**[0012]** Thus, there are ample preclinical studies that provide evidence for the crucial role of the CD40-CD40L dyad in driving an efficient T cell-dependent immune response. Blocking of CD40 signaling is therefore recognized as a suitable and needed therapeutic strategy to suppress a pathogenic autoimmune response in diseases such as RA, multiple sclerosis or psoriasis. However, to date, there are no CD40 antibodies that have been approved for therapeutic intervention of such disorders due to the findings that anti-CD40 antibodies previously in development were shown to have significant side effects. Thus, there remains a significant need for therapeutic agents that can be used to intervene in the action of the CD40-CD40L and block CD40 signaling. This need could be addressed by new humanized anti-CD40 antibodies that specifically bind CD40 and which show the antigen binding specificity, affinity, and pharmacokinetic and pharmacodynamic properties that allow use thereof in therapeutic intervention of CD40 based disorders.

## BRIEF SUMMARY

**[0013]** The present disclosure provides a humanized monoclonal antibody wherein said antibody specifically binds to human CD40 having an antagonistic activity IC50 of less than 1nM and has no agonism up to 100 μg/ml in B cell proliferation and wherein said antibody is further characterized in that the antibody has an in vivo half life in non-human primates that is at least 10 days.

**[0014]** The humanized monoclonal antibody may be further characterized in that the antibody has a half-life in cynomolgus monkeys of greater than 8 days at a dose of less than 30 mg/kg.

**[0015]** In exemplary embodiments, the antibody of the disclosure comprises a heavy chain sequence selected from the group consisting of any of SEQ ID NO:1 to SEQ ID NO:4 and a light chain sequence selected from the group consisting of any of SEQ ID NO:5 to SEQ ID NO:8.

**[0016]** In other embodiments, the antibody is a humanized antibody or antigen binding fragment of an antibody having the heavy chain variable region amino acid sequence of any of SEQ ID NO: 1 to 4, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO: 29, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID

NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO: 40, SEQ ID NO: 42, SEQ ID NO: 44, SEQ ID NO: 46, SEQ ID NO: 48, SEQ ID NO. 50 SEQ ID NO: 53, SEQ ID NO: 57, SEQ ID NO: 58, SEQ ID NO: 59, SEQ ID NO: 60, SEQ ID NO: 61, SEQ ID NO: 62, SEQ ID NO: 63, SEQ ID NO: 64, SEQ ID NO: 65, SEQ ID NO: 66, SEQ ID NO: 67, SEQ ID NO: 68, SEQ ID NO: 69, SEQ ID NO: 70, SEQ ID NO: 71, SEQ ID NO: 72, or SEQ ID NO: 73.

**[0017]** In other embodiments, the antibody is a humanized antibody or antigen binding fragment of an antibody that comprises a light chain variable domain amino acid sequence of SEQ ID NO: 5 to SEQ ID NO:8, SEQ ID NO:26, SEQ ID NO:31, SEQ ID NO:36, SEQ ID NO:41, SEQ ID NO:43, SEQ ID NO:45, SEQ ID NO:47, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:74, SEQ ID NO:75, or SEQ ID NO:76.

**[0017a]** In one aspect, there is provided a humanized antibody, wherein said antibody comprises a heavy chain and a light chain, wherein the heavy chain sequence and light chain sequence are selected from the group consisting of: a) a heavy chain CDR1 sequence selected from the group consisting of SEQ ID NO: 9 through SEQ ID NO:11, a heavy chain CDR2 sequence selected from the group consisting of SEQ ID NO:12 through SEQ ID NO:15, and a heavy chain CDR3 sequence selected from the group consisting of SEQ ID NO:16 through SEQ ID NO:17; and b) the light chain CDR1 sequence has a sequence selected from the group consisting of SEQ ID NO:18 through SEQ ID NO:21, a light chain CDR2 sequence of SEQ ID NO:22 through SEQ ID NO:23, and a light chain CDR3 sequence selected from the group consisting of SEQ ID NO:24 through SEQ ID NO:25.

