YTNYNQKFKDKATLTADKSSSTASMQLSLTSEDSAVYYCARERAVLPYAMDYW
 GQGTSVTVSSAKTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTS
 GVHTFPAVLQSSGLYSLSSVVTVPSSSLGKTYTCNVDPHKPSNTKVDKRVESKYGPP
 CPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVE
 VHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAK
 GQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPV
 LDDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMEALHNHYTQKSLSLGLKAS (SEQ
 ID NO:49).

[00187] The above sequence is a chimera between the H chain variable region of the mAb 15E2.5 and the C region of hIgG4.

[00188] The H chain variable region of the mAb 15E2.5 is shown in SEQ ID NO:50:
 QVQLQQSGAELARPGASVKMSCKASGYTFTTYTMHWVKQRPGQGLEWIGYINPSSG
 YTNYNQKFKDKATLTADKSSSTASMQLSLTSEDSAVYYCARERAVLPYAMDYW
 GQGTSVTVSSAKTK (SEQ ID NO:50).

[00189] [manti-Dectin-1-15E2.5-K-V-hIgGK-C] is the corresponding L chain chimera; SEQ ID NO:51:

QIVLTQSPAVMSASPGEKVTITCTASSSLSYMHWFFQKPGTSPKLWLYSTSILASGVP
TRFSGSGSGTSYSLTISRMEAEDAATYYCQQRSSSPFTFGSGTKLEIKRTVAAPS VFIFP
PSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSL
SSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO:51).

[00190] The L chain variable region of the manti-Dectin-1-15E2.5-K-V-hIgGK-C is shown in SEQ ID NO:52:

QIVLTQSPAVMSASPGEKVTITCTASSSLSYMHWFFQKPGTSPKLWLYSTSILASGVP
TRFSGSGSGTSYSLTISRMEAEDAATYYCQQRSSSPFTFGSGTK (SEQ ID NO:52).

[00191] manti-Dectin-1-2D8.2D4-H-V-hIgG4H-C]; SEQ ID NO:53:

EVQLQQSGPELEKPGASVKISCKASGYSFTGYNMNWKQSNNGKSLEWIGNIDPYYG
DTNYNQKFKGKATLTVDKSSSTAYMHLKSLTSEDSAVYYCARPYGSEAYFAYWGQ
GTLVTVSAAKTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSG
VHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPC
PPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVE
VHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAK
GQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPV
LDSGDGSFFLYSRLTVDKSRWQEGNVFSCSVMHREALHNHYTQKSLSLGLKAS (SEQ
ID NO:53).

[00192] The above sequence is a chimera between the H chain variable region of the mAb 2D8.2D4 and the C region of hIgG4.

[00193] The H chain variable region of the mAb 2D8.2D4 is shown in SEQ ID NO:54:
EVQLQQSGPELEKPGASVKISCKASGYSFTGYNMNWKQSNNGKSLEWIGNIDPYYG
DTNYNQKFKGKATLTVDKSSSTAYMHLKSLTSEDSAVYYCARPYGSEAYFAYWGQ
GTLVTVSAAKTK (SEQ ID NO:54).

[00194] [manti-Dectin-1-2D8.2D4-K-V-hIgGK-C] is the corresponding L chain chimera; SEQ ID NO:55:

DIVMTQSPATLSVTPGDRVSLSCRASQISDYLHWYQQKSHESPRLLIKYAAQSISGIP
SRFSGSGSGSDFTLSINGVEPEDVGVYYCQNGHSFPYTFGGGTKLEIKRTVAAPS VFIF
PPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYS
LSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO:55).

[00195] The L chain variable region of the manti-Dectin-1-2D8.2D4-K-V-hIgGK-C is shown in SEQ ID NO:56:

DIVMTQSPATLSVTPGDRVSLSCRASQSISDYLHWYQQKSHESPRLLIKYAAQSISGIP
SRFSGSGSGSDFTLSINGVEPEDVGVIYCCQNGHSFPYTFGGGTK (SEQ ID NO:56).

Anti-DC ASGPR mAbs

[00196] [mAnti-ASGPR—4G2.2-Hv-V-hIgG4H-C]; SEQ ID NO.:57:

QIQLVQSGPELKKPGETVKISKASGYTFTNYGMNWVKQVPGKGLRWMGWMDTFT
GEPTYADDFKGRFAFSLETSASTAYLQINSLKNEDTATYFCARGGILRLNYFDYWGQ
GTTTLTVSSAKTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGV
HTFPAVLQSSGLYSLSSVTVPSSSLGKTYTCNVDPKPSNTKVDKRVESKYGPCCPP
CPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSDQEDPEVQFNWYVDGVEVH
NAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQ
PREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD
SDGSFFLYSRLTVDKSRWQEGNVFSCSVMEALHNHYTQKSLSLGLKAS (SEQ ID
NO:57).

[00197] The above sequence is a chimera between the H chain variable of the mAb
4G2.2 and the C region of hIgG4.

[00198] The H chain variable of the mAb 4G2.2 is shown in SEQ ID NO.:58:

QIQLVQSGPELKKPGETVKISKASGYTFTNYGMNWVKQVPGKGLRWMGWMDTFT
GEPTYADDFKGRFAFSLETSASTAYLQINSLKNEDTATYFCARGGILRLNYFDYWGQ
GTTTLTVSSAKTK (SEQ ID NO:58).

[00199] [mAnti-ASGPR—4G2.2-Kv-V-hIgGK-C] is the corresponding L chain
chimera; SEQ ID NO.:59:

DIQMTQSSSSFSVSLGDRVITITCKASEDIYNRLGWYQQKPGNAPRLLISGATSLETGV
PSRFSGSGSGKDYSITSLQTEDLATYYCQQCWTSPTFTFGGGTKLEIKRTVAAPSVF
IFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKIDSTY
SLSTLTLSKADYEEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO:59).

[00200] The L chain variable region of the mAnti-ASGPR—4G2.2-Kv-V-hIgGK-C is
shown in SEQ ID NO.:60:

DIQMTQSSSSFSVSLGDRVITITCKASEDIYNRLGWYQQKPGNAPRLLISGATSLETGV
PSRFSGSGSGKDYSITSLQTEDLATYYCQQCWTSPTFTFGGGTKLEI (SEQ ID
NO:60).

[00201] [mAnti-ASGPR—5F10H-LV-hIgG4H-C] (SEQ ID NO.:61):

EVQLQQSGPELVKPGASVKMSCKASGYTFTDYYMKWVKQSHGKSLEWIGDINPNY

GDTFYNQKFEGKATLTVDKSSRTAYMQLNSLTSEDSAVYYCGRGDYGYFDVWGAG
 TTVTVSSAKTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVH
 TFP AVLQSSGLYSLSSVVTVPSSSLGTKTYTCNV DHKPSNTKVDKR VESKYGPPCPPC
 PAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSDQEDPEVQFNWYVDGVEVHN
 AKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQP
 REPQVYTLPPS QEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD S
 DGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLLSLGKAS (SEQ ID
 NO:61).

[00202] The above sequence is a chimera between the H chain variable of the mAb 5F10 and the C region of hIgG4.

[00203] The H chain variable of the mAb 5F10 is shown in SEQ ID NO.:62:
 EVQLQQSGPELVKPGASVKMSCKASGYTFTDYMKWVKQSHGKSLEWIGDINPNY
 GDTFYNQKFEGKATLTVDKSSRTAYMQLNSLTSEDSAVYYCGRGDYGYFDVWGAG
 TTVTVSSAKTK (SEQ ID NO:62).

[00204] [mAnti-ASGPR—5F10K-LV-hIgGK-C] is the corresponding L chain chimera; SEQ ID NO.:63:
 DIVMTQSHKFMSTSVGDRVSITCKASQDVGTAVAWYQQKPGQSPKLLIYWASTRHT
 GVPDRFTGSGSGTDFTLTINNVSQEDLADYFCQQYSSNPYMFGGGKLEIKRTVAAP
 SVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKD
 STYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO:63).

[00205] The L chain variable region of the mAnti-ASGPR-5F10K-LV-hIgGK-C is shown in SEQ ID NO.:64:
 DIVMTQSHKFMSTSVGDRVSITCKASQDVGTAVAWYQQKPGQSPKLLIYWASTRHT
 GVPDRFTGSGSGTDFTLTINNVSQEDLADYFCQQYSSNPYMFGGGKLEI (SEQ ID
 NO:64).

[00206] [mAnti-ASGPR-1H11H-V-hIgG4H-C] (SEQ ID NO.:65):
 QLQQSGPELVKPGASVKISCKTSGYTFTEYTMHWVRQSHGKSLEWIGGINPINGGPT
 YNQKFKGKATLTVDKSSSTAYMELRSLTSEDSAVYYCARWDYGSRDVMDYWGQG
 TSVTVSSAKTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVH
 TFP AVLQSSGLYSLSSVVTVPSSSLGTKTYTCNV DHKPSNTKVDKR VESKYGPPCPPC
 PAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSDQEDPEVQFNWYVDGVEVHN
 AKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQP

REPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSLRTVLDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLGLGKAS (SEQ ID NO:65).

[00207] The above sequence is a chimera between the H chain variable of the mAb 1H11 and the C region of hIgG4.

[00208] The H chain variable of the mAb 1H11 is shown in SEQ ID NO.:66:
QLQQSGPELVKPGASVKISCKTSGYTFTETMHWVRQSHGKSLEWIGGINPINGGPT
YNQKFKGKATLTVDKSSSTAYMELRSLTSEDSAVYYCARWDYGSRDVMDYWGQG
TSVTVSSAKTK (SEQ ID NO:66).

[00209] [mAnti-ASGPR-1H11K-LV-hIgGK-C] is the corresponding L chain chimera, SEQ ID NO.:67:

NIVMTQSPKSMMSVGERVTLSCKASENVGTYVSWYQQRPEQSPKLLIYGASNRYT
GVPDRFTGSGSATDFTLTISVQAEDLADYHCGQTYSYIFTFGSGTKLEIKRTVAAPS
VFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDS
TYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO:67).

[00210] The L chain variable region of the mAnti-ASGPR-1H11K-LV-hIgGK-C is shown in SEQ ID NO.:68:

NIVMTQSPKSMMSVGERVTLSCKASENVGTYVSWYQQRPEQSPKLLIYGASNRYT
GVPDRFTGSGSATDFTLTISVQAEDLADYHCGQTYSYIFTFGSGTKLE (SEQ ID NO:68).

[00211] manti-hASGPR-6.3H9.1D11H (heavy chain) SEQ ID NO: 69:

VQLQQSGAELVRPGTSVKMSCEAARFTFSNYWIGWVKQRPGHGLEWIGDIFPGGDY
TNYNKKFKDKATLTADTSSSTAYMQLSSLTSEDSAIYYCARSDYGGYYVFDYWGQG
TTLTVSSAKTKGPSVFPLAPCSRSTSESTAALGLVKDYFPEPVTVSWNSGALTSGVH
TFPAVLQSSGLYSLSSVVTVPSSSLGTKYTCNVDPKPSNTKVDKRVESKYGPCCPPC
PAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHN
AKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQP
REPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSLRTVLDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLGLGK (SEQ ID NO:69).

[00212] manti-hASGPR_6.3H9.1D11K (light chain) SEQ ID NO: 70:

DIVMSQSPSSLA VSVGEKVTMSCKSSQNLLYSSNQKNYLAWYQQKPGQSPKLLIYW

ASTRESGVPDRFTGSGSGTDFTLTISSVKAEDLAVYYCQQYYSPYTFGGGKLEIKR
TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTE
QDSKDYSLSSLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID
NO:70).

[00213] manti-hASGPR-5H8.1D4H (heavy chain) SEQ ID NO: 71:

AQIQLVQSGPELKKPGETVKISCKASGYTFTDYSVHWVKQAPGKGLKWMGWINTET
GEPTYADDLKGRFAFSLETSASTAYLQINNLTNEDTATYFCAKPTYRFFDYWGQGT
LTASSAKTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTF
PAVLQSSGLYSLSSVVTVPSSSLGKTKYTCNVDHKPSNTKVDKRVESKYGPPCPPCPA
PEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVDVVSQEDPEVQFNWYVDGVEVHNAK
TKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPRE
PQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDG
SFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLGLGK (SEQ ID NO:71).

[00214] manti-hASGPR-5H8.1D4K (light chain) SEQ ID NO: 72:

DIVMSQSPSSLAVSAGEKVTMSCKSSQSLNSTRKNYLAWYQQKPGQSPKLLIYW
ASTRESGVPDRFTGSGSGTDFTLTISSVQAEDLAVYYCKQSYNLWTFGGGKLEIKRT
VAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQ
DSKDYSLSSLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID
NO:72).

anti-CD40 mAbs

[00215] anti-CD40-12B4.2C10, heavy chain, (SEQ ID NO:73:

MEWSWIFLFLLSGTAGVHSEVQLQQSGPELVKPGASVKMSCKASGYTFTDYVLHW
VKQKPGQGLEWIGYINPYNDGTYNEKFKGKATLTSDKSSSTAYMELSSLTSEDSAV
YYCARGYPAYSGYAMDYWGQGTSTVTVSSAKTTPPSVYPLAPGSAAQTNSMVTLC
LVKGYFPEPVTVTWNSGSLSSGVHTFPAVLQKGEFV (SEQ ID NO:73).

[00216] anti-CD40-12B4.2C10, light chain, SEQ ID NO:74:

MMSSAQFLGLLLLCFQGTRCDIQMTQTSSLSASLGDRVTISCRASQDISNYLNWYQ
QKPDGTVKLLIYYTSRLHSGVPSRFSGSGSGTDYSLTISNLEQEDIATYFCHHGNTLP
WTFGGGKLEIKRADAAPTVSIFPPSSEQLTSGGASVVCFLNNTFYPKDINVKWKIDGS
ERQNGVLNSWTDQDSKDYSLSSLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
RNEC (SEQ ID NO:74).

[00217] anti-CD40-12B4.2C10, light chain - alternative clone (17K6), SEQ ID NO:75:
MDFQVQIFSFLISASVIMSRGQIVLTQSPAILSASPGEKVTMTCSASSSVSYMRYQQ
KPGSSPKPWIYGTSNLASGVPARFSGSGSGTSYSLTISSMEAEDAATYYCQQYHSYPL
TFGAGTKLELKRADAAPTVSIFPPSSEQLTSGGASVVCFLNNFYPKDINVKWKIDGSE
RQNGVLNSWTDQDSKDSTYSMSSTLTTLTKDEYERHNSYTCEATHKTSTSPIVKSFNR
NEC (SEQ ID NO:75).

