

THERAPEUTIC ANTI-CD40 LIGAND ANTIBODIES

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This PCT application claims the benefit of U.S. Provisional Application No. 62/510,471, filed May 24, 2017, the disclosure of which is hereby incorporated by reference in its entirety.

SEQUENCE LISTING

[0002] This application incorporates by reference in its entirety the sequence listing entitled “224823-431206_ST25.txt” created on May 23, 2018, at 2:40 pm, that is 100 KB, and filed electronically herewith.

FIELD

[0003] Anti-CD40L antibodies, compositions comprising the antibodies, and method of using same for treatment of CD40L-related diseases or disorders.

BACKGROUND

[0004] The interaction of CD40 with its ligand CD40L plays a critical role in regulating immune responses. Binding of CD40L to CD40 triggers activation of the CD40 pathway which up-regulates costimulatory molecules such as CD80 and CD86. Blockade of the interaction between CD40 and CD40L by monoclonal antibodies has been shown to result in protection from autoimmunity and graft rejection in various preclinical models. Recently, in a mouse model of amyotrophic lateral sclerosis, an antibody directed to CD40L was shown to delay disease onset and prolong survival the onset of disease. (United States Patent No. 8,435,514, hereby incorporated by reference). In early clinical studies, the humanized anti-CD40L antibody hu5c8 showed efficacy in patients with lupus and in patients with immune thrombocytopenic purpura. However, incidents of thromboembolism in the patients treated with hu5c8 halted further trials. Further *in vitro* and preclinical animal studies established that interaction of the Fc with the Fc receptor FcγRIIa caused platelet activation, and aggregation, that resulted in thromboembolic events. In addition, it has been reported that binding of the Fc to complement may reduce or prevent induction of immune tolerance. Various approaches have been taken to reduce or eliminate the interaction of the immunoglobulin Fc region with FcγRIIa, and/or to reduce or eliminate the interaction with complement, including introducing point mutation(s) in the Fc region to make anti-CD40L antibodies which lack Fc effector function. Other approaches use fragments of antibodies lacking the Fc region or antibodies that contain multiple amino acid substitutions in the Fc region. Although the anti-CD40L antibody, hu5c8, showed efficacy in human patients there is no anti-CD40L antibody on the market.

Accordingly, there is a need for improved anti-CD40L antibodies for administration to humans that are efficacious and do not cause platelet activation or aggregation or bind to complement yet are stable and bind to CD40L.

SUMMARY

[0005] Novel antibody polypeptides and antigen binding fragments thereof, of the present invention provide such improved anti-CD40L antibodies. The following section only summarizes certain aspects of the present disclosure and is not intended to be limiting in nature. These aspects and other aspects and embodiments are described more fully below. All references cited in this specification are hereby incorporated by reference in their entirety. In the event of a discrepancy between the express disclosure of this specification and the references incorporated by reference, the express disclosure of this specification shall control.

[0006] The present invention provides isolated, engineered, non-naturally occurring antibodies and antigen binding fragments thereof, that bind human CD40L and block the binding of CD40 to CD40L. The antibody and antigen binding fragments thereof, are engineered to have the desired activity and binding. In some embodiments the antibody or antigen binding fragment thereof, are engineered to have decreased Fc effector function in comparison to some previous anti-CD40L antibodies. The antibodies and antigen binding fragments thereof as disclosed in the present application are useful in the treatment of diseases involving CD40L activation, including neurodegenerative or neuromuscular diseases or disorders, inflammatory or immune diseases or disorders and autoimmune diseases.

[0007] In one aspect the present disclosure provides isolated antibodies or antigen-binding fragments thereof that specifically binds to CD40L which comprise: (a) a heavy chain variable region (V_H) comprising: i) a CDRH1 domain comprising the sequence set forth in SEQ ID NO: 9; ii) a CDRH2 domain comprising the sequence set forth in SEQ ID NO: 10, 11, 12, 13, or 14; iii) a CDRH3 domain comprising the sequence set forth in SEQ ID NO: 15; and (b) a light chain variable region (V_L) comprising: i) a CDRL1 domain comprising the sequence set forth in SEQ ID NO: 16 or 17; ii) a CDRL2 domain comprising the sequence set forth in SEQ ID NO: 18 or 19; and iii) a CDRL3 domain comprising the sequence set forth in SEQ ID NO: 20.