**[0018]** In specific embodiments, the monoclonal antibody described herein is characterized in that it comprises a heavy chain and a light chain, wherein the heavy chain CDR1 sequence selected from the group consisting of SEQ ID NO: 9 through SEQ ID NO:11, a heavy chain CDR2 sequence selected from the group consisting of SEQ ID NO:12 through SEQ ID NO:15 and a heavy chain CDR3 sequence selected from the group consisting of SEQ ID NO:16 through SEQ ID NO:17; and wherein the light chain CDR1 sequence has a sequence selected from the group consisting of SEQ ID NO:18 through SEQ ID NO:21, a light chain CDR2 sequence of SEQ ID NO:22

through SEQ ID NO:23 and a light chain CDR3 sequence selected from the group consisting of SEQ ID NO:24 through SEQ ID NO:25.

**[0019]** In specific embodiments, the monoclonal antibody described herein is characterized in that it comprises a heavy chain CDR1 sequence of SEQ ID NO: 10, a heavy chain CDR2 sequence of SEQ ID NO:13 and a heavy chain CDR3 sequence of SEQ ID NO:16; and wherein said antibody comprises a light chain CDR1 sequence of SEQ ID NO:19, a light chain CDR2 sequence of SEQ ID NO:22 and a light chain CDR3 sequence of SEQ ID NO:24.

**[0020]** In other specific embodiments, the monoclonal antibody described herein is characterized in that it comprises a heavy chain CDR1 sequence of SEQ ID NO: 9, a

heavy chain CDR2 sequence of SEQ ID NO:14 and a heavy chain CDR3 sequence of SEQ ID NO:16; and wherein said antibody comprises a light chain CDR1 sequence of SEQ ID NO:20, a light chain CDR2 sequence of SEQ ID NO:22 and a light chain CDR3 sequence of SEQ ID NO:24.

**[0021]** In another specific embodiment, the monoclonal antibody described herein is characterized in that it comprises a heavy chain CDR1 sequence of SEQ ID NO: 9, a heavy chain CDR2 sequence of SEQ ID NO:14 and a heavy chain CDR3 sequence of SEQ ID NO:16; and wherein said antibody comprises a light chain CDR1 sequence of SEQ ID NO:20, a light chain CDR2 sequence of SEQ ID NO:22 and a light chain CDR3 sequence of SEQ ID NO:24.

**[0022]** In another specific embodiment, the monoclonal antibody described herein is characterized in that it comprises a heavy chain CDR1 sequence of SEQ ID NO: 11, a heavy chain CDR2 sequence of SEQ ID NO:15 and a heavy chain CDR3 sequence of SEQ ID NO:17; and wherein said antibody comprises a light chain CDR1 sequence of SEQ ID NO:21, a light chain CDR2 sequence of SEQ ID NO:23 and a light chain CDR3 sequence of SEQ ID NO:25.

**[0023]** Also described herein are individual sequences for heavy chains of the preferred antibodies of the disclosure. The disclosure, for example, relates to an anti-CD40 antibody comprising a heavy chain variable domain sequence of any one of SEQ ID NOs:1 to 4. The anti-CD40 antibody is further characterized as comprising a light chain variable domain sequence of any one of SEQ ID NOs: 5 to SEQ ID NO:8.

**[0024]** Also contemplated is a humanized antibody or antibody fragment having a heavy chain variable domain and a light chain variable region comprising the amino acid sequences of SEQ ID NO:27 and SEQ ID NO:26, respectively; SEQ ID NO:28 and SEQ ID NO:26, respectively; SEQ ID NO:29 and SEQ ID NO:26, respectively; SEQ ID NO:30 and SEQ ID NO:26, respectively; SEQ ID NO:32 and SEQ ID NO:31, respectively; SEQ ID NO:33 and SEQ ID NO:31, respectively; SEQ ID NO:34 and SEQ ID NO:31, respectively; SEQ ID NO:35 and SEQ ID NO:31, respectively; SEQ ID NO:37 and SEQ

ID NO:36, respectively; SEQ ID NO:38 and SEQ ID NO:36, respectively; SEQ ID NO:39 and SEQ ID NO:36, respectively; SEQ ID NO:40 and SEQ ID NO: 36, respectively.