[00218] anti-CD40_11B6.1C3, heavy chain, SEQ ID NO:76:
MGWSWIFLFLLSGTAGVLSEVQLQQSGPELVKPGASVKISCKASGYSTGYMHVW
KQSHVKSLEWIGRINPYNGATSYNQNFKDKASLTVDKSSSTAYMELHSLTSEDSAVY
YCAREDYVYWGQGTTTLTVSSAKTTPPSVYPLAPGSAAQTNSMVTLGCLVKGYFPEP
VTVTWNSGSLSSGVHTFPAVLQKGEFV (SEQ ID NO:76).

[00219] anti-CD40_11B6.1C3, light chain, SEQ ID NO:77:
MKLPVRLLVLMFWIPASSSDVVMQTPLSLPVSLGDQASISCRSSQSLVHSNGNTYL
HWYLVKPGQSPKLLIYKVSNRFSGVPRDFSGSGSGTDFALKISRVEAEDLGVIYFCSQS
THVPWTFGGGTKLEIKRADAAPTVSIFPPSSEQLTSGGASVVCFLNNFYPKDINVKWK
IDGSERQNGVLNSWTDQDSKDSTYSMSSTLTTLTKDEYERHNSYTCEATHKTSTSPIV
KSFNRNEC (SEQ ID NO:77).

anti-LOX-1 Abs

[00220] [mAnti-LOX-1-11C8H-LV-hIgG4H-C], heavy chain, SEQ ID NO:78:
EVQLQQSGTVLARPGASVKMSCKASGYTFTSYWMHWVKQRPGQGLEWIGAIYPGN
SDTTYNQKFKGKAKLTAVTSTSTAYMELSSLTNEDSAVYYCTPTYFQDYWGQGTSL
TVSSAKTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPA
AVLQSSGLYSLSVTVPSSSLGKTYTCNVDPKPSNTKVDKRVESKYGPPCPPCPAP
EFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSDPEVQFNWYVDGVEVHNAKT
KPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREP
QVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGS
FFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLGLKAS (SEQ ID
NO:78).

[00221] The H chain variable of the Ab 11C8 is shown in SEQ ID NO:79:
EVQLQQSGTVLARPGASVKMSCKASGYTFTSYWMHWVKQRPGQGLEWIGAIYPGN
SDTTYNQKFKGKAKLTAVTSTSTAYMELSSLTNEDSAVYYCTPTYFQDYWGQGTSL
TVSSAKTK (SEQ ID NO:79).

[00222] [mAnti-LOX-1-11C8K-LV-hIgGK-C], light chain, SEQ ID NO:80:
 DVVMTQTPLTSLVTIGQPASISCKSSQSLLDSDGKTYLNWFLQRPQGSPKRLIYLVSK
 LD SGVPDRFTGSGSGTDFTLKISRVEAEDLG VYYCWQGTHFPWTFGGG TKLEIKRTV
 AAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQD
 SKDSTYLSSTLTLSKADYEKHKVYACE VTHQGLSSPVTKSFNRGEC (SEQ ID
 NO:80).

[00223] The L chain variable of the Ab 11C8 is shown in SEQ ID NO:81:
 DVVMTQTPLTSLVTIGQPASISCKSSQSLLDSDGKTYLNWFLQRPQGSPKRLIYLVSK
 LD SGVPDRFTGSGSGTDFTLKISRVEAEDLG VYYCWQGTHFPWTFGGG TKLE (SEQ
 ID NO:81)

[00224] [mAnti-LOX-1-10F9H-LV-hIgG4H-C], heavy chain, SEQ ID NO:82:
 QVQLQQSGAELMKPGASVKISCKATGYTFGSYWIEWVKQRPGHGLEWIGEILPGSG
 NTNYNENFKGKATFTADTSSNTAYMQLTSLTSEDSAVYYCARAGIYWGGQGLTVTS
 AAKTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAV
 LQSSGLYSLSSVVTVPSSSLGTQTYTCNV DHKPSNTKVDKRVESKYGPPCPPCPAPEF
 EGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSQEDPEVQFNWYVDGVEVHNAKTK
 PREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQ
 VYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSF
 FLYSRLTVDKSRWQEGNVFSCSV MHEALHNHYTQKSLSLGLKAS (SEQ ID NO:82).

[00225] The H chain variable of the Ab 10F9 is shown in SEQ ID NO:83:
 QVQLQQSGAELMKPGASVKISCKATGYTFGSYWIEWVKQRPGHGLEWIGEILPGSG
 NTNYNENFKGKATFTADTSSNTAYMQLTSLTSEDSAVYYCARAGIYWGGQGLTVTS
 AAKTK (SEQ ID NO:83).

[00226] [mAnti-LOX_1-10F9K-LV-hIgGK-C], light chain, SEQ ID NO:84:
 DIVLTQSPAFLAVSLGQRATISCRASESDNYGISFMNWFQQKPGQPPKLLIYVASKQ
 GSGVPARFSGSGSGTDFSLNIHPMEEDDTAMYFCQQSKEVPRTFGGG TKLEIKRTVA
 APSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDS
 KDSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO:84).

[00227] The L chain variable of the Ab 10F9 is shown in SEQ ID NO:85:
 DIVLTQSPAFLAVSLGQRATISCRASESDNYGISFMNWFQQKPGQPPKLLIYVASKQ
 GSGVPARFSGSGSGTDFSLNIHPMEEDDTAMYFCQQSKEVPRTFGGG TKLE (SEQ ID
 NO:85).

[00228] [mAnti-LOX-1-15C4H-LV-hIgG4H-C], heavy chain, SEQ ID NO:86:
 EIQLQQTGPPELVKPGASVKISCKASGYPTDYIMVWVKQSHGKSLEWIGNISPYYGTT
 NYNLKFKGKATLTVDKSSSTAYMQLNSLTSEDSAVYYCARSPNWDGAWFAHWGQ
 GALVTVSAAKTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSG
 VHTFPAVLQSSGLYSLSSVVTVPSSSLGKTYTCNVDPHKPSNTKVDKRVESKYGPPC
 PPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVE
 VHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAK
 GQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPV
 LDDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLGLKAS (SEQ
 ID NO:86).

[00229] The H chain variable of the Ab 15C4 is shown in SEQ ID NO:87:
 EIQLQQTGPPELVKPGASVKISCKASGYPTDYIMVWVKQSHGKSLEWIGNISPYYGTT
 NYNLKFKGKATLTVDKSSSTAYMQLNSLTSEDSAVYYCARSPNWDGAWFAHWGQ
 GALVTVSAAKTK (SEQ ID NO:87).

[00230] [mAnti-LOX-1-15C4K-LV-hIgGK-C], light chain, SEQ ID NO: 88:
 DIVLTQSPASLAVSLGQRATISCKASQSVSDYDGDSYMNWFQQKPGQPPKLLIYAASN
 LESGIPARFSGSGSGTDFTLNIHPVEEEDAATYYCQQSNEDPFTFGSGTKLEIKRTVAA
 PSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSK
 DSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO:88).

[00231] The L chain variable of the Ab 15C4 is shown in SEQ ID NO:89:
 DIVLTQSPASLAVSLGQRATISCKASQSVSDYDGDSYMNWFQQKPGQPPKLLIYAASN
 LESGIPARFSGSGSGTDFTLNIHPVEEEDAATYYCQQSNEDPFTFGSGTKLE (SEQ ID
 NO:89).

Anti-DCIR Abs

[00232] Anti-DCIR_24A5.4A5_H-V-hIgG4H-C, heavy chain, SEQ ID NO:90:
 MDWLWNLLFLMAAAQSAQAQIQLVQSGPELKKPGETVKISCKASGYSTNYGMNW
 VKQAPGKGLKWMGWINTYTGESTYADDFKGRFAFSLETSASTAYLQISNLKNEDMA
 TYFCARGDFRYYYFDYWGQGTTLTGSSAKTKGPSVFPLAPCSRSTSESTAALGCLVK
 DYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGKTYTCNVDPH
 KPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVD
 VSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYK
 CKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIA

VEWESNGQPENNYKTTTPVLDS

GSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGKAS (SEQ ID NO:90).

[00233] Anti-DCIR_24A5.4A5_K-V-hIgGK-C, light chain, SEQ ID NO:91: MSVLTQVLALLLLWLTGARCDIQMTQSPASLSASVGETVTITCRASGNIHNYLAWYQ QKQKGKSPQLLVYNAKTLADGVPSRFSGSGSGTQYSLKINTLQPEDFGSYQCQHFWD S WTFGGGKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDN ALQSGNSQESVTEQDSKDYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSF NRGE (SEQ ID NO:91).

[00234] Anti-DCIR_24E7.3H9_H-V-hIgG4H-C, heavy chain, SEQ ID NO:92: MEWTWVFLFLLSVTAGVHSQVQLQQSGAELMKPGASVKISCKATGYTFSSYWIEW VKQRPBGHGLEWIGEILPGSGRTNDNEKFKGKATFTADTSSKKAYMQLSSLTSEDSAV YYCARRGGYSFAYWGQGLTVTSAAKTKGPSVFPLAPCSRSTSESTAALGCLVKDY FPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVPSSSLGKTKYTCNVDPKPS NTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVDVVSQ EDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCK VSNKGLPSSIEKTKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTTPVLDSGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHY TQKSLSLSLGKAS (SEQ ID NO:92).

[00235] Anti-DCIR_24E7.3H9_K-V-hIgGK-C, light chain, SEQ ID NO:93: MTMFSLALLLSLLLLCVSDSRAETTVTQSPASLSMAIGEKVTIRCVTSTDIDDDVNWY QKQKPGEPPKLLISEGNTLRPGVPSRFSSSGYGTDVFTIENMLSEDVADYYCLQSGNL PYTFGGGKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVD NALQSGNSQESVTEQDSKDYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKS FNRGE (SEQ ID NO:93).

[00236] Anti-DCIR_29E9.2E2_H-VhIgG4H-C, heavy chain, SEQ ID NO:94: MAWVWTLFLMAAAQSAQAQIQLVQSGPELKKPGETVKISCKASGYTFTNYGMNW VKQAPGKGLKWVGWINTFTGEPTYVDDFKGRFAFSLETSASTAYLQINNLLKNE DTA TYFCARGNFRYYYFDYWGQGTTLTVSSAKTKGPSVFPLAPCSRSTSESTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVPSSSLGKTKYTCNVDP KPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVD VSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYK

CKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIA
VEWESNGQPENNYKTTPPVLDSD
GSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLGLKAS (SEQ ID
NO:94).

[00237] Anti-DCIR_29E9.2E2_K-V-hIgGK-C, light chain, SEQ ID NO:95:
MSVLTQVLALLLLWLTGARCDIQMTQSPASLSASVGETVTITCRTSGNIRNYLAWYQ
QKQGKSPQLLVYNAKTLADGVPSRFGGSGSGTQYSLKINSLQPEDFGNYCYCQHFWS
SPYTFGGGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVD
NALQSGNSQESVTEQDSKDYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKS
FNRGEC (SEQ ID NO:95).

[00238] Anti-DCIR_29G10.3D9_H-V-hIgG4H-C, heavy chain, SEQ ID NO:96:
MMGWSYIILFLVATATDVHSQVQLQQPGAELVKPGASVKLSCKASGYTFTSYWMH
WVKQRPGEGLWIGEINPSYGRDYNKFKNKATLTVAKSSSTAYMQLSSLTSEDSA
VYYCARGDYWGSSSFAYWGQGLTVTVSAAKTKGPSVFPLAPCSRSTSESTAALGCL
VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGKTYTCNV
DHKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVV
VDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKE
YKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSD
IAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEAL
HNHYTQKSLSLGLKAS (SEQ ID NO:96).

[00239] Anti-DCIR_29G10.3D9_K-Var1-V-hIgGK-C, light chain, SEQ ID NO:97:
MDFQVQIFSFLMSASVIMSRGQIVLTQSPALMSASPGEKVTMTCSASSNISYMYWY
QQKPRSSPKWIYLTSLASGVPARFSGSGSGTSYSLTSSMEAEDAATYCCQQWSS
NPPTFGAGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVD
NALQSGNSQESVTEQDSKDYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKS
FNRGEC (SEQ ID NO:97).

[00240] Anti-DCIR_29G10.3D9_K-Var2-V-hIgGK-C, light chain, SEQ ID NO:98:
MDFRVQIFSFLMSASVIMSRGQIVLTQSPALMSASPGEKVTMTCSASSNISYMYWY
QQKPRSSPKWIYLTSLASGVPARFSGSGSGTSYSLTISSMEAEDAATYCYCQQWSSN
PPTFGAGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDN
ALQSGNSQESVTEQDSKDYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSF
NRGEC (SEQ ID NO:98).

[00241] Anti-DCIR_31A6.1F5_H-var2-V-hIgG4H-C, heavy chain, SEQ ID NO:99:
 MECNWILPFILSVISGVYSEVQLQQSGTVLARPGASVNMSCKAAGYSFTSYWVYWW
 KQRPQGQLEWIGAIYPKNSRTSYNQKFQDKATLTAVTSASTAYMELSSLTNEDSAVY
 YCTRPHYDSFGYWGQGLTVTVSAAKTKGPSVFPLAPCSRSTSESTAALGCLVKDYFP
 EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDPKPSN
 TKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSQE
 DPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKV
 NKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWE
 SNGQPENNYKTTTPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQ
 KSLSLSLGKAS (SEQ ID NO:99).

[00242] Anti-DCIR_31A6.1F5_K-var2-V-hIgGK-C, light chain, SEQ ID NO:100:
 METDTLLLWVLLLWVPGSTGDIVLTQSPASLAIVSLGQRATISCRASESVDSYGISFMH
 WYQQKPGQPPKLLIYRASNQESGIPARFSGSGSRTDFTLTINPVEADDAATYYCQQSN
 EDPLTFTGAGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKV
 DNALQSGNSQESVTEQDSKDYSLSSLTLSKADYEKHKVYACEVTHQGLSSPVTK
 SFNRGEC (SEQ ID NO:100).

[00243] Anti-DCIR_3C2.2D9_H-LV-hIgG4H-C, heavy chain, SEQ ID NO:101:
 NRLTSSLLLLIVPAYVLSQQVTLKESGPGILQPSQTLSTCSFSGFSLSTSGMGSWIR
 QPSGKGLEWLAHIYWDDDKRYNPSLKSRLTIFKDPSSNQVFLRITSVDTADTATYYC
 ARNSHYYGSTYGGYFDVWGAGTTVTVSSAKTKGPSVFPLAPCSRSTSESTAALGCLV
 KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDP
 HKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVV
 DVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEY
 KCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDI
 AVEWESNGQPENNYKTTTPVLDSD
 GSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGKAS (SEQ ID
 NO:101).