[0008] In some embodiments of the above aspect the present disclosure provides isolated antibodies or antigen-binding fragments thereof that specifically binds to CD40L which comprise: (a) a heavy chain variable region (V_H) comprising: i) a CDRH1 domain consisting of the sequence set forth in SEQ ID NO: 9; ii) a CDRH2 domain consisting of the sequence set forth in SEQ ID NO: 10, 11, 12, 13, or 14; iii) a CDRH3 domain consisting of the sequence set forth in SEQ ID NO: 15; and (b) a light chain variable region (V_L) comprising: i) a CDRL1

domain consisting of the sequence set forth in SEQ ID NO: 16 or 17; ii) a CDRL2 domain consisting of the sequence set forth in SEQ ID NO: 18 or 19; and iii) a CDRL3 domain consisting of the sequence set forth in SEQ ID NO: 20.

[0009] The present disclosure also provides for isolated antibodies or antigen-binding fragments thereof that specifically binds to CD40L comprising: (a) a heavy chain variable region (V_H) having the amino acid sequence as set forth in SEQ ID NOs: 1, 2, 3, or 4; and (b) a light chain variable region (V_L) having the amino acid sequence as set forth in SEQ ID NOs: 5, 6, 7, or 8.

[0010] In some embodiments the isolated antibody or antigen binding fragment thereof according to the disclosure comprises an Fc region and the Fc region has been engineered to reduce or eliminate one or more Fc effector function. In some embodiments the isolated antibodies are of the IgG1 isotype, and the heavy chain constant region comprises the amino acid sequence as set forth in SEQ ID NO: 21. In yet other embodiments the antibody comprises a heavy chain constant region wherein the heavy chain constant region comprises the amino acid sequence as set forth in SEQ ID NO: 22. In still other embodiments the antibody comprises a heavy chain constant region wherein the heavy chain constant region comprises the amino acid sequence as set forth in SEQ ID NO: 23. In another embodiment the antibody comprises a heavy chain constant region wherein the heavy chain constant region comprises the amino acid sequence as set forth in SEQ ID NO: 24.

[0011] Another aspect of the present disclosure provides for methods for treating a subject with a CD40L-associated disease or disorder comprising administering to the subject a therapeutically effective amount of an antibody or antibody fragment according to the present disclosure. In another aspect the present disclosure provides for methods for inhibiting an immune response in a subject comprising administering to the subject a therapeutically effective amount of an antibody or antibody fragment according to the present disclosure.

BRIEF DESCRIPTION OF THE DRAWING(S)

[0012] Figure 1A is a bar graph showing the ranked potency of 16 antibody clones versus the anti-CD40L antibody 5c8. Ranked potency is $IC_{50} \text{ clone} / IC_{50} \text{ of } 5c8 \times 100$.

[0013] Figure 1B is a bar graph showing the ranked potency of 16 antibody clones versus the anti-CD40L antibody AT-1501. Ranked potency is $IC_{50} \text{ clone} / IC_{50} \text{ of } AT-1501 \times 100$.

[0014] Figures 2A-2G and 2I-2Q show the binding curves of the antibodies from each of the clones with the binding curve for 5c8. Figure 2H shows the binding curves of AT-1501 and 5c8.

[0015] Figures 3A-3G and 3I-3Q show the binding curves of the antibodies from each of the

clones with the binding curve for AT-1501. Figure 3H shows the binding curves of AT-1501 and 5c8.

[0016] Figures 4A and 4B are graphs, each of which shows binding of eight of the antibody clones, 5c8, AT-1501 and abatacept to FcγRI. The only antibody having significant binding is the 5c8 antibody.

[0017] Figures 5A and 5B are graphs, each of which shows binding of eight of the antibody clones, 5c8, AT-1501 and abatacept to FcγRIIa. The only antibody having significant binding is the 5c8 antibody.

[0018] Figures 6A and 6B are graphs, each of which shows binding of eight of the antibody clones, 5c8, AT-1501 and abatacept to FcγRIIIa. None of the antibodies showed significant binding to FcγRIIIa. Figures 6C and 6D are graphs, each of which shows binding of eight of the antibody clones, 5c8, AT-1501 and abatacept to FcγRIIIb. None of the antibodies showed significant binding to FcγRIIIb.

[0019] Figures 7A and 7B are graphs, each showing the binding of eight of the antibody clones, 5c8, AT-1501 and abatacept to C1q. The only antibody having significant binding to C1q was the 5c8 antibody.

DETAILED DESCRIPTION

[0020] Definitions

[0021] For convenience, the meaning of certain terms and phrases used in the specification, examples, and appended claims, are provided below.

[0022] The terms such as “comprises”, “comprised”, “comprising”, “contains”, “containing” and the like have the meaning attributed in United States patent law; these terms are inclusive or open-ended and do not exclude additional, unrecited elements or method steps. Terms such as “consisting essentially of” and “consists essentially of” have the meaning attributed to them in United States patent law; these terms allow for the inclusion of additional ingredients or steps that do not materially affect the basic and novel characteristics of the claim invention. The terms “consists of” and “consisting of” have the meaning ascribed to them in United States patent law; these terms are close ended.