**[0024a]** In another aspect, there is provided a humanized monoclonal antibody or antibody fragment having a heavy chain variable domain and a light chain variable region comprising the amino acid sequences of SEQ ID NO:27 and SEQ ID NO:26, respectively; SEQ ID NO:28 and SEQ ID NO:26, respectively; SEQ ID NO:29 and SEQ ID NO:26, respectively; SEQ ID NO:30 and SEQ ID NO:26, respectively; SEQ ID NO:32 and SEQ ID NO:31, respectively; SEQ ID NO:33 and SEQ ID NO:31, respectively; SEQ ID NO:34 and SEQ ID NO:31, respectively; SEQ ID NO:35 and SEQ ID NO:31, respectively; SEQ ID NO:37 and SEQ ID NO:36, respectively; SEQ ID NO:38 and SEQ ID NO:36, respectively; SEQ ID NO:39 and SEQ ID NO:36, respectively; SEQ ID NO:40 and SEQ ID NO: 36, respectively.

**[0025]** In another embodiment, the disclosure relates to a humanized antibody or antibody fragment having a heavy chain variable domain and a light chain variable region comprising the amino acid sequences of SEQ ID NO:27 and SEQ ID NO:26, respectively.

**[0026]** In another embodiment, the disclosure relates to a humanized antibody or antibody fragment having a heavy chain variable domain and a light chain variable region comprising the amino acid sequences of SEQ ID NO:28 and SEQ ID NO:26, respectively.

**[0027]** In another embodiment, the disclosure relates to a humanized antibody or antibody fragment having a heavy chain variable domain and a light chain variable region comprising the amino acid sequences of SEQ ID NO:29 and SEQ ID NO:26, respectively.

**[0028]** In another embodiment, the disclosure relates to a humanized antibody or antibody fragment having a heavy chain variable domain and a light chain variable region comprising the amino acid sequences of SEQ ID NO:30 and SEQ ID NO:26, respectively.

**[0029]** In another embodiment, the disclosure relates to a humanized antibody or antibody fragment having a heavy chain variable domain and a light chain variable region comprising the amino acid sequences of SEQ ID NO:32 and SEQ ID NO:31, respectively.

**[0030]** In another embodiment, the disclosure relates to a humanized antibody or antibody fragment having a heavy chain variable domain and a light chain variable region comprising the amino acid sequences of SEQ ID NO:33 and SEQ ID NO:31, respectively.

**[0031]** In another embodiment, the disclosure relates to a humanized antibody or antibody fragment having a heavy chain variable domain and a light chain variable region comprising the amino acid sequences of SEQ ID NO:34 and SEQ ID NO:31, respectively.

**[0032]** In another embodiment, the disclosure relates to a humanized antibody or antibody fragment having a heavy chain variable domain and a light chain variable region comprising the amino acid sequences of SEQ ID NO:35 and SEQ ID NO:31, respectively.

**[0033]** In another embodiment, the disclosure relates to a humanized antibody or antibody fragment having a heavy chain variable domain and a light chain variable region comprising the amino acid sequences of SEQ ID NO:37 and SEQ ID NO:36, respectively.

**[0034]** In another embodiment, the disclosure relates to a humanized antibody or antibody fragment having a heavy chain variable domain and a light chain variable region comprising the amino acid sequences of SEQ ID NO:38 and SEQ ID NO:36, respectively.

**[0035]** In another embodiment, the disclosure relates to a humanized antibody or antibody fragment having a heavy chain variable domain and a light chain variable region comprising the amino acid sequences of SEQ ID NO:39 and SEQ ID NO:36, respectively.