[00244] Anti-DCIR_3C2.2D9_K-LV-hIgGK-C, light chain, SEQ ID NO:102:
 METDTLLLWVLLLGVPSTGNIVLTQSPTSFTVSLGQRATISCRASESVHSYGNSFMH
 WYQQKPGQPPKLLIYLASNVESGVPARFSGSGSRTDFTLTIDPVEADDAATYYCQQN
 SEDPWTFGGGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQW
 KVDNALQSGNSQESVTEQDSKDYSLSSLTLSKADYEKHKVYACEVTHQGLSSPV
 TKSFNREGEC (SEQ ID NO:102).

[00245] Anti-DCIR_6C8.1G9_H-V-hIgG4H-C, heavy chain, SEQ ID NO:103:
 MEWTWVFLFLLSVTAGVHSQVQLQQSGTELMKPGASVKISCKATGYTFSTYWIEWV
 KQRPGHGLEWIGEILPGSGRTNDNEKFKGKATITADTSSKKAYMQLSSLTSEDSAVY
 YCARRGGYSFAFWGQGTLVSVSAAKTKGPSVFPLAPCSRSTSESTAALGCLVKDYFP
 EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGKTKYTCNVDHKPSN
 TKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQE
 DPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKV
 NKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWE
 SNGQPENNYKTTTPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQ
 KSLSLSLGKAS (SEQ ID NO:103).

[00246] Anti-DCIR_6C8.1G9_K-V-hIgGK-C, light chain, SEQ ID NO:104:
 MTMFSLALLLSLLLLCVSDSRAETTVTQSPASLSMAIGEKVTIRCVTSTDIDDDVNWY
 QQKPGEPKLLISEGNTLRAGVPSRFSSSGYGTDVFVTIENMLSEDVADYYCLQSGNL
 PYTFGGGKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVD
 NALQSGNSQES
 VTEQDSKDYSLSSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ
 ID NO:104).

[00247] Anti-DCIR2C9H-LV-hIgG4H-V-hIgG4H-C, heavy chain, SEQ ID NO:105:
 MKCSWVIFFLMAVVTGVNSEVQLQQSGAELVRPGALVKLSCKASGFNINDYYIHWV
 KQRPEQGLERIGWIDPDNGNTIYDPKFQGKASITADTSPNTAYLQLSSLTSEDVAVYY
 CARTRSPMVTTFGVYWGQGTVTVVSAAKTKGPSVFPLAPCSRSTSESTAALGCLVK
 DYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGKTKYTCNVDH
 KPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVD
 VSQEDPEVQFNWYVDGVEVHNAKXKPREEQFNSTYRVVSVLTVLHQDWLNGKEY
 KCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDI
 AVEWESNGQPENNYKTTTPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALH
 NHYTQKSLSLSLGK (SEQ ID NO:105).

[00248] Anti-DCIR_2C9K-V-hIgGK-C, light chain, SEQ ID NO:106:
 METDTLLLWVLLLWVPGSTGDIVLIQSPASLAVSLGQRATISCRASESVDSYVNSFM
 HWYQQKPGQPPKLLIYRVSNLESGIPARFSGSGSRDFTLTINPVEADDVATYYCQQS
 NEDPFTFGSGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWK
 VDNALQSGNSQESVTEQDSKDYSLSSSTLTLSKADYEKHKVYACEVTHQGLSSPV
 TKSFNREGEC (SEQ ID NO:106).

Anti-Langerin Abs

[00249] Anti-Langerin-15B10H-LV-hIgG4H-C, heavy chain, SEQ ID NO:107: QVQLRQSGPELVKPGASVKMSCKASGYTFTDYVISWVKQRTGQGLEWIGDIYPGSG YSFYNENFKGKATLTADKSSTTAYMQLSSLTSEDSAVYFCATYYNYPFAYWGQGT L VTVSAAKTTGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTF PAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPA PEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVDVVSQEDPEVQFNWYVDGVEVHNAK TKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPRE PQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDS DG SFFLYSRLTVDKSRWQEGNVFSCS VMHEALHNHYTQKSLSLGLKAS (SEQ ID NO:107).

[00250] The H chain variable of the Ab 15B10 is shown in SEQ ID NO:108: SVKMSCKASGYTFTDYVISWVKQRTGQGLEWIGDIYPGSGYSFYNNENFKGKATLTA DKSSTTAYMQLSSLTSEDSAVYFCA (SEQ ID NO:108).

[00251] Anti-Langerin-15B10K-LV-hIgGK-C, light chain, SEQ ID NO:109: DVVMTQTPLSLPVRLGDQASISCRSSQSLVHSNGNTYLHWYLQKPGQSPKLLIYKVS N R FSGVPDRFSGSGSGTNFTLKISRVEAEDLGLYFCSQSTHVPYTFGGGTKLEIKRTV AAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQD SKDSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO:109).

[00252] The L chain variable of the Ab 15B10 is shown in SEQ ID NO:110: ASISCRSSQSLVHSNGNTYLHWYLQKPGQSPKLLIYKVS N R FSGVPDRFSGSGSGTNF TLKISRVEAEDLGLYFCS (SEQ ID NO:110).

[00253] Anti-Langerin-2G3H-LV-hIgG4H-C, heavy chain, SEQ ID NO:111: MTLNMLLGLRWVFFVVFYQGVHCEVQLVESGGGLVQPKGSLKLSCAASGLTFNIYA MNWVRQAPGKGLEWVARIRNKSNNYATYYADSVKDRFTISRDDSQSLLYLQMNNL KTEDTAMYYCVGRDWFYWGQGT L VTVSAAKTKGPSVFPLAPCSRSTSESTAALGC LVKD Y FPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCN VDHKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFY P

SDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHE
ALHNHYTQKSLSLGLKAS (SEQ ID NO:111).

[00254] The H chain variable of the Ab 2G3 is shown in SEQ ID NO:112:
SLKLSCAASGLTFNIYAMNWVRQAPGKGLEWVARIRNKSNNYATYYADSVKDRFTI
SRDDSQSLLYLQMNNLKTEDTAMYYC (SEQ ID NO:112).

[00255] Anti-Langerin-2G3L-LV-hIgGK-C, light chain, SEQ ID NO:113:
MAWISLILSLLALSSGAISQAVVTQESALTTSPGETVTLTCRSSTGAVTTSNYANWVQ
EKPDHLFTGLIGGTNNRVSGVPARFSGSLIGDKAALTITGAQTEDEAIYFCALWYSNH
WVFGGGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDN
ALQSGNSQESVTEQDSKSTYSLSSLTLSKADYEKHKVYACEVTHQGLSSPVTKSF
NRGEC (SEQ ID NO:113).

[00256] The L chain variable of the Ab 2G3 is shown in SEQ ID NO:114:
VTLTCRSSTGAVTTSNYANWVQEKPDHLFTGLIGGTNNRVSGVPARFSGSLIGDKAA
LTITGAQTEDEAIYFCA (SEQ ID NO:114).

II. Interleukin 10 (IL-10)

[00257] Interleukin-10 (IL-10), also known as human cytokine synthesis inhibitory factor (CSIF), is an anti-inflammatory cytokine. In humans, IL-10 is encoded by the *IL10* gene. The mRNA sequence of human IL-10 is represented by accession No.: NM_000572.2. The amino acid sequence of human IL-10 is represented by accession No.: NP_000563.1 and SEQ ID NO:5.

[00258] In some embodiments, the APC-targeted antibody or fragment thereof is operatively linked to an IL-10 polypeptide comprising a sequence corresponding to a protein sequence of an NCBI accession number NP_000563.1. In some embodiments, the IL-10 polypeptide comprises the amino acid sequence of SEQ ID NO:5 or a fragment thereof.

III. Antigens

[00259] Certain aspects of the disclosure include methods and compositions concerning antigenic components including segments, fragments, or epitopes of polypeptides, peptides, nucleic acids, carbohydrates, lipids and other molecules that provoke or induce an antigenic response, generally referred to as antigens. In one embodiment, the antigen is a peptide. In particular, antigens, or antigenic segments or fragments of such antigens, which

lead to the destruction of a cell via an immune response, can be identified and used in the methods and compositions described herein.

[00260] Antigens associated with various diseases and disorders are known in the art. It is contemplated that any antigen may be used in the methods and compositions described herein. In certain aspects, the antigen is one that is involved in the etiology of an autoimmune, allergic, or inflammatory disease known in the art and/or described herein.

[00261] In certain aspects, the antigen is one known in the art to be involved in rheumatoid arthritis, allergy, asthma, systemic onset juvenile arthritis, inflammatory bowel disease, systemic lupus erythematosus, type 1 diabetes, and Crohn's disease.

V. Peptide Components and Proteinaceous Compositions

[00262] Polypeptides and peptides may be modified by various amino acid deletions, insertions, and/or substitutions. In particular embodiments, modified polypeptides and/or peptides are capable of modulating an immune response in a subject. As used herein, a "protein" or "polypeptide" or "peptide" refers to a molecule comprising at least five amino acid residues. In some embodiments, a wild-type version of a protein or peptide are employed, however, in many embodiments, a modified protein or polypeptide is employed to generate the antibody conjugates described herein. A "modified protein" or "modified polypeptide" or "modified peptide" refers to a protein or polypeptide whose chemical structure, particularly its amino acid sequence, is altered with respect to the wild-type protein or polypeptide.

[00263] Peptides include peptides that are found to be specific to cancerous or pre-cancerous cells in the body. These peptides may be associated with the APC-targeted antibodies described herein. Administration of combinations of these peptides includes administering a population of antibody conjugates having multiple peptides attached and/or administering multiple conjugate populations, each having a specific peptide attached or a combination of such conjugates that includes nanoparticles with 1, 2, 3, 4, 5, 6, or more peptides attached to the APC-targeted antibody, antigen binding fragment thereof, or IL-10 protein.

[00264] Proteinaceous compositions may be made by any technique known to those of skill in the art, including (i) the expression of proteins, polypeptides, or peptides through standard molecular biological techniques, (ii) the isolation of proteinaceous compounds from natural sources, or (iii) the chemical synthesis of proteinaceous materials. The nucleotide as

well as the protein, polypeptide, and peptide sequences for various genes have been previously disclosed, and may be found in the recognized computerized databases. One such database is the National Center for Biotechnology Information's GenBank and GenPept databases (on the World Wide Web). The all or part of the coding regions for these genes may be amplified and/or expressed using the techniques disclosed herein or as would be known to those of ordinary skill in the art.

[00265] Amino acid sequence variants of antigenic epitopes and other polypeptides of these compositions can be substitutional, insertional, or deletion variants. A modification in a polypeptide may affect 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, 250, 251, 252, 253, 254, 255, 256, 257, 258, 259, 260, 261, 262, 263, 264, 265, 266, 267, 268, 269, 270, 271, 272, 273, 274, 275, 276, 277, 278, 279, 280, 281, 282, 283, 284, 285, 286, 287, 288, 289, 290, 291, 292, 293, 294, 295, 296, 297, 298, 299, 300, 301, 302, 303, 304, 305, 306, 307, 308, 309, 310, 311, 312, 313, 314, 315, 316, 317, 318, 319, 320, 321, 322, 323, 324, 325, 326, 327, 328, 329, 330, 331, 332, 333, 334, 335, 336, 337, 338, 339, 340, 341, 342, 343, 344, 345, 346, 347, 348, 349, 350, 351, 352, 353, 354, 355, 356, 357, 358, 359, 360, 361, 362, 363, 364, 365, 366, 367, 368, 369, 370, 371, 372, 373, 374, 375, 376, 377, 378, 379, 380, 381, 382, 383, 384, 385, 386, 387, 388, 389, 390, 391, 392, 393, 394, 395, 396, 397, 398, 399, 400, 401, 402, 403, 404, 405, 406, 407, 408, 409, 410, 411, 412, 413, 414, 415, 416, 417, 418, 419, 420, 421, 422, 423, 424, 425, 426, 427, 428, 429, 430, 431, 432, 433, 434, 435, 436, 437, 438, 439, 440, 441, 442, 443, 444, 445, 446, 447, 448, 449, 450, 451, 452, 453, 454, 455, 456, 457, 458, 459, 460, 461, 462, 463, 464, 465, 466,

467, 468, 469, 470, 471, 472, 473, 474, 475, 476, 477, 478, 479, 480, 481, 482, 483, 484, 485, 486, 487, 488, 489, 490, 491, 492, 493, 494, 495, 496, 497, 498, 499, 500 or more non-contiguous or contiguous amino acids of a peptide or polypeptide, as compared to wild-type. A peptide or polypeptide that results in an immune response is contemplated for use in embodiments.

[00266] Deletion variants typically lack one or more residues of the native or wild-type amino acid sequence. Individual residues can be deleted or a number of contiguous amino acids can be deleted. A stop codon may be introduced (by substitution or insertion) into an encoding nucleic acid sequence to generate a truncated protein. Insertional mutants typically involve the addition of material at a non-terminal point in the polypeptide. This may include the insertion of one or more residues. Terminal additions, called fusion proteins, may also be generated.

[00267] Substitutional variants typically contain the exchange of one amino acid for another at one or more sites within the protein, and may be designed to modulate one or more properties of the polypeptide, with or without the loss of other functions or properties. Substitutions may be conservative, that is, one amino acid is replaced with one of similar shape and charge. Conservative substitutions are well known in the art and include, for example, the changes of: alanine to serine; arginine to lysine; asparagine to glutamine or histidine; aspartate to glutamate; cysteine to serine; glutamine to asparagine; glutamate to aspartate; glycine to proline; histidine to asparagine or glutamine; isoleucine to leucine or valine; leucine to valine or isoleucine; lysine to arginine; methionine to leucine or isoleucine; phenylalanine to tyrosine, leucine or methionine; serine to threonine; threonine to serine; tryptophan to tyrosine; tyrosine to tryptophan or phenylalanine; and valine to isoleucine or leucine. Alternatively, substitutions may be non-conservative such that a function or activity of a polypeptide or peptide is affected, such as avidity or affinity for a cellular receptor(s). Non-conservative changes typically involve substituting a residue with one that is chemically dissimilar, such as a polar or charged amino acid for a nonpolar or uncharged amino acid, and vice versa.

[00268] Proteins may be recombinant, or synthesized *in vitro*. Alternatively, a recombinant protein may be isolated from bacteria or other host cell.

[00269] The term “functionally equivalent codon” is used herein to refer to codons that encode the same amino acid, such as the six codons for arginine or serine, and also refers to codons that encode biologically equivalent amino acids.

[00270] It also will be understood that amino acid and nucleic acid sequences may include additional residues, such as additional N- or C-terminal amino acids, or 5' or 3' nucleic acid sequences, respectively, and yet still be essentially as set forth in one of the sequences disclosed herein, so long as the sequence meets the criteria set forth above, including the maintenance of biological protein activity (e.g., immunogenicity). The addition of terminal sequences particularly applies to nucleic acid sequences that may, for example, include various non-coding sequences flanking either of the 5' or 3' portions of the coding region.

[00271] It is contemplated that in composition embodiments, there is between about 0.001 mg and about 10 mg of total protein per ml. Thus, the concentration of protein in a composition can be about, at least about or at most about 0.001, 0.010, 0.050, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 8.5, 9.0, 9.5, 10.0, 50, 100 .mu.g/ml or mg/ml or more (or any range derivable therein).

[00272] Embodiments include in some cases the administration of an APC-targeted antibody. In some embodiments, the methods and compositions further comprise an antigen. U.S. Pat. No. 4,554,101 (Hopp), teaches the identification and preparation of antigenic epitopes from primary amino acid sequences on the basis of hydrophilicity. Through the methods disclosed in Hopp, one of skill in the art would be able to identify potential antigenic epitopes from within an amino acid sequence and confirm their immunogenicity. Numerous scientific publications have also been devoted to the prediction of secondary structure and to the identification of epitopes, from analyses of amino acid sequences (Chou & Fasman, 1974a,b; 1978a,b; 1979). Any of these may be used, if desired, to supplement the teachings of Hopp in U.S. Pat. No. 4,554,101.

IV. Pharmaceutical Compositions

[00273] Embodiments include methods and compositions for increasing immune responses in a subject in need thereof. They include compositions that can be used to induce or modify an immune response against an antigen e.g., a polypeptide, a peptide, a carbohydrate, a lipid or other molecule or molecular fragment and against developing a condition or disease associated with such antigen.

[00274] It is contemplated that the APC-targeted antibody or antigen binding fragment thereof (and optionally antigen and optionally linked to IL-10) may be administered with additional adjuvants known in the art such as TLR agonists. TLR agonists may include an agonist to TLR1 (e.g. peptidoglycan or triacyl lipoproteins), TLR2 (e.g. lipoteichoic acid; peptidoglycan from *Bacillus subtilis*, *E. coli* 0111:B4, *Escherichia coli* K12, or *Staphylococcus aureus*; atypical lipopolysaccharide (LPS) such as *Leptospirosis* LPS and *Porphyromonas gingivalis* LPS; a synthetic diacylated lipoprotein such as FSL-1 or Pam2CSK4; lipoarabinomannan or lipomannan from *M. smegmatis*; triacylated lipoproteins such as Pam3CSK4; lipoproteins such as MALP-2 and MALP-404 from mycoplasma; *Borrelia burgdorferi* OspA; Porin from *Neisseria meningitidis* or *Haemophilus influenza*; *Propionibacterium acnes* antigen mixtures; *Yersinia* LcrV; lipomannan from *Mycobacterium* or *Mycobacterium tuberculosis*; *Trypanosoma cruzi* GPI anchor; *Schistosoma mansoni* lysophosphatidylserine; *Leishmania major* lipophosphoglycan (LPG); *Plasmodium falciparum* glycoposphatidylinositol (GPI); zymosan; antigen mixtures from *Aspergillus fumigatus* or *Candida albicans*; and measles hemagglutinin), TLR3 (e.g. double-stranded RNA, polyadenylic-polyuridylic acid (Poly(A:U)); polyinosine-polycytidylic acid (Poly(I:C)); polyinosine-polycytidylic acid high molecular weight (Poly(I:C) HMW); and polyinosine-polycytidylic acid low molecular weight (Poly(I:C) LMW)), TLR4 (e.g. LPS from *Escherichia coli* and *Salmonella* species); TLR5 (e.g. Flagellin from *B. subtilis*, *P. aeruginosa*, or *S. typhimurium*), TLR8 (e.g. single stranded RNAs such as ssRNA with 6UUAU repeats, RNA homopolymer (ssPolyU naked), HIV-1 LTR-derived ssRNA (ssRNA40), or ssRNA with 2 GUCCUUCAA repeats (ssRNA-DR)), TLR7 (e.g. imidazoquinoline compound imiquimod, Imiquimod VacciGrade™, Gardiquimod VacciGrade™, or Gardiquimod™; adenine analog CL264; base analog CL307; guanosine analog loxoribine; TLR7/8 (e.g. thiazoquinoline compound CL075; imidazoquinoline compound CLO97, R848, or R848 VacciGrade™), TLR9 (e.g. CpG ODNs); and TLR11 (e.g. *Toxoplasma gondii* Profilin). In certain embodiments, the TLR agonist is a specific agonist listed above. In further embodiments, the TLR agonist is one that agonizes either one TLR or two TLRs specifically.

[00275] In certain embodiments, the methods and compositions specifically exclude the administration of a TLR ligand and/or agonist.

[00276] Administration of the compositions will typically be via any common route. This includes, but is not limited to oral, parenteral, orthotopic, intradermal, subcutaneous,

intramuscular, intraperitoneal, intranasal, by inhalation, by using a nebulizer, or by intravenous injection. In certain embodiments, a vaccine composition may be inhaled (e.g., U.S. Pat. No. 6,651,655). Additional formulations which are suitable for other modes of administration include oral formulations. Oral formulations include such normally employed excipients as, for example, pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate and the like. These compositions take the form of solutions, suspensions, tablets, pills, capsules, sustained release formulations or powders and contain about 10% to about 95% of active ingredient, preferably about 25% to about 70%.

[00277] Typically, compositions are administered in a manner compatible with the dosage formulation, and in such amount as will be therapeutically effective and immune modifying. The quantity to be administered depends on the subject to be treated. Precise amounts of active ingredient required to be administered depend on the judgment of the practitioner.

[00278] The manner of application may be varied widely. Any of the conventional methods for administration of an antibody are applicable. These are believed to include oral application on a solid physiologically acceptable base or in a physiologically acceptable dispersion, parenterally, by injection and the like. The dosage of the pharmaceutical composition will depend on the route of administration and will vary according to the size and health of the subject.

[00279] In many instances, it will be desirable to have multiple administrations of at most about or at least about 3, 4, 5, 6, 7, 8, 9, 10 or more. The administrations may range from 2 day to twelve week intervals, more usually from one to two week intervals. The course of the administrations may be followed by assays for reactive immune responses and T cell activity.

[00280] The phrases “pharmaceutically acceptable” or “pharmacologically acceptable” refer to molecular entities and compositions that do not produce an adverse, allergic, or other untoward reaction when administered to an animal, or human. As used herein, “pharmaceutically acceptable carrier” includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like. The use of such media and agents for pharmaceutical active substances is well known in

the art. Except insofar as any conventional media or agent is incompatible with the active ingredients, its use in immunogenic and therapeutic compositions is contemplated.

[00281] The antibodies or antigen binding fragments can be formulated for parenteral administration, e.g., formulated for injection via the intravenous, intradermal, intramuscular, sub-cutaneous, or even intraperitoneal routes. In a specific embodiment, the composition is administered by intradermal injection. In further embodiments, the composition is administered by intravenous injection. The preparation of an aqueous composition that contains a APC-targeted antibody that modifies the subject's immune condition will be known to those of skill in the art in light of the present disclosure. Typically, such compositions can be prepared as injectables, either as liquid solutions or suspensions; solid forms suitable for use to prepare solutions or suspensions upon the addition of a liquid prior to injection can also be prepared; and, the preparations can also be emulsified.

[00282] The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions; formulations including sesame oil, peanut oil, or aqueous propylene glycol; and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases the form must be sterile and must be fluid to the extent that it may be easily injected. It also should be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms, such as bacteria and fungi.

[00283] The compositions may be formulated into a neutral or salt form. Pharmaceutically acceptable salts, include the acid addition salts (formed with the free amino groups of the protein) and which are formed with inorganic acids such as, for example, hydrochloric or phosphoric acids, or such organic acids as acetic, oxalic, tartaric, mandelic, and the like. Salts formed with the free carboxyl groups can also be derived from inorganic bases such as, for example, sodium, potassium, ammonium, calcium, or ferric hydroxides, and such organic bases as isopropylamine, trimethylamine, histidine, procaine and the like.

[00284] The carrier can also be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), suitable mixtures thereof, and vegetable oils. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars

or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

[00285] Sterile injectable solutions are prepared by incorporating the active ingredients in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the various sterilized active ingredients into a sterile vehicle which contains the basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum-drying and freeze-drying techniques, which yield a powder of the active ingredient, plus any additional desired ingredient from a previously sterile-filtered solution thereof.

[00286] An effective amount of therapeutic or prophylactic composition is determined based on the intended goal. The term “unit dose” or “dosage” refers to physically discrete units suitable for use in a subject, each unit containing a predetermined quantity of the composition calculated to produce the desired responses discussed above in association with its administration, i.e., the appropriate route and regimen. The quantity to be administered, both according to number of treatments and unit dose, depends on the result and/or protection desired. Precise amounts of the composition also depend on the judgment of the practitioner and are peculiar to each individual. Factors affecting dose include physical and clinical state of the subject, route of administration, intended goal of treatment (alleviation of symptoms versus cure), and potency, stability, and toxicity of the particular composition. Upon formulation, solutions will be administered in a manner compatible with the dosage formulation and in such amount as is therapeutically or prophylactically effective. The formulations are easily administered in a variety of dosage forms, such as the type of injectable solutions described above.

VII. *In Vitro* or *Ex Vivo* Administration

[00287] As used herein, the term *in vitro* administration refers to manipulations performed on cells removed from or outside of a subject, including, but not limited to cells in culture. The term *ex vivo* administration refers to cells which have been manipulated *in vitro*, and are subsequently administered to a subject. The term *in vivo* administration includes all manipulations performed within a subject, including administrations.

[00288] In certain aspects, the compositions may be administered either *in vitro*, *ex vivo*, or *in vivo*. In certain *in vitro* embodiments, isolated immune cells are incubated with compositions described herein. For example, isolated APCs may be incubated with the antibody or antibody conjugates as described herein. The cells can then be used for *in vitro* analysis, or alternatively for *ex vivo* administration.

VIII. Therapeutic Applications

[00289] Methods include treatment of inflammatory and autoimmune disorders. Methods may be employed with respect to individuals who has tested positive for such disorders or who are deemed to be at risk for developing such a condition or related condition.

[00290] The antibody or antigen binding fragment of the disclosure (in some embodiments, conjugated to IL-10) can be given to induce or modify an immune response in a person having, suspected of having, or at risk of developing an autoimmune condition or complication relating to an allograft. Methods may be employed with respect to individuals who have tested positive for autoreactivity or allo-reactivity or who are deemed to be at risk for developing such a condition or related condition.

[00291] The methods described herein are particularly useful in treating or preventing disorders for which antigenic determinants are poorly characterized. Such disorders include, for example, rheumatoid arthritis, allergy, asthma, systemic onset juvenile arthritis, inflammatory bowel disease, and Crohn's disease. The methods described herein are also particularly useful for disorders such as GVHD and graft rejection since the antigenic determinants of such diseases may not be known or may be different depending on the tissue and/or individual from which the tissue was obtained from.

[00292] It is contemplated that targeting dendritic cells (e.g. with an anti-DC-ASGPR antibody) inhibits autoimmune diseases but does not interfere with pathogen-specific T cell responses.

[00293] Embodiments can be used to treat or ameliorate a number of immune-mediated, inflammatory, or autoimmune-inflammatory diseases, e.g., allergies, asthma, diabetes (e.g. type 1 diabetes), graft rejection, etc. Examples of such diseases or disorders also include, but are not limited to arthritis (rheumatoid arthritis such as acute arthritis, chronic rheumatoid arthritis, gout or gouty arthritis, acute gouty arthritis, acute immunological arthritis, chronic inflammatory arthritis, degenerative arthritis, type II

collagen-induced arthritis, infectious arthritis, Lyme arthritis, proliferative arthritis, psoriatic arthritis, Still's disease, vertebral arthritis, and systemic juvenile-onset rheumatoid arthritis, osteoarthritis, arthritis chronica progrediente, arthritis deformans, polyarthritis chronica primaria, reactive arthritis, and ankylosing spondylitis), inflammatory hyperproliferative skin diseases, psoriasis such as plaque psoriasis, guttate psoriasis, pustular psoriasis, and psoriasis of the nails, atopy including atopic diseases such as hay fever and Job's syndrome, dermatitis including contact dermatitis, chronic contact dermatitis, exfoliative dermatitis, allergic dermatitis, allergic contact dermatitis, dermatitis herpetiformis, nummular dermatitis, seborrheic dermatitis, non-specific dermatitis, primary irritant contact dermatitis, and atopic dermatitis, x-linked hyper IgM syndrome, allergic intraocular inflammatory diseases, urticaria such as chronic allergic urticaria and chronic idiopathic urticaria, including chronic autoimmune urticaria, myositis, polymyositis/dermatomyositis, juvenile dermatomyositis, toxic epidermal necrolysis, scleroderma (including systemic scleroderma), sclerosis such as systemic sclerosis, multiple sclerosis (MS) such as spino-optical MS, primary progressive MS (PPMS), and relapsing remitting MS (RRMS), progressive systemic sclerosis, atherosclerosis, arteriosclerosis, sclerosis disseminata, ataxic sclerosis, neuromyelitis optica (NMO), inflammatory bowel disease (IBD) (for example, Crohn's disease, autoimmune-mediated gastrointestinal diseases, colitis such as ulcerative colitis, colitis ulcerosa, microscopic colitis, collagenous colitis, colitis polyposa, necrotizing enterocolitis, and transmural colitis, and autoimmune inflammatory bowel disease), bowel inflammation, pyoderma gangrenosum, erythema nodosum, primary sclerosing cholangitis, respiratory distress syndrome, including adult or acute respiratory distress syndrome (ARDS), meningitis, inflammation of all or part of the uvea, iritis, choroiditis, an autoimmune hematological disorder, rheumatoid spondylitis, rheumatoid synovitis, hereditary angioedema, cranial nerve damage as in meningitis, herpes gestationis, pemphigoid gestationis, pruritis scroti, autoimmune premature ovarian failure, sudden hearing loss due to an autoimmune condition, IgE-mediated diseases such as anaphylaxis and allergic and atopic rhinitis, encephalitis such as Rasmussen's encephalitis and limbic and/or brainstem encephalitis, uveitis, such as anterior uveitis, acute anterior uveitis, granulomatous uveitis, nongranulomatous uveitis, phacoantigenic uveitis, posterior uveitis, or autoimmune uveitis, glomerulonephritis (GN) with and without nephrotic syndrome such as chronic or acute glomerulonephritis such as primary GN, immune-mediated GN, membranous GN (membranous nephropathy), idiopathic membranous GN or idiopathic membranous nephropathy, membrano- or membranous proliferative GN (MPGN), including Type I and