**[0036]** In another embodiment, the disclosure relates to a humanized antibody or antibody fragment having a heavy chain variable domain and a light chain variable region comprising the amino acid sequences of SEQ ID NO:40 and SEQ ID NO: 36, respectively,

**[0037]** Another embodiment relates to an isolated antibody or antigen-binding fragment that specifically binds to human CD40, comprising a humanized heavy chain variable domain comprising a framework region having an amino acid sequence at least 90% identical to the amino acid sequence of the framework region of the human variable domain heavy chain amino acid sequence of SEQ ID NO: 27, SEQ ID NO:28, SEQ ID NO:29 or SEQ ID NO:30, and comprising a light chain amino acid sequence at least 90% identical to a corresponding light chain variable domain of SEQ ID NO:26.

**[0038]** Another embodiment relates to an isolated antibody or antigen-binding fragment that specifically binds to human CD40, comprising a humanized heavy chain

variable domain comprising a framework region having an amino acid sequence at least 90% identical to the amino acid sequence of the framework region of the human variable domain heavy chain amino acid sequence of SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34 or SEQ ID NO:35, and comprising a light chain amino acid sequence at least 90% identical to a corresponding light chain variable of SEQ ID NO:31.

**[0039]** The disclosure also relates to the isolated antibody or antigen-binding fragment described in the embodiment immediately above, wherein the heavy chain amino acid sequence is SEQ ID NO:32; in another embodiment, the heavy chain amino acid sequence is SEQ ID NO:33; in another embodiment, the heavy chain amino acid sequence is SEQ ID NO:34; and in another embodiment, the heavy chain amino acid sequence is SEQ ID NO:35,

**[0040]** Also contemplated is an isolated antibody or antigen-binding fragment that specifically binds to human CD40, comprising a humanized heavy chain variable domain comprising a framework region having an amino acid sequence at least 90% identical to the amino acid sequence of the framework region of the human variable domain heavy chain amino acid sequence of SEQ ID NO: 37, SEQ ID NO:38; SEQ ID NO:39 or SEQ ID NO: 40, and comprising a light chain amino acid sequence at least 90% identical to a corresponding light chain of SEQ ID NO:36.

**[0041]** The disclosure also relates to the isolated antibody or antigen-binding fragment described in the embodiment immediately above, wherein the heavy chain amino acid sequence is SEQ ID NO:37; in another embodiment, the heavy chain amino acid sequence is SEQ ID NO:38; in another embodiment, the heavy chain amino acid sequence is SEQ ID NO:39; and in another embodiment, the heavy chain amino acid sequence is SEQ ID NO:40,

**[0042]** The antibodies of the present disclosure may be further characterized in that said antibodies fail to stimulate production of cytokines from B cells in that absence of CD40L.

**[0043]** The antibodies of the present disclosure may be further characterized in that said antibodies bind to human CD40 in the presence of 50% human serum with a reduction of on rate less than two fold.

**[0044]** The antibodies of the present disclosure may be further characterized in that said antibody produces inhibition of IgM and IgG production in a mammal at a concentration of 1 mg/kg.

**[0045]** The antibodies of the present disclosure may be used in various therapeutic, prophylactic, diagnostic and other methods. For example, the present disclosure describes a method of blocking the function of human CD40 in a mammal comprising administering to said mammal a composition comprising an antibody of the disclosure in an amount sufficient to block a CD40 mediated immune response in said mammal. In another aspect, there is provided an antibody as defined herein for use in blocking the function of human CD40 in a mammal, wherein said antibody is in an amount sufficient to block a CD40 mediated immune response in said mammal.

**[0046]** Also contemplated herein is a method of treating or ameliorating graft vs host disease in a mammal comprising administering to said mammal a composition comprising an antibody of the disclosure in an amount sufficient to decrease one or more of the symptoms of graft vs. host disease in said animal. In another aspect, there is provided an antibody as defined herein for use in treating or ameliorating a disesase or disorder in a mammal, wherein said antibody is in an amount sufficient to decrease one or more of the symptoms of the disease or disorder in the mammal.

**[0047]** By way of example, the autoimmune or inflammatory disease may include but is not limited to rheumatoid arthritis, multiple sclerosis, proliferative lupus glomerulonephritis, inflammatory bowel disease (IBD), psoriasis, idiopathic thrombocytopenic purpura (ITP), Crohn's Disease and systemic lupus erythematosus (SLE), Hashimoto's thyroiditis, primary myxoedema, thyrotoxicosis/Graves disease, pernicious anaemia, autoimmune atrophic gastritis, autoimmune carditis, Addison's disease, premature menopause, type 1-diabetes mellitus, Good pasture's syndrome, myasthenia gravis, autoimmune haemolytic anaemia, idiopathic leucopenia, primary biliary cirrhosis, active chronic hepatitis (HBs Ag negative), cryptogenic cirrhosis, Sjogren's syndrome, dermatomyositis, scleroderma, mixed tissues connective disease, discoid lupus erythematosus, and systemic vasculitis. In exemplary embodiments, the mammal has rheumatoid arthritis.

**[0048]** The methods of the disclosure may further comprise administering a second therapeutic agent selected from the group consisting of a TNF-antagonist, a disease-modifying antirheumatic drug, a CTLA4-antagonist, an anti-IL-6 receptor mAb and an anti-CD20 mAb.

**[0049]** In specific embodiments, the inflammatory disease or autoimmune disease is an inflammatory disease or autoimmune disease that is associated with cells expressing both CD40 and CD20.

**[0050]** In specific methods the treatment involves administering the antibody composition by a parenteral route of administration.

**[0051]** In specific methods the treatment involves administering the antibody composition intravenously or subcutaneously.

**[0052]** Additional methods of the disclosure comprise inhibiting antibody production by B cells in a human patient comprising administering to said human patient an effective amount of an anti-CD40 antibody of the disclosure.

**[0053]** More specifically, the human patient has an inflammatory disease or autoimmune disease that is associated with CD40-expressing cells.

**[0054]** In exemplary embodiments the human patient is suffering from an autoimmune disease selected from the group consisting of autoimmune or inflammatory disease selected from the group consisting of rheumatoid arthritis, multiple sclerosis, proliferative lupus glomerulonephritis, inflammatory bowel disease (IBD), psoriasis, idiopathic thrombocytopenic purpura (ITP), Crohn's Disease and systemic lupus erythematosus (SLE), Hashimoto's thyroiditis, primary myxoedema, thyrotoxicosis/Graves disease, pernicious anaemia, autoimmune atrophic gastritis, autoimmune carditis, Addison's disease, premature menopause, type 1-diabetes mellitus, Good pasture's syndrome, myasthenia gravis, autoimmune haemolytic anaemia, idiopathic leucopenia, primary biliary cirrhosis, active chronic hepatitis (HBs Ag negative), cryptogenic cirrhosis, Sjogren's syndrome, dermatomyositis, scleroderma, mixed tissues connective disease, discoid lupus erythematosus, and systemic vasculitis.

**[0055]** Another method of the disclosure relates to inhibiting the growth of cells expressing human CD40 antigen, comprising administering the antibody or antigen-binding fragment of the disclosure to the cells, which antibody or antigen-binding fragment specifically binds to the human cell surface CD40 antigen, wherein the binding

of the antibody or antigen-binding fragment to the CD40 antigen inhibits the growth or differentiation of the cells.

**[0056]** Also contemplated is a method of treating a subject having a CD40-associated disorder, comprising administering to the subject the antibody or antigen-binding fragment of the disclosure, which antibody or antigen-binding fragment specifically binds to human CD40, wherein the binding of the antibody or antigen-binding fragment to CD40 inhibits the growth or differentiation of cells of the CD40-associated disorder. The cells may be but are not limited to B lymphoblastoid cells, pancreatic, lung cells, breast cells, ovarian cells, colon cells, prostate cells, skin cells, head and neck cells, bladder cells, bone cells or kidney cells.

**[0057]** The treatment method for inhibiting growth or differentiation of cells may be useful in the treatment for chronic lymphocytic leukemia, Burkitt's lymphoma, multiple myeloma, a T cell lymphoma, Non-Hodgkin's Lymphoma, Hodgkin's Disease, Waldenstrom's macroglobulinemia or Kaposi's sarcoma.