Type II, and rapidly progressive GN, proliferative nephritis, autoimmune polyglandular endocrine failure, balanitis including balanitis circumscripta plasmacellularis, balanoposthitis, erythema annulare centrifugum, erythema dyschromicum perstans, erythema multiform, granuloma annulare, lichen nitidus, lichen sclerosus et atrophicus, lichen simplex chronicus, lichen spinulosus, lichen planus, lamellar ichthyosis, epidermolytic hyperkeratosis, premalignant keratosis, pyoderma gangrenosum, allergic conditions and responses, allergic reaction, eczema including allergic or atopic eczema, asteatotic eczema, dyshidrotic eczema, and vesicular palmoplantar eczema, asthma such as asthma bronchiale, bronchial asthma, and auto-immune asthma, conditions involving infiltration of T cells and chronic inflammatory responses, immune reactions against foreign antigens such as fetal A-B-O blood groups during pregnancy, chronic pulmonary inflammatory disease, autoimmune myocarditis, leukocyte adhesion deficiency, lupus, including lupus nephritis, lupus cerebritis, pediatric lupus, non-renal lupus, extra-renal lupus, discoid lupus and discoid lupus erythematosus, alopecia lupus, systemic lupus erythematosus (SLE) such as cutaneous SLE or subacute cutaneous SLE, neonatal lupus syndrome (NLE), and lupus erythematosus disseminatus, juvenile onset (Type I) diabetes mellitus, including pediatric insulin-dependent diabetes mellitus (IDDM), and adult onset diabetes mellitus (Type II diabetes) and autoimmune diabetes. Also contemplated are immune responses associated with acute and delayed hypersensitivity mediated by cytokines and T-lymphocytes, sarcoidosis, granulomatosis including lymphomatoid granulomatosis, Wegener's granulomatosis, agranulocytosis, vasculitides, including vasculitis, large-vessel vasculitis (including polymyalgia rheumatica and giant cell (Takayasu's) arteritis), medium-vessel vasculitis (including Kawasaki's disease and polyarteritis nodosa/periarteritis nodosa), microscopic polyarteritis, immunovascularitis, CNS vasculitis, cutaneous vasculitis, hypersensitivity vasculitis, necrotizing vasculitis such as systemic necrotizing vasculitis, and ANCA-associated vasculitis, such as Churg-Strauss vasculitis or syndrome (CSS) and ANCA-associated small-vessel vasculitis, temporal arteritis, aplastic anemia, autoimmune aplastic anemia, Coombs positive anemia, Diamond Blackfan anemia, hemolytic anemia or immune hemolytic anemia including autoimmune hemolytic anemia (AIHA), Addison's disease, autoimmune neutropenia, pancytopenia, leukopenia, diseases involving leukocyte diapedesis, CNS inflammatory disorders, Alzheimer's disease, Parkinson's disease, multiple organ injury syndrome such as those secondary to septicemia, trauma or hemorrhage, antigen-antibody complex-mediated diseases, anti-glomerular basement membrane disease, anti-phospholipid antibody syndrome, allergic neuritis, Behcet's disease/syndrome, Castleman's syndrome, Goodpasture's syndrome,

Reynaud's syndrome, Sjogren's syndrome, Stevens-Johnson syndrome, pemphigoid such as pemphigoid bullous and skin pemphigoid, pemphigus (including pemphigus vulgaris, pemphigus foliaceus, pemphigus mucus-membrane pemphigoid, and pemphigus erythematosus), autoimmune polyendocrinopathies, Reiter's disease or syndrome, thermal injury, preeclampsia, an immune complex disorder such as immune complex nephritis, antibody-mediated nephritis, polyneuropathies, chronic neuropathy such as IgM polyneuropathies or IgM-mediated neuropathy, autoimmune or immune-mediated thrombocytopenia such as idiopathic thrombocytopenic purpura (ITP) including chronic or acute ITP, scleritis such as idiopathic cerato-scleritis, episcleritis, autoimmune disease of the testis and ovary including autoimmune orchitis and oophoritis, primary hypothyroidism, hypoparathyroidism, autoimmune endocrine diseases including thyroiditis such as autoimmune thyroiditis, Hashimoto's disease, chronic thyroiditis (Hashimoto's thyroiditis), or subacute thyroiditis, autoimmune thyroid disease, idiopathic hypothyroidism, Grave's disease, polyglandular syndromes such as autoimmune polyglandular syndromes (or polyglandular endocrinopathy syndromes), paraneoplastic syndromes, including neurologic paraneoplastic syndromes such as Lambert-Eaton myasthenic syndrome or Eaton-Lambert syndrome, stiff-man or stiff-person syndrome, encephalomyelitis such as allergic encephalomyelitis or encephalomyelitis allergica and experimental allergic encephalomyelitis (EAE), experimental autoimmune encephalomyelitis, myasthenia gravis such as thymoma-associated myasthenia gravis, cerebellar degeneration, neuromyotonia, opsoclonus or opsoclonus myoclonus syndrome (OMS), and sensory neuropathy, multifocal motor neuropathy, Sheehan's syndrome, autoimmune hepatitis, chronic hepatitis, lupoid hepatitis, giant cell hepatitis, chronic active hepatitis or autoimmune chronic active hepatitis, lymphoid interstitial pneumonitis (LIP), bronchiolitis obliterans (non-transplant) vs NSIP, Guillain-Barre syndrome, Berger's disease (IgA nephropathy), idiopathic IgA nephropathy, linear IgA dermatosis, acute febrile neutrophilic dermatosis, subcorneal pustular dermatosis, transient acantholytic dermatosis, cirrhosis such as primary biliary cirrhosis and pneumonocirrhosis, autoimmune enteropathy syndrome, Celiac or Coeliac disease, celiac sprue (gluten enteropathy), refractory sprue, idiopathic sprue, cryoglobulinemia, amyotrophic lateral sclerosis (ALS; Lou Gehrig's disease), coronary artery disease, autoimmune ear disease such as autoimmune inner ear disease (AIED), autoimmune hearing loss, polychondritis such as refractory or relapsed or relapsing polychondritis, pulmonary alveolar proteinosis, Cogan's syndrome/nonsyphilitic interstitial keratitis, Bell's palsy, Sweet's disease/syndrome, rosacea autoimmune, zoster-associated pain, amyloidosis, a non-cancerous lymphocytosis, a primary

lymphocytosis, which includes monoclonal B cell lymphocytosis (e.g., benign monoclonal gammopathy and monoclonal gammopathy of undetermined significance, MGUS), peripheral neuropathy, paraneoplastic syndrome, channelopathies such as epilepsy, migraine, arrhythmia, muscular disorders, deafness, blindness, periodic paralysis, and channelopathies of the CNS, autism, inflammatory myopathy, focal or segmental or focal segmental glomerulosclerosis (FSGS), endocrine ophthalmopathy, uveoretinitis, chorioretinitis, autoimmune hepatological disorder, fibromyalgia, multiple endocrine failure, Schmidt's syndrome, adrenalitis, gastric atrophy, presenile dementia, demyelinating diseases such as autoimmune demyelinating diseases and chronic inflammatory demyelinating polyneuropathy, Dressler's syndrome, alopecia areata, alopecia totalis, CREST syndrome (calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyl), and telangiectasia), male and female autoimmune infertility, e.g., due to anti-spermatozoan antibodies, mixed connective tissue disease, Chagas' disease, rheumatic fever, recurrent abortion, farmer's lung, erythema multiforme, post-cardiotomy syndrome, Cushing's syndrome, bird-fancier's lung, allergic granulomatous angiitis, benign lymphocytic angiitis, Alport's syndrome, alveolitis such as allergic alveolitis and fibrosing alveolitis, interstitial lung disease, transfusion reaction, leprosy, malaria, parasitic diseases such as leishmaniasis, kypansomiasis, schistosomiasis, ascariasis, aspergillosis, Sampter's syndrome, Caplan's syndrome, dengue, endocarditis, endomyocardial fibrosis, diffuse interstitial pulmonary fibrosis, interstitial lung fibrosis, pulmonary fibrosis, idiopathic pulmonary fibrosis, cystic fibrosis, endophthalmitis, erythema elevatum et diutinum, erythroblastosis fetalis, eosinophilic fasciitis, Shulman's syndrome, Felty's syndrome, filariasis, cyclitis such as chronic cyclitis, heterochronic cyclitis, iridocyclitis (acute or chronic), or Fuch's cyclitis, Henoch-Schönlein purpura, human immunodeficiency virus (HIV) infection, SCID, acquired immune deficiency syndrome (AIDS), echovirus infection, sepsis, endotoxemia, pancreatitis, thyrotoxicosis, parvovirus infection, rubella virus infection, post-vaccination syndromes, congenital rubella infection, Epstein-Barr virus infection, mumps, Evan's syndrome, autoimmune gonadal failure, Sydenham's chorea, post-streptococcal nephritis, thromboangitis obliterans, thyrotoxicosis, tabes dorsalis, chorioiditis, giant cell polymyalgia, chronic hypersensitivity pneumonitis, keratoconjunctivitis sicca, epidemic keratoconjunctivitis, idiopathic nephritic syndrome, minimal change nephropathy, benign familial and ischemia-reperfusion injury, transplant organ reperfusion, retinal autoimmunity, joint inflammation, bronchitis, chronic obstructive airway/pulmonary disease, silicosis, aphthae, aphthous stomatitis, arteriosclerotic disorders, aspernigenese, autoimmune hemolysis, Boeck's

disease, cryoglobulinemia, Dupuytren's contracture, endophthalmia phacoanaphylactica, enteritis allergica, erythema nodosum leprosum, idiopathic facial paralysis, chronic fatigue syndrome, febris rheumatica, Hamman-Rich's disease, sensorineural hearing loss, haemoglobinuria paroxysmatica, hypogonadism, ileitis regionalis, leucopenia, mononucleosis infectiosa, transverse myelitis, primary idiopathic myxedema, nephrosis, ophthalmia sympathica, orchitis granulomatosa, pancreatitis, polyradiculitis acuta, pyoderma gangrenosum, Quervain's thyroiditis, acquired splenic atrophy, non-malignant thymoma, vitiligo, toxic-shock syndrome, food poisoning, conditions involving infiltration of T cells, leukocyte-adhesion deficiency, immune responses associated with acute and delayed hypersensitivity mediated by cytokines and T-lymphocytes, diseases involving leukocyte diapedesis, multiple organ injury syndrome, antigen-antibody complex-mediated diseases, antiglomerular basement membrane disease, allergic neuritis, autoimmune polyendocrinopathies, oophoritis, primary myxedema, autoimmune atrophic gastritis, sympathetic ophthalmia, rheumatic diseases, mixed connective tissue disease, nephrotic syndrome, insulinitis, polyendocrine failure, autoimmune polyglandular syndrome type I, adult-onset idiopathic hypoparathyroidism (AOIH), cardiomyopathy such as dilated cardiomyopathy, epidermolysis bullosa acquisita (EBA), hemochromatosis, myocarditis, nephrotic syndrome, primary sclerosing cholangitis, purulent or nonpurulent sinusitis, acute or chronic sinusitis, ethmoid, frontal, maxillary, or sphenoid sinusitis, an eosinophil-related disorder such as eosinophilia, pulmonary infiltration eosinophilia, eosinophilia-myalgia syndrome, Löffler's syndrome, chronic eosinophilic pneumonia, tropical pulmonary eosinophilia, bronchopneumonic aspergillosis, aspergilloma, or granulomas containing eosinophils, anaphylaxis, seronegative spondyloarthritides, polyendocrine autoimmune disease, sclerosing cholangitis, sclera, episclera, chronic mucocutaneous candidiasis, Bruton's syndrome, transient hypogammaglobulinemia of infancy, Wiskott-Aldrich syndrome, ataxia telangiectasia syndrome, angiectasis, autoimmune disorders associated with collagen disease, rheumatism, neurological disease, lymphadenitis, reduction in blood pressure response, vascular dysfunction, tissue injury, cardiovascular ischemia, hyperalgesia, renal ischemia, cerebral ischemia, and disease accompanying vascularization, allergic hypersensitivity disorders, glomerulonephritides, reperfusion injury, ischemic re-perfusion disorder, reperfusion injury of myocardial or other tissues, lymphomatous tracheobronchitis, inflammatory dermatoses, dermatoses with acute inflammatory components, multiple organ failure, bullous diseases, renal cortical necrosis, acute purulent meningitis or other central nervous system inflammatory disorders, ocular and orbital inflammatory disorders,

granulocyte transfusion-associated syndromes, cytokine-induced toxicity, narcolepsy, acute serious inflammation, chronic intractable inflammation, pyelitis, endarterial hyperplasia, peptic ulcer, valvulitis, graft versus host disease, contact hypersensitivity, asthmatic airway hyperreaction, and endometriosis.

[00294] Embodiments can be used to prevent, treat or ameliorate a number of allergic disorders. Non-limiting examples include asthma, type 1 diabetes, chronic obstructive pulmonary disease, interstitial lung disease, chronic obstructive lung disease, chronic bronchitis, eosinophilic bronchitis, eosinophilic pneumonia, pneumonia, inflammatory bowel disease, atopic dermatitis, atopy, allergy, allergic rhinitis, idiopathic pulmonary fibrosis, scleroderma, emphysema, breast cancer, and ulcerative colitis. Non-limiting examples of allergic disorders include allergic atopy and dermatitis, allergic rhinitis, allergic asthma, allergic responses to food (*e.g.* milk, egg, wheat, nut, fish, shellfish, sulfite, soy, and casein), environmental allergens (*e.g.* plant and animal allergens such as dander, dust mites, pollen, cedar, poison ivy, poison oak, poison sumac, etc...), insect bites (*e.g.* bee, wasp, yellow jacket, hornet, or fire ant stings), hay fever, allergic conjunctivitis, hives, mold, medication allergies (*e.g.* aspirin and penicillin), and cosmetic allergies.

[00295] In some embodiments, the compositions and methods described herein are used to treat an inflammatory component of a disorder listed herein and/or known in the art. Accordingly, the methods and compositions described herein can be used to treat a subject suffering from inflammation. In some embodiments, the inflammation is acute. In other embodiments, the inflammation is chronic. In further embodiments, the compositions and methods described herein are used to treat or prevent a cancer by treating or preventing an inflammatory component associated with the cancer. In some embodiments, the cancer is breast cancer.

IX. Combination Therapy

[00296] The compositions and related methods disclosed herein, particularly administration of an APC-targeted antibody or antigen binding fragment may also be used in combination with the administration of traditional therapies. These include, but are not limited to, the administration of immunosuppressive or modulating therapies or treatments. Non-limiting examples of existing immunosuppressive therapies include administration of immunosuppressive compounds such as cyclosporine A, cyclophosphamide, FK506,

tacrolimus, corticosteroids, azathioprine, mycophenolate mofetil, sirolimus, rapamycin, rapamycin analogs, deoxyspergualin, and prednisone

[00297] In one aspect, it is contemplated that an APC-targeted antibody or antigen binding fragment is used in conjunction with a cytokine treatment. Alternatively, antibody administration may precede or follow the other treatment by intervals ranging from minutes to weeks. In embodiments where the other agents are administered separately, one would generally ensure that a significant period of time did not expire between the time of each delivery, such that the agent and antibody would still be able to exert an advantageously combined effect on the subject. In such instances, it is contemplated that one may administer both modalities within about 12-24 h of each other and, more preferably, within about 6-12 h of each other. In some situations, it may be desirable to extend the time period for administration significantly, however, where several days (2, 3, 4, 5, 6 or 7) to several weeks (1, 2, 3, 4, 5, 6, 7 or 8) lapse between the respective administrations.