**[0058]** Also contemplated is a method for inducing depletion of peripheral B cells, comprising administering to the cells the antibody or antigen-binding fragment of the disclosure, which antibody or antigen-binding fragment specifically binds to a human cell surface CD40 antigen, wherein the binding of the antibody or antigen-binding fragment to the CD40 antigen induces depletion of the cells.

**[0059]** In specific embodiments, the antibody or antigen-binding fragment is administered to a subject having an immune disorder. For example, the immune disorder is rheumatoid arthritis or systemic lupus erythematosus.

**[0060]** Also contemplated is a method of treating rheumatoid arthritis in a subject comprising administering to said subject an antibody of the disclosure, wherein said antibody is an antagonistic antibody that blocks the function of CD40 in said subject.

**[0061]** Preferably, the antibody is administered in an amount effective to inhibit B cell differentiation and antibody isotype switching in said subject.

**[0062]** In other embodiments, the antibody is administered in an amount effective to inhibit cytokine and chemokine production and up-regulation of adhesion molecules

in T-cells and macrophages in said subject. Preferably, the antibody is administered in an amount effective to inhibit activation of dendritic cells in said subject.

**[0063]** In other embodiments, the method is further characterized in that the antibody is administered in an amount effective to inhibit production of proinflammatory cytokines, chemokines, matrix metalloproteinases, prostaglandins, and down-regulate adhesion molecules in non-immune cells in said subject.

**[0064]** In specific embodiments, the antibody is administered in combination with a regimen comprising methotrexate administration and/or administration of Enbrel/Humira.

**[0065]** The subject for receiving the therapy is one that has rheumatoid arthritis and has been non-responsive to methotrexate treatment alone.

**[0066]** In specific embodiments, the method comprises treating said subject with a regimen comprising methotrexate administration and/or administration of Enbrel/Humira.

**[0067]** The method of the disclosure may be further characterized wherein treatment of said subject with said antagonistic anti-CD40 antibody has a superior efficacy to treatment with methotrexate alone, Enbrel alone, a combination of Enbrel+methotrexate.

**[0068]** The method of the disclosure may be further characterized wherein treatment of said subject with said antagonistic anti-CD40 antibody has a superior efficacy to treatment with Enbrel +MTX in patients who have had an inadequate response to methotrexate.

**[0069]** In specific embodiments, the antibody is administered in combination with a regimen comprising an anti-TNF agent.

**[0070]** In specific embodiments, subject is characterized as one who has rheumatoid arthritis and has been non-responsive to treatment with an anti-TNF agent alone. In such embodiments, the method may comprise treating said subject with a regimen comprising treatment with an anti-TNF agent in combination with said antagonistic anti-CD40 antibody.

**[0071]** In specific embodiments, the treatment of said subject with said antagonistic anti-CD40 antibody has a superior efficacy to treatment with an anti-TNF agent.

**[0072]** In still other embodiments, the method is characterized in that the treatment of said subject with said antagonistic anti-CD40 antibody has a superior efficacy to treatment with Orencia or Rituxan in patients who have had an inadequate response to an anti-TNF agent alone.

**[0073]** The present disclosure further contemplates a pharmaceutical composition comprising:(i) the antibody or antigen-binding fragment as described herein; and(ii) a pharmaceutically acceptable excipient. In such compositions, the antibody or antigen binding fragment thereof may advantageously be conjugated to a second agent, such as for example, a cytotoxic agent, a PEG-carrier, an enzyme or a marker. Hence, in another aspect, there is provided a pharmaceutical composition comprising: (i) the antibody as defined herein; and (ii) a pharmaceutically acceptable excipient; and wherein the antibody or antigen binding fragment thereof is optionally conjugated to a second agent.