[00298] Administration of the anti-DC-ASGPR antibody or antigen binding fragment compositions to a patient/subject will follow general protocols for the administration of such compounds, taking into account the toxicity, if any. It is expected that the treatment cycles would be repeated as necessary. It also is contemplated that various standard therapies, such as hydration, may be applied in combination with the described therapy.

X. Examples

[00299] The following examples are included to demonstrate certain embodiments. It should be appreciated by those of skill in the art that the techniques disclosed in the examples which follow represent techniques discovered by the inventor to function well in the practice of the invention, and thus can be considered to constitute preferred modes for its practice. However, those of skill in the art should, in light of the present disclosure, appreciate that many changes can be made in the specific embodiments which are disclosed and still obtain a like or similar result without departing from the spirit and scope of the invention.

Example 1: Targeting IL-10 to Antigen Presenting Cells

[00300] With targeted *in vivo* delivery of IL-10 to APCs followed by alterations of pathogenic functions of APC as well as the enhancement of regulatory T cell responses, this therapeutic strategy can be more effective and durable than non-targeted anti-inflammatory cytokines. Compared to non-targeted methods, targeted method described herein requires much less amount of IL-10 to show the same or similar effects. With the dose-sparing-effect

along with the delivery of IL-10 to subsets of patient's APCs, this strategy is expected to significantly reduce side effects of anti-inflammatory cytokine treatment, but with better effects.

[00301] To study the effects of APC-targeted IL-10, recombinant fusion protein of antibody and human IL-10 were made. Monoclonal antibodies (anti-CD40 clone 12E12, anti-CD40 clone 24A3, anti-DCIR clone 9E8, anti-DC-ASGPR clone 49C11, and control IgG4) and human IL-10 fusion proteins were made.

[00302] It was found that different antibodies fused to human IL-10 can target subsets of human DCs in distinct patterns. The ability of antibody-IL-10 fusion proteins to bind to human DCs was measured. Both myeloid DC (mDCs) and plasmacytoid DCs (pDCs) were purified from human blood. DCs were incubated for 20 min in ice in the presence of different concentrations of recombinant fusion proteins of antibody and IL-10 (FIG. 1). After vigorous washing, DCs were further stained with anti-human IL-10 to detect surface bound antibody-IL-10 fusion proteins using flow cytometry. As shown in FIG. 1, all the recombinant fusion proteins of antibody-IL-10 (except for the control IgG4-IL-10) could bind to mDCs. However, binding patterns of the individual proteins to mDCs were not the same. For example, anti-DCIR (9E8)-IL-10 binds to mDCs more efficiently than do the others. In addition, anti-CD40 (12E12)-IL-10 shows better binding to mDCs than anti-CD40 (24A3)-IL-10. Although both anti-CD40 (12E12)-IL-10 and anti-CD40 (24A3)-IL-10 bind to pDCs, anti-DCIR (9E8)-IL-10 shows the besting binding to pDCs.

[00303] Taken together, these data indicate that anti-inflammatory cytokines (including IL-10) fused to different antibodies can target different subsets of human APCs in different levels, which can result in different outcomes of immune responses.

[00304] It was also found that antibody-IL-10 fusion proteins can suppress DC maturation. DCs are the major APCs that can induce and direct host immune responses toward either immunity or tolerance. It is also known that matured DCs induce immunity whereas immature DCs induce immune tolerance. Therefore, the effectiveness of antibody-IL-10 fusion proteins on the maturation of DCs induced by *Escherichia coli* lipopolysaccharide (LPS; toll-like receptor 4 ligand) was tested. Purified blood mDCs were cultured overnight with 0, 10, and 100 ng/ml LPS in the presence or absence of 10 µg recombinant fusion proteins indicated or the same molar concentration of recombinant IL-10. mDCs were then stained with anti-CD83 and anti-CD86 to measure the expression levels of

these two surface molecules (indicators for DC maturation) using flow cytometry. FIG. 2 shows that untargeted human IL-10 slightly decreased CD83 and CD86 expression. Compared to untargeted IL-10, targeted delivery of IL-10 using recombinant fusion proteins of antibody and IL-10 were far more efficient to suppress the LPS-induced DC maturation. Anti-CD40 (12E12)-IL-10 was slightly more efficient than others to suppress the expression of CD86.

[00305] These data demonstrate that recombinant fusion proteins of antibody and IL-10 can efficiently target human DCs and thus can effectively suppress DC maturation. This indicates that targeted delivery of anti-inflammatory cytokines to human APCs can efficiently suppress ongoing inflammatory responses by the inhibition of APC, including DCs, maturation.

[00306] It was next found that targeted delivery of IL-10 to DCs using recombinant fusion proteins of antibody and IL-10 can efficiently suppress T cell responses. The effectiveness of recombinant fusion proteins of antibody and IL-10 in T cell responses (FIG. 3) was further assessed. Purified mDCs were incubated for 2h with different concentrations of either recombinant human IL-10 or fusion proteins of antibody and IL-10. CFSE-labeled allogeneic CD4+ T cells were co-cultured for 5 days and T cell proliferation was assessed by measuring CFSE dilution with flow cytometry. Compared to IL-10 alone, recombinant fusion proteins of antibody and IL-10 were far more efficient to suppress the allogeneic CD4+ T cell proliferation. To result in 50% inhibition of T cell proliferation, 54nM IL-10 was required, while only less than 5.4-0.054 nM (IL-10) was required to result in similar effect on T cell proliferation when IL-10 was delivered to DCs in a targeted fashion.

[00307] Taken together, the data (FIGS. 1, 2, 3) demonstrate that 1) recombinant fusion proteins of antibody and anti-inflammatory cytokines can effectively target human APCs with different patterns, depending on APC subsets (FIG. 1); 2) they can suppress human APCs (including DCs) activation and maturation; and 3) can effectively suppress T cell responses.

Example 2: Treating GVHD with anti-DC-ASGPR

[00308] Tolerance to specific antigens is the ultimate goal for the success of transplantation. Over the past several decades, a large array of immunosuppressive agents has been developed and is being used for patients. However, immunosuppression does not guarantee the prevention of alloreaction over time in patients who receive organs, tissues, and

hematopoietic stem cell (HPSC) transplantation. As a consequence, patients succumb to graft-versus-host disease (GVHD) as well as serious side effects due to life-long immunosuppression. T cell depletion also compromises the graft-versus-leukemia (GVL) effects in alloHPSC transplantation. Furthermore, controlling GVHD with nonspecific immunosuppression neither spares pre-existing memory cells nor discriminates between alloreactive and non-alloreactive T cells. Thus, although GVHD could be controlled to some degree by immunosuppression, it is at the cost of increased incidence of graft failure, leukemia relapse, and compromised immunity to post-transplant infections, such as cytomegalovirus (CMV). Therefore, a new therapeutic strategy that can prevent GVHD while preserving host immunity to infections will bring great benefit to patients.

[00309] Dendritic cells (DCs), major antigen presenting cells (APCs), can induce host immune responses. DCs also display functional plasticity to control immune responses. The ability of DCs, as immune controllers, is in part by the expression of pattern-recognition receptors (PRRs), including lectins. It was discovered that a lectin expressed on human DCs, DC-asialoglycoprotein receptor (DC-ASGPR), shows a unique ability to generate antigen-specific IL-10-producing regulatory T cells (Tregs). This applies to both self (prostate specific antigen) and foreign antigens (influenza HA1), as demonstrated in human *in vitro* and non-human primates *in vivo*. DC-ASGPR-induced antigen-specific Tregs efficiently suppress effector T cell proliferation and inflammatory cytokine expression. It was further discovered that signals via DC-ASGPR induce DCs to express IL-10, and this IL-10 promotes the generation of antigen-specific Tregs. Applicants sought out to test whether activation of DCs via DC-ASGPR can generate alloantigen-specific Tregs and thus can prevent GVHD and allograft transplantation. Data shows that targeting DC-ASGPR with anti-DC-ASGPR antibody results in decreased allogeneic T cell responses. These T cells can also secrete high level of IL-10 during their reactivation in response to alloantigens. Thus, Applicants surmise that DC-ASGPR can be a novel therapeutic target to inhibit such unwanted types of immune responses in patients who undergo transplantation surgery. This strategy is focusing on the induction of alloantigen-specific Tregs and thus may not interfere with host immunity to post-transplantation infections. Therefore, it was hypothesized that targeting DC-ASGPR with an anti-DC-ASGPR antibody not fused to an antigen prevents GVHD and allograft rejection but does not interfere with host immunity to infections.

[00310] Establishment of alloantigen-specific immune tolerance is an ultimate goal for the success of transplantation. The novel immunotherapeutic strategy described herein may

eventually permit the production of alloantigen-specific Tregs in patients without interfering with host immunity to post-transplantation infections. Therefore, this study has a high significance in both medical and immunological implications.

[00311] The approach to controlling GVHD and transplant rejection by targeting DC-ASGPR is highly novel and innovative in the aspects of both basic immunology and medical implications.

[00312] DC-ASGPR has a specialized function to generate antigen-specific Tregs. DC-ASGPR, a scavenger receptor, is expressed on subsets of human DCs (blood myeloid DCs: mDCs and skin dermal DCs but not plasmacytoid DCs: pDCs or Langerhans cells: LCs), monocytes, macrophages, and B cells. Endothelial cells express ASGPR, but not DC-ASGPR. DC-ASGPR is expressed in non-human primates (NHPs), but not in mice. Mice have two closely linked genes called Mgl-1 and Mgl-2 which are distantly related to human DC-ASGPR, the former having a closer tissue distribution profile to the single human gene (not shown).

A. Anti-DC-ASGPR antibody treatment suppresses allogeneic CD4+ and CD8+ T cell proliferation

[00313] To study the immunological function of DC-ASGPR, mouse monoclonal antibodies (mAbs) specific for human DC-ASGPR were first generated. To abolish their non-specific bindings to FcRs, recombinant mAbs carrying mouse variable region chimeras with human κ chain and human IgG4 carrying two site mutations were made. Recombinant control mAb was also made in the same way.

[00314] It is important to note that both DC-ASGPR and Dectin-1 carry an immunoreceptor tyrosine-based activation motif (ITAM) and can induce IL-10 expression in DCs. However, DC-ASGPR is superior to Dectin-1 to generate Tregs (data not shown). In addition, anti-DC-ASGPR mAb does not induce DCs to express IL-1 β , IL-23 or IL-12, while anti-Dectin-1 mAb does induce these cytokines, as previously described.

[00315] Anti-DC-ASGPR mAb can suppress MHC-mismatched allogeneic T cell responses: The effects of anti-DC-ASGPR mAb in MHC-mismatched allogeneic T cell responses was tested (**FIG. 4**). Different numbers of PKH25-labeled PBMCs from healthy

donors were incubated overnight in the presence of anti-DC-ASGPR or control mAb, and then CFSE-labeled PBMCs from MHC-mismatched donors (total 6 pairs of MHC-mismatched donors) were co-cultured for 5 days. The percents of CFSE⁺CD4⁺ and CFSE⁺CD8⁺ T cells are presented. In the presence of control mAb, both CD4⁺ and CD8⁺ T cell proliferations were correlated with the numbers of stimulators (PBMCs from other donors). However, anti-DC-ASGPR mAb significantly decreased allogeneic CD4⁺ and CD8⁺ T cell proliferation, particularly when the number of stimulators (X-axis) was greater than 12.5 x 10³/well. Interestingly, total numbers of CD4⁺ and CD8⁺ T cells counted at the end of cultures were similar in both groups (control and anti-DC-ASGPR mAb-treated groups) (not shown).

B. IL-10 secreted from PBMC activated with anti-DC-ASGPR contributes to the suppression of allogeneic CD4⁺ and CD8⁺ T cell responses

[00316] Applicants further found that the decreased allogeneic T cell proliferation by anti-DC-ASGPR mAb was recovered (~60-70%) by neutralizing IL-10 on day 1 (2 h before adding MHC-mismatched PBMCs to the culture) (FIG. 5). This suggests that IL-10 secreted from anti-DC-ASGPR-activated APCs contributes to the decreased proliferation of T cells from MHC-mismatched donors.

C. Anti-DC-ASGPR antibody treatment results in decreased IFN γ -producing, but increased IL-10-producing regulatory T cell responses

[00317] On day 8 of the co-culture of PBMCs from MHC-mismatched healthy donors, CFSE^{low}CD4⁺ T cells were FACS-sorted, and then restimulated for 48h with T cell-depleted PBMCs (from stimulators). The amounts of IL-10 and IFN γ in the supernatants were measured (FIG. 6). MHC-mismatched CD4⁺ T cells co-cultured anti-DC-ASGPR-treated PBMCs secreted decreased amount of IFN γ but increased amount of IL-10 compared to CD4⁺ T cells co-cultured with the same PBMC treated with control mAb. This suggests that treatment of PBMCs with anti-DC-ASGPR mAb promote the induction of alloantigen-specific Tregs which could play important roles in the inhibition of GVHD and allograft rejection *in vivo*.

D. Anti-DC-ASGPR antibody treatment results in the suppression of GVHD in vivo

[00318] Applicants further assessed the *in vivo* effects of anti-DC-ASGPR mAb. NOD/SCID/ γ c^{-/-} (NOG) mice (5 mice/group) were injected intravenously (i.v.) on day 0 with 50x10⁶ PBMCs from healthy donors. Animals also received 3 i.v. doses of antibodies (250

µg/dose) or PBS on days 0, 2, and 4. **FIG. 7** shows that anti-DC-ASGPR treatment resulted in enhanced survival of animals ($p < 0.001$) compared to control IgG or PBS treatment.

[00319] Taken together, this data demonstrates that targeting DC-ASGPR with anti-DC-ASGPR mAb promotes antigen-specific Treg responses. It is contemplated that this could also apply to the *in vivo* establishment of alloantigen-specific Tregs. This data and methodology described herein is useful in the research and development of a novel therapeutic that can efficiently inhibit GVHD and allograft rejection without interfering with host immune responses to infections.