**[0074]** Also contemplated herein is an isolated polynucleotide encoding a heavy chain variable region amino acid sequence of any of SEQ ID NO: 1 to 4, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO: 29, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO: 40, SEQ ID NO: 42, SEQ ID NO: 44, SEQ ID NO: 46, SEQ ID NO: 48, SEQ ID. NO. 50, SEQ ID NO: 53, SEQ ID NO: 57, SEQ ID NO: 58, SEQ ID NO: 59, SEQ ID NO: 60, SEQ ID NO: 61, SEQ ID NO: 62, SEQ ID NO: 63, SEQ ID NO: 64, SEQ ID NO: 65, SEQ ID NO: 66, SEQ ID NO: 67, SEQ ID NO: 68, SEQ ID NO: 69, SEQ ID NO: 70, SEQ ID NO: 71, SEQ ID NO: 72, or SEQ ID NO: 73.

**[0075]** Also contemplated herein is an isolated polynucleotide encoding a light chain variable region amino acid sequence of any of SEQ ID NO: 5 to SEQ ID NO:8, SEQ ID NO:26, SEQ ID NO:31, SEQ ID NO:36, SEQ ID NO:41, SEQ ID NO:43, SEQ ID NO:45, SEQ ID NO:47, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:74, SEQ ID NO:75, or SEQ ID NO:76.

**[0075a]** In another aspect, there is provided an isolated polynucleotide or polynucleotides encoding: light chain SEQ ID NO:26 with one of heavy Chain SEQ ID NOs 27-30 (Antibody A); light chain SEQ ID NO:31 with one of heavy Chain SEQ ID NOs 32-35 (Antibody B); light chain SEQ ID NO:36 with one of heavy Chain SEQ ID NOs 37-40 (Antibody C); variable heavy and variable light chain of SEQ ID NOs 44/43 (antibody A); variable heavy and variable light chain of SEQ ID NOs 53/52 (antibody B); or variable heavy and variable light chain of SEQ ID NOs 58/56 (antibody C).

**[0076]** The disclosure further relates to the use of the antibodies described herein for the manufacture of a medicament for blocking the function of human CD40 in a

mammal wherein the medicament blocks a CD40 mediated immune response in said mammal.

**[0077]** In an embodiment the disclosure relates to the manufacture of a medicament for treating or ameliorating graft vs host disease in a mammal.

**[0077a]** In another aspect, there is provided use of an antibody as defined herein in the manufacture of a medicament for the treatment or amelioration of a disease or disorder selected from the group consisting of: graft v. host disease, autoimmune or inflammatory disease, and CD40-related disorder.

**[0078]** In exemplary embodiments, the medicament is manufactured for the treatment of an autoimmune or inflammatory disease selected from the group consisting of rheumatoid arthritis, multiple sclerosis, proliferative lupus glomerulonephritis, inflammatory bowel disease (IBD), psoriasis, idiopathic thrombocytopenic purpura (ITP), Crohn's Disease and systemic lupus erythematosus (SLE), Hashimoto's thyroiditis, primary myxoedema, thyrotoxicosis/Graves disease, pernicious anaemia, autoimmune atrophic gastritis, autoimmune carditis, Addison's disease, premature menopause, type 1-diabetes mellitus, Good pasture's syndrome, myasthenia gravis, autoimmune haemolytic anaemia, idiopathic leucopenia, primary biliary cirrhosis, active chronic hepatitis (HBs Ag negative), cryptogenic cirrhosis, Sjogren's syndrome, dermatomyositis, scleroderma, mixed tissues connective disease, discoid lupus erythematosus, and systemic vasculitis.

**[0079]** In some embodiments, the medicament may further comprise a second therapeutic agent selected from the group consisting of a TNF-antagonist, a disease-modifying antirheumatic drug, a CTLA4-antagonist, an anti-IL-6 receptor mAb and an anti-CD20 mAb.

**[0080]** The medicament may be manufactured for use in a parenteral route of administration. The medicament may be manufactured for use intravenously or subcutaneously.

**[0081]** Another embodiment contemplates a use of the antibodies described herein for the manufacture of a medicament for the inhibition of antibody production by B cells in a human patient.