[00320] Applicants focused on novel antibodies that bind the DC-ASGPR that can induce DCs to secrete IL-10 and to induce IL-10-producing alloantigen-specific Tregs in the presence of alloantigens. Therefore, the strategy to inhibit GVHD and allograft rejection is based on two distinct but compensatory mechanisms (**FIG. 8**). First (Direct Pathway), IL-10 secreted from DC-ASGPR-activated DCs will directly inhibit allogeneic T cell responses in the early time point, as shown in **FIG. 5**. Second (Indirect Pathway), DC-ASGPR-induced IL-10 can contribute to the induction of IL-10-producing alloantigen-specific Tregs, as shown in **FIG. 6**. These two pathways could result in the enhanced survival of human PBMC-transferred NOG mice (**FIG. 7**). Such alloantigen-specific Tregs express IL-10 when they are activated at the place where alloantigens are available *in vivo* (Sagoo, et al., 2011).

* * *

[00321] It is specifically contemplated that embodiments of the invention may include one or more elements listed or exclude one or more elements listed throughout the specification. For example, specific embodiments may include one specific item listed (*e.g.* antibody framework) as described herein or embodiments of the invention may encompass multiple items from a specific list, such as 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, or more. The invention may also exclude one or more listed elements, for example, some embodiments exclude 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, or more elements listed. Furthermore, when ranges or numerical values are provided, it is specifically contemplated that certain ranges or numerical values may be excluded from the invention. Last, when the inventions is described in terms of including a particular feature, it is specifically contemplated that the invention may also exclude such feature.

[00322] All of the methods disclosed and claimed herein can be made and executed without undue experimentation in light of the present disclosure. While the compositions and

methods of this invention have been described in terms of preferred embodiments, it will be apparent to those of skill in the art that variations may be applied to the methods and in the steps or in the sequence of steps of the method described herein without departing from the concept, spirit and scope of the invention. More specifically, it will be apparent that certain agents which are both chemically and physiologically related may be substituted for the agents described herein while the same or similar results would be achieved. All such similar substitutes and modifications apparent to those skilled in the art are deemed to be within the spirit, scope and concept of the invention as defined by the appended claims.

WHAT IS CLAIMED IS:

1. Use of a pharmaceutical composition for inducing immune tolerance in a subject in need thereof, said pharmaceutical composition comprising an anti-DC-ASGPR antibody operatively linked to IL-10 and a pharmaceutically acceptable carrier or excipient, with the proviso that said pharmaceutical composition does not comprise an antigen associated with an autoimmune disease or inflammatory condition.
2. Use of a pharmaceutical composition for preventing or treating graft versus host disease (GVHD) in a subject in need thereof, said pharmaceutical composition comprising an anti-DC-ASGPR antibody operatively linked to IL-10 and a pharmaceutically acceptable carrier or excipient, with the proviso that said pharmaceutical composition does not comprise an antigen associated with an autoimmune disease or inflammatory condition.
3. The use of claim 2, wherein the anti-DC-ASGPR antibody is a humanized antibody having three heavy chain CDRs and three light chain CDRs from the variable regions of an anti-DC-ASGPR heavy chain and light chain variable region pairs selected from SEQ ID NO:3 and 8; SEQ ID NO:58 and 60; SEQ ID NO:62 and 64; or SEQ ID NO:66 and 68; or is a humanized antibody having three heavy chain CDRs and three light chain CDRs from the heavy and light chains of an anti-DC-ASGPR heavy chain and light chain pair selected from SEQ ID NO:69 and 70 and SEQ ID NO:71 and 72.
4. Use of a pharmaceutical composition for inhibiting an inflammatory or autoimmune response in a subject in need thereof, said pharmaceutical composition comprising an anti-DC-ASGPR antibody operatively linked to IL-10 and a pharmaceutically acceptable carrier or excipient, with the proviso that said pharmaceutical composition does not comprise an antigen associated with an autoimmune disease or inflammatory condition.
5. Use of a pharmaceutical composition for suppressing a T cell response in a subject in a subject having or at risk of developing an inflammatory response, said pharmaceutical composition comprising an anti-DC-ASGPR antibody operatively linked to IL-10 and a pharmaceutically acceptable carrier or excipient, with the proviso that said pharmaceutical composition does not comprise an antigen associated with an autoimmune

disease or inflammatory condition.

6. The use of any one claims 1-5, wherein the anti-DC-ASGPR antibody targets dendritic cells.

7. The use of claim 1 or 2, wherein the antibody is a human antibody, humanized antibody, recombinant antibody, bi-specific antibody, chimeric antibody, a nanobody, a DARPIn, an antibody derivative, a veneered antibody, a diabody, a monoclonal antibody, or a polyclonal antibody.

8. The use of claim 7, wherein the antibody is a humanized antibody.

9. The use of any one of claims 1-8, wherein the subject is a human subject.

10. The use of any one of claims 3-9, wherein the subject has an autoimmune disease or an inflammatory disorder.

11. The use of any one of claims 1-10, wherein the subject is suffering from inflammation.

12. The use of claim 11, wherein the inflammation is acute.

13. The use of claim 11, wherein the inflammation is chronic.

14. The use of claim 10, wherein the subject has a complication from the transplanted tissue, wherein the complication is graft rejection.

15. The use of claim 10, wherein the subject has a complication from the transplanted tissue, wherein the complication is GVHD.

16. The use of claim 14 or 15, after tissue transplantation.

17. The use of claim 16, for further treating a complication from the transplanted tissue, wherein the complication comprises GVHD or graft rejection.

18. The use of any one of claims 1-17, wherein IL-10 is covalently linked to the antibody.

19. The use of any one of claims 1-18, wherein IL-10 is covalently linked to the antibody through a peptide bond.
20. The use of any one of claims 1-12, wherein the antibody is operatively linked to IL-10 through binding polypeptides.
21. The use of claim 20, wherein the binding polypeptides are dockerin and cohesin.
22. The use of any one of claims 1-21, wherein the antibody operatively linked to IL-10 is formulated for oral administration, intravenous administration, subcutaneous administration, intradermal administration, intramuscular administration, intranasal administration, for injection, for inhalation, for mucosal administration, or for use with a nebulizer.
23. The use of any one of claims 1-22, wherein the IL-10 comprises a peptide with the amino acid sequence of SEQ ID NO:5.
24. Use of an anti-DC-ASGPR antibody operatively linked to IL-10 for inhibiting an inflammatory or autoimmune response in a subject in need thereof, wherein the anti-DC-ASGPR antibody is a humanized antibody having three heavy chain CDRs and three light chain CDRs from the variable regions of an anti-DC-ASGPR heavy chain and light chain variable region pairs selected from SEQ ID NO:3 and 8; SEQ ID NO:58 and 60; SEQ ID NO:62 and 64; or SEQ ID NO:66 and 68; or is a humanized antibody having three heavy chain CDRs and three light chain CDRs from the heavy and light chains of an anti-DC-ASGPR heavy chain and light chain pair selected from SEQ ID NO:69 and 70 and SEQ ID NO:71 and 72.
25. A pharmaceutical composition comprising an anti-DC-ASGPR antibody operatively linked to IL-10 and a pharmaceutically acceptable carrier or excipient, wherein the pharmaceutical composition does not comprise an antigen associated with an autoimmune disease or inflammatory condition.
26. The pharmaceutical composition of claim 25, wherein the anti-DC-ASGPR antibody targets dendritic cells.

27. The pharmaceutical composition of claim 25 or 26, wherein the antibody is a human antibody, humanized antibody, recombinant antibody, bi-specific antibody, chimeric antibody, a nanobody, a DARPIn, an antibody derivative, a veneered antibody, a diabody, a monoclonal antibody, or a polyclonal antibody.
28. The pharmaceutical composition of claim 27, wherein the antibody is a humanized antibody.
29. The pharmaceutical composition of any one of claims 25-28, wherein IL-10 is covalently linked to the antibody.
30. The pharmaceutical composition of any one of claims 25-29, wherein IL-10 is covalently linked to the antibody through a peptide bond.
31. The pharmaceutical composition of any one of claims 25-28, wherein the antibody is operatively linked to IL-10 through binding polypeptides.
32. The pharmaceutical composition of claim 31, wherein the binding polypeptides are dockerin and cohesin.
33. The pharmaceutical composition of any one of claims 25-32, wherein the composition is formulated for oral, intravenous, subcutaneous, intradermal, intramuscular, mucosal, or nasal administration or by injection, inhalation, or a nebulizer.
34. The pharmaceutical composition of any one of claims 25-33, wherein the IL-10 comprises a peptide with the amino acid sequence of SEQ ID NO:5.
35. The pharmaceutical composition of any one of claims 25-34 for preventing or treating an autoimmune disease or inflammatory condition.
36. Use of the pharmaceutical composition according to any one of claims 25-34 for the preparation of a medicament for treating or preventing autoimmune or inflammatory disorders.
37. Use of the composition of any one of claims 25-34 for inducing immune tolerance to a subject in need thereof.

38. Use of a pharmaceutical composition for preventing or treating graft versus host disease (GVHD) in a subject in need thereof, said pharmaceutical composition comprising an anti-DC-ASGPR antibody or antigen binding fragment thereof operatively linked to IL-10 and a pharmaceutically acceptable carrier or excipient, with the proviso that said pharmaceutical composition does not comprise an antigen associated with an autoimmune disease or inflammatory condition.

39. The use of claim 38, wherein the anti-DC-ASGPR antibody or antigen binding fragment thereof comprises three heavy chain CDRs and three light chain CDRs from the variable regions of an anti-DC-ASGPR heavy chain and light chain variable region pair selected from SEQ ID NO:3 and 8; SEQ ID NO:58 and 60; SEQ ID NO:62 and 64; or SEQ ID NO:66 and 68.

40. The use of claim 38, wherein the anti-DC-ASGPR antibody or antigen binding fragment thereof comprises a $\gamma 4$ constant region comprising a substitution of glutamic acid at residue 235 and/or a substitution of proline at residue 228 in the hinge region.

41. The use of any one of claims 38-40, wherein the subject has been diagnosed as having GVHD.

42. The use of any one of claims 38-41, wherein the anti-DC-ASGPR antibody or antigen binding fragment thereof is formulated for intravenous administration.