**[0082]** Another embodiment contemplates a use of the antibodies described herein for the manufacture of a medicament for inhibiting the growth and/or differentiation of cells expressing human CD40 antigen.

**[0083]** Another embodiment contemplates a use of the antibodies described herein for the manufacture of a medicament for the treatment of a subject having a CD40-associated disorder wherein the binding of the antibody or antigen-binding fragment in said medicament to CD40 inhibits the growth or differentiation of cells of the CD40-associated disorder.

**[0084]** The medicament may be manufactured for use in the treatment of cells of a CD40-associated disorder selected from B lymphoblastoid cells, pancreatic, lung cells, breast cells, ovarian cells, colon cells, prostate cells, skin cells, head and neck cells, bladder cells, bone cells or kidney cells.

**[0085]** The medicament may be manufactured for use in the treatment of chronic lymphocytic leukemia, Burkitt's lymphoma, multiple myeloma, a T cell lymphoma, Non-Hodgkin's Lymphoma, Hodgkin's Disease, Waldenstrom's macroglobulinemia or Kaposi's sarcoma.

**[0086]** Another embodiment contemplates a use of antibodies of the disclosure in the manufacture of a medicament for inducing depletion of peripheral B cells wherein the antibody or antigen-binding fragment of the medicament specifically binds to a human cell surface CD40 antigen, wherein the binding of the antibody or antigen-binding fragment to the CD40 antigen induces depletion of the cells.

**[0087]** The medicament may be manufactured for use in the treatment of a subject having an immune disorder.

**[0088]** The medicament may be manufactured for use in the treatment of rheumatoid arthritis or systemic lupus erythematosus.

**[0089]** Another embodiment contemplates a use of antibodies of the disclosure in the manufacture of a medicament for the treatment of rheumatoid arthritis in a subject.

**[0090]** The medicament may be manufactured for use in inhibition of B cell differentiation and antibody isotype switching in said subject.

**[0091]** The medicament may be manufactured for use in inhibition of cytokine and chemokine production and up-regulation of adhesion molecules in T-cells and macrophages in said subject.

**[0092]** The medicament may be manufactured for use in inhibition of activation of dendritic cells in said subject.

**[0093]** The medicament may be manufactured for use in inhibition of production of proinflammatory cytokines, chemokines, matrix metalloproteinases, prostaglandins, and down-regulation of adhesion molecules in non-immune cells in said subject.

**[0094]** In certain embodiments, the medicament is manufactured as a combination medicament to be administered in combination with a regimen comprising methotrexate administration and/or administration of Enbrel/Humira.

**[0095]** In other embodiments, the medicament is manufactured as a combination medicament and the medicament in addition to comprising the antibodies of the disclosure further comprises an anti-TNF agent.

## BRIEF DESCRIPTION OF SEVERAL VIEWS OF THE DRAWINGS

**[0096]** Figure 1: A. Binding curves and corresponding EC50 values of humanized antibodies on CD40 transfected HEK-293 cells measured by flow cytometry. B. Comparison of binding of Antibody A, Antibody B and Antibody C to CD40 transfected HEK cells measured by flow cytometry. Representative data for one experiment is shown

**[0097]** Figure 2: Binding curves and corresponding EC50 values of humanized antibodies on RAMOS cells measured by flow cytometry. Representative data for one experiment is shown.

**[0098]** Figure 3: Testing of mouse and humanized antibodies for antagonistic activity in a human primary B cell proliferation assay. (A) Representative antibody titration curves and resulting IC50 values is depicted for each mouse precursor antibody. Representative data for one donor is shown. (B) Overlay of inhibition curves depicting antagonism of various humanized anti-CD40 antibodies in comparison to 4D11.

**[0099]** Figure 4: Summary of the results of testing the humanized antibodies for antagonistic (IC50) and agonistic (SI= stimulation index) activity in a human primary B cell proliferation assay. Various anti-CD40 antibodies, 4D11, G28.5 and 5D12, are shown for comparison.