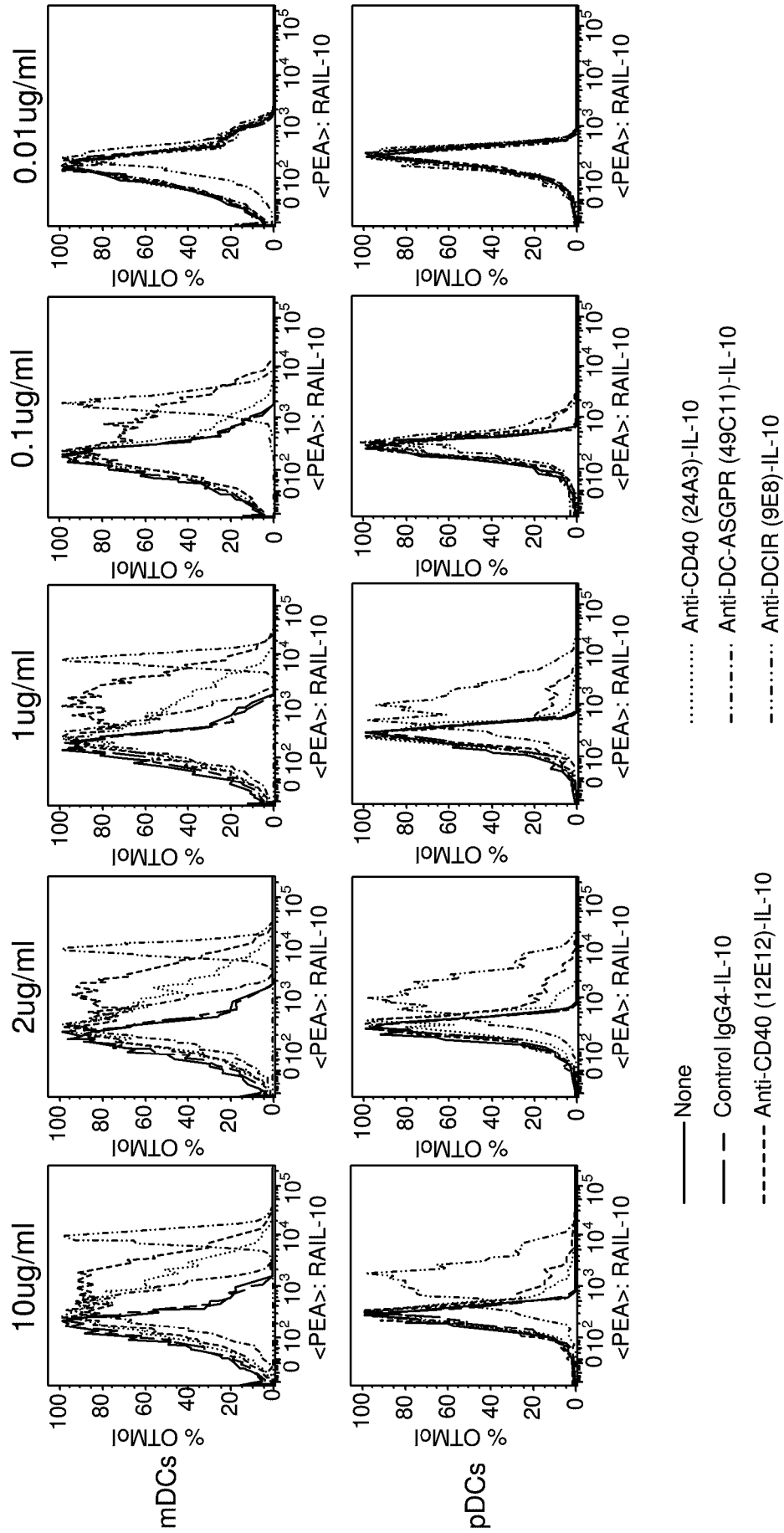


FIG. 1

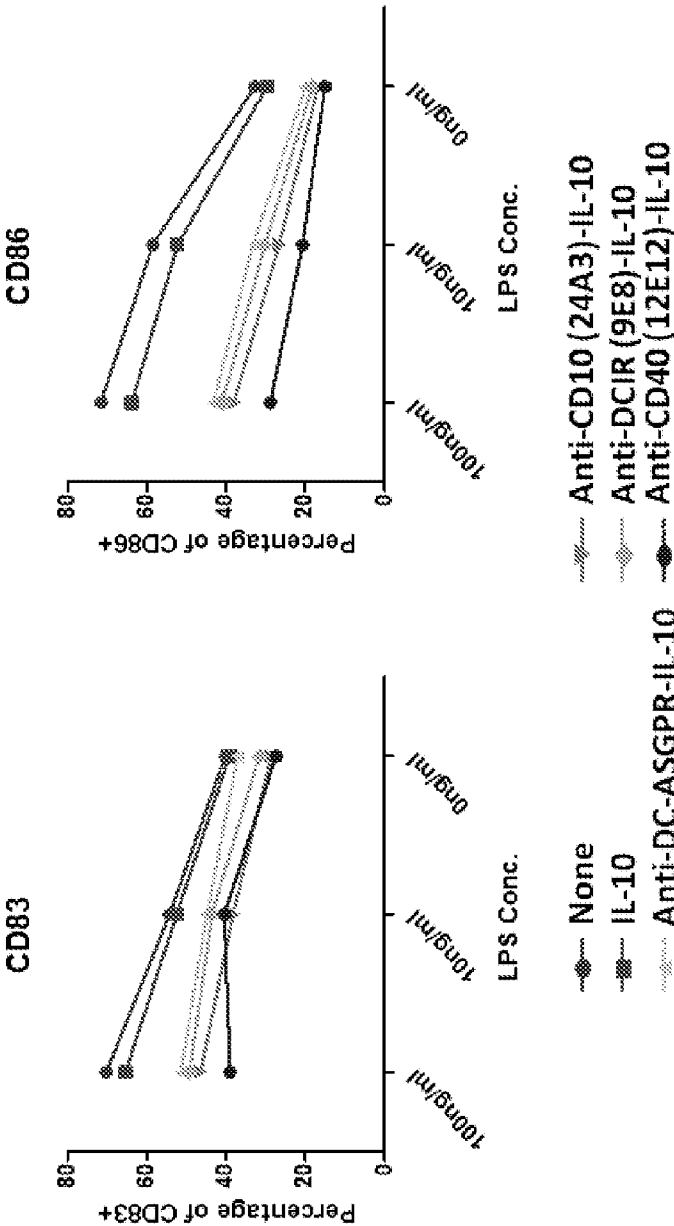
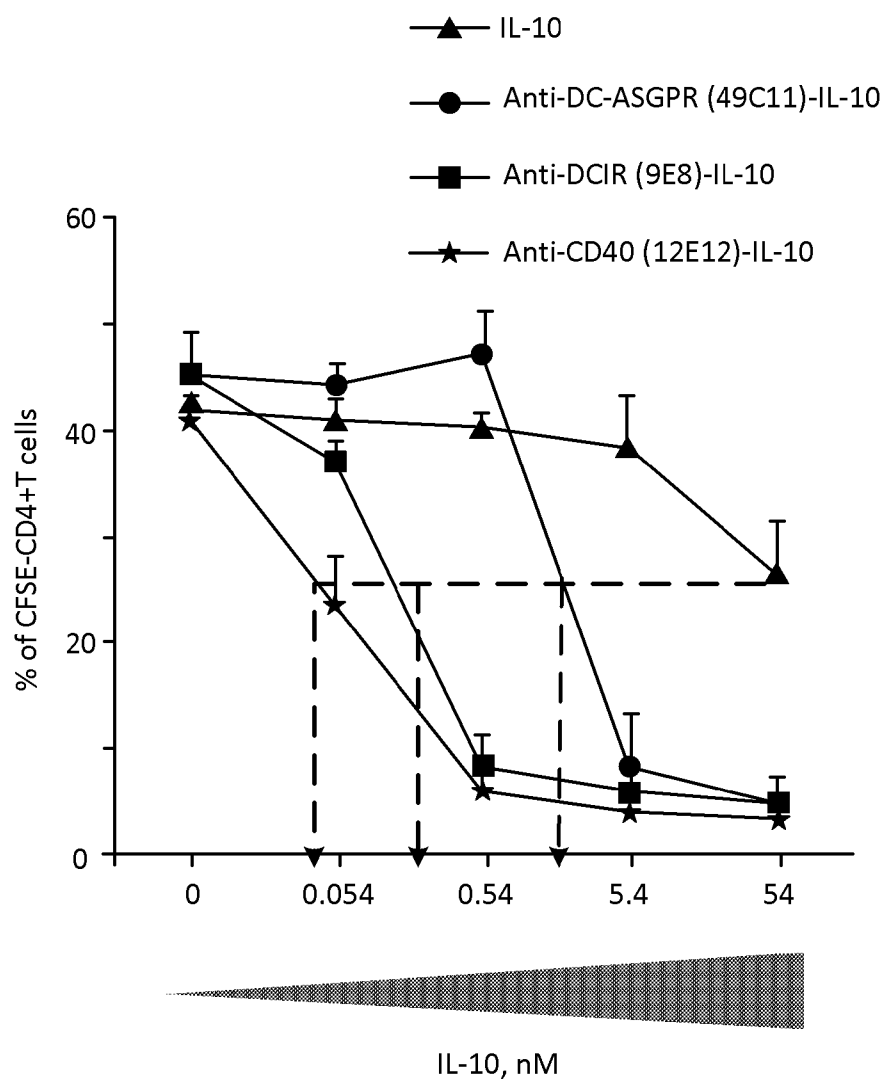


FIG. 2

**FIG. 3**

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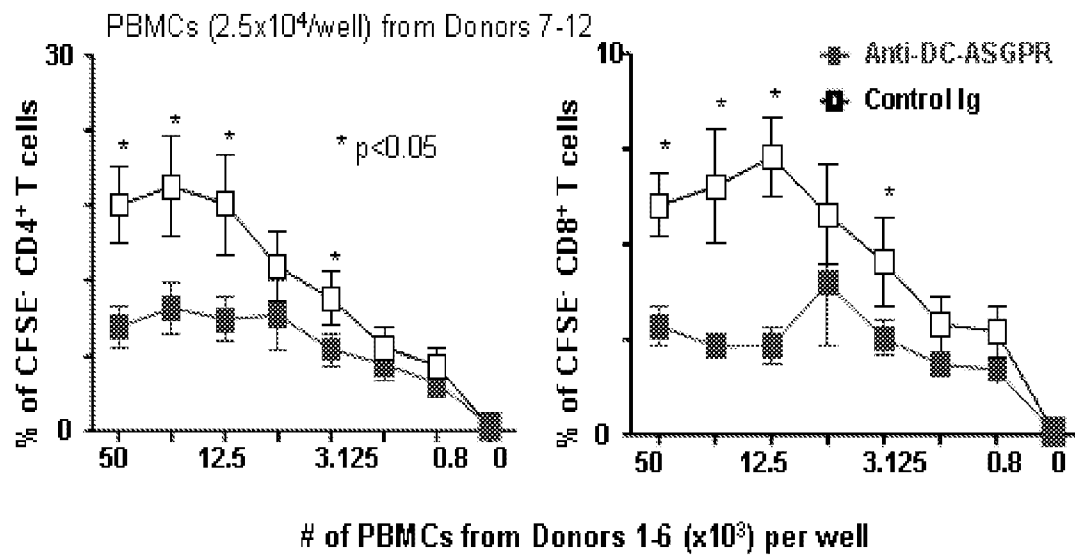


FIG. 4

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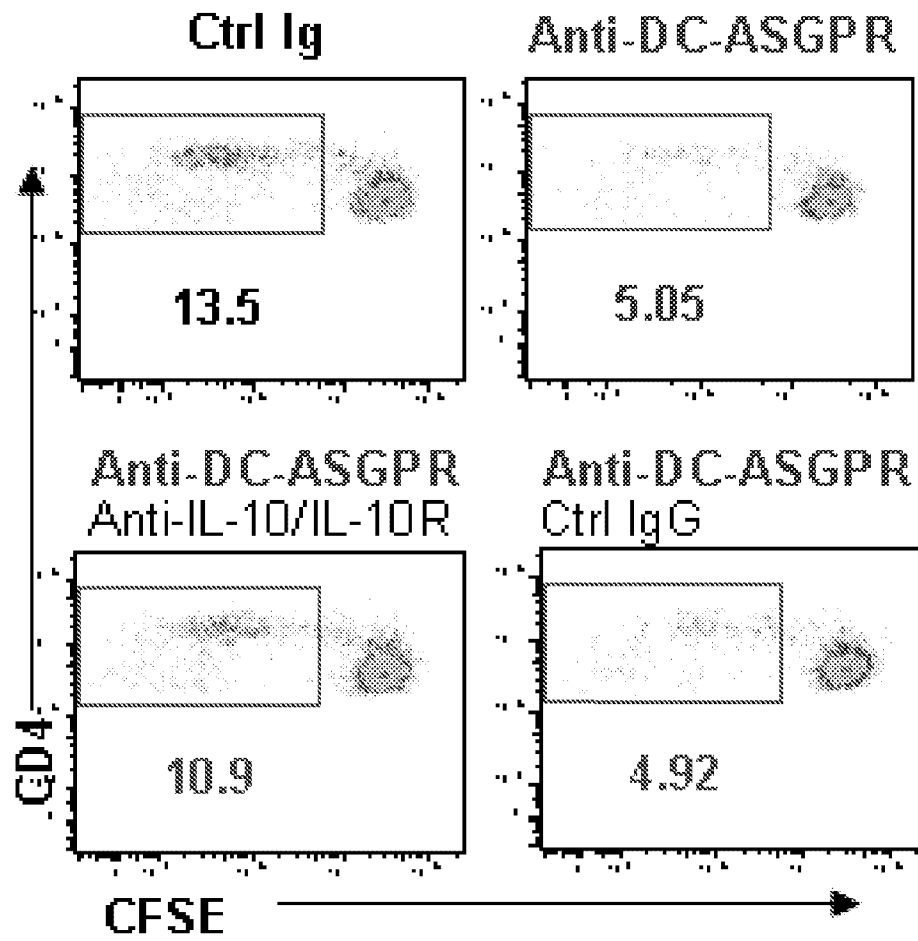


FIG. 5

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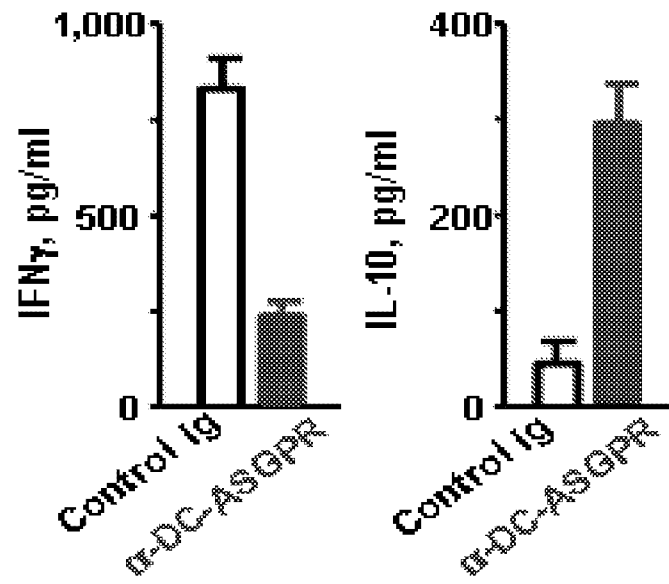


FIG. 6

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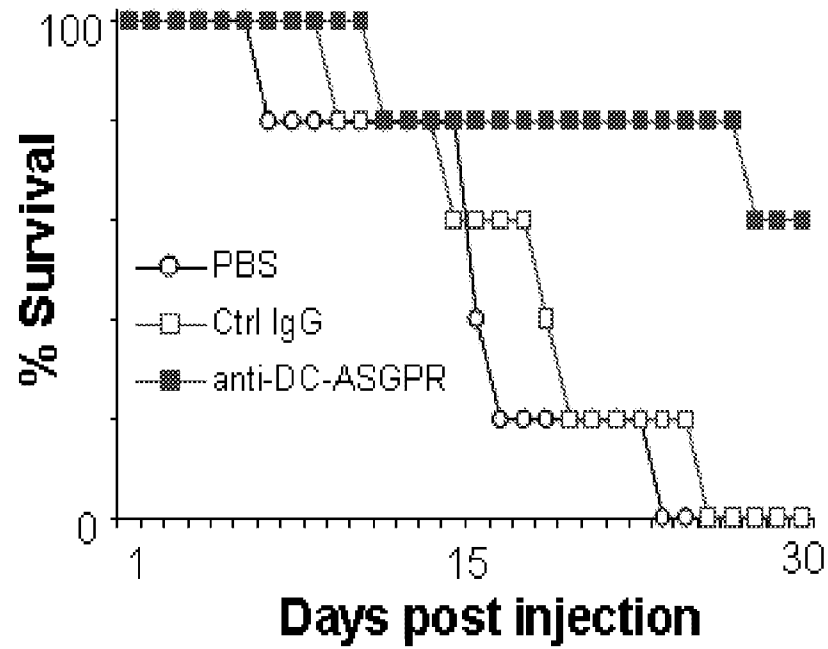


FIG. 7

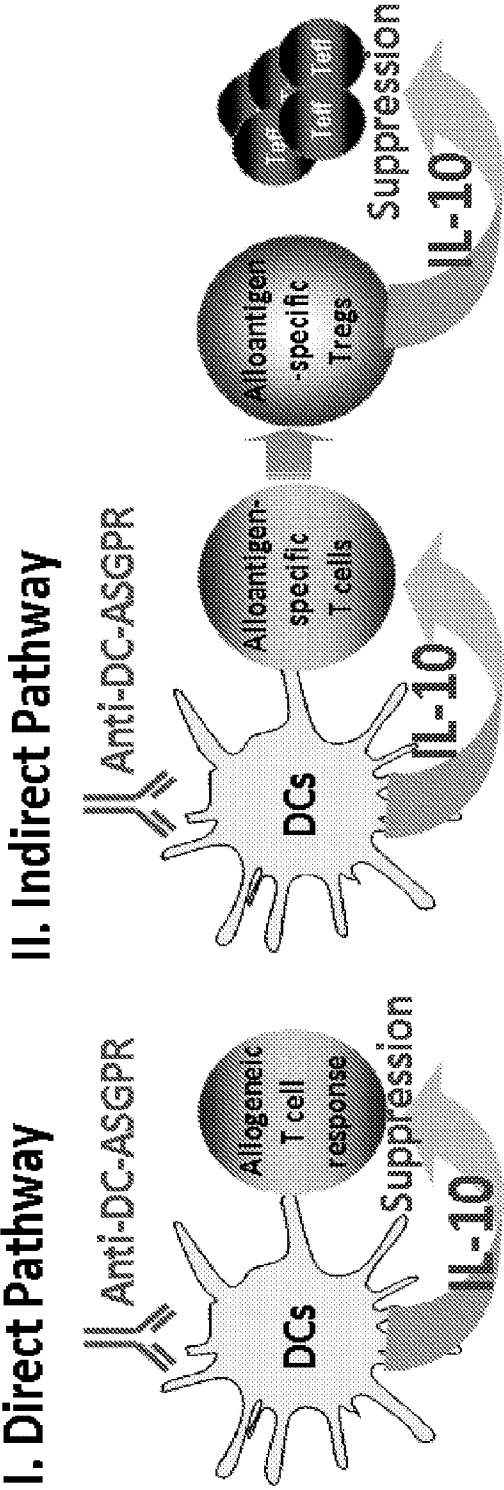


FIG. 8