[0023] TMB is an abbreviation of 3,3',5,5'-Tetramethylbenzidine.

[0024] “CDR domain” as used herein means an antibody complementary determining region with or without flanking sequences.

[0025] The invention illustratively described herein suitably may be practiced in the absence of any element or elements, limitation or limitations which is not specifically disclosed herein.

[0026] "Effector functions" refer to those biological activities attributable to the Fc region of an antibody, which vary with the antibody isotype. Examples of antibody effector functions include: C1q binding and complement dependent cytotoxicity (CDC); Fc receptor binding; antibody-dependent cell-mediated cytotoxicity (ADCC); phagocytosis; down regulation of cell surface receptors (e.g. B cell receptor); and B cell activation. One effector function is ability of the Fc or constant region of an antibody to bind proteins including, but not limited to, an Fc receptor (FcR) (e.g., high affinity Fc region of IgG receptor Ia (FC γ RIa) (CD64) (SEQ ID NO: 34), low affinity immunoglobulin gamma Fc region acceptor IIa (FC γ RIIa) (CD32) (SEQ ID NO: 35), low affinity immunoglobulin gamma Fc region receptor IIIa (FC γ RIIIa) (CD16a) (SEQ ID NO: 36), low affinity immunoglobulin gamma Fc region receptor IIIb (FC γ RIIIb) (CD16b)) (SEQ ID NO: 37). In embodiments of the present invention where the antibodies and antigen binding fragments thereof, have an Fc domain, the Fc domain has been engineered to reduce or eliminate one or more Fc effector function. In a preferred embodiment the Fc domain has been engineered to reduce or eliminate platelet activation and/or platelet aggregation and the concomitant risk of thromboembolism.

[0027] As used herein, the singular forms "a", "an", and "the" include plural referents unless the context clearly dictates otherwise. The use of "or" or "and" means "and/or" unless stated otherwise. Furthermore, use of the term "including" as well as other forms, such as "include", "includes", and "included", is not limiting.

[0028] The use of the conjunction "or" is used interchangeably with at "least one of". For example: where a composition comprises A or B, the method must comprise at least one of A and B but may also comprise both A and B. Likewise a composition comprising "A, B, C or D" must comprise at least one of the group of A, B, C and D, but may also comprise all or any combination of A, B, C and D.

[0029] The term "about" indicates that the stated numerical value allows some slight imprecision (with some approach to exactness in the value; approximately or reasonably close to the value; nearly). If the imprecision provided by "about" is not otherwise understood in the art with this ordinary meaning, then "about" as used herein encompasses variations of up to $\pm 10\%$ from the specified value. Unless otherwise indicated, all numbers expressing quantities of ingredients, properties such as molecular weight, reaction conditions, etc., used herein are to be understood as being modified by the term "about".

[0030] CD40L is also known as CD154, gp39, T-BAM, 5c8 antigen, or TNF related activation protein (TRAP).

[0031] The terms "treat," "treatment" and the like, include therapeutic treatment and

prophylactic treatment. Therapeutic treatment is treatment of a subject that has signs or symptoms of the disease, condition or disorder to be treated. Prophylactic treatments refers to treatment of a subject that is predisposed to the disease, condition or disorder that does not show overt signs of the disease, condition or disorder. Thus, treatment may result in stasis of, partial or total alleviation, or reduction of signs or symptoms of illness, and specifically includes, without limitation, prolongation of survival and cure.

[0032] An "effective amount" of an agent, e.g., a pharmaceutical formulation, refers to an amount effective, at dosages and for periods of time necessary, to achieve the desired therapeutic or prophylactic result.

[0033] "Affinity" refers to the strength of the sum total of noncovalent interactions between a single binding site of a molecule (e.g., an antibody) and its binding partner (e.g., an antigen). Unless indicated otherwise, as used herein, "binding affinity" refers to intrinsic binding affinity which reflects a 1:1 interaction between members of a binding pair (e.g., antibody and antigen). The affinity of a molecule X for its partner Y may generally be represented by the equilibrium dissociation constant (KD), a ratio of koff/kon, between the antibody and its antigen. KD and affinity are inversely related. The KD value relates to the concentration of antibody (the amount of antibody needed for a particular experiment) and so the lower the KD value (lower concentration) and thus the higher the affinity of the antibody. Affinity may be measured by common methods known in the art, including those described herein. Specific, illustrative, and exemplary embodiments for measuring binding affinity may be measured by radioimmunoassays (RIA), Surface Plasmon Resonance (SPR) on a BIAcore® instrument (GE Healthcare Europe GmbH, Glattbrugg, Switzerland) by capturing the antibody on a protein-A coupled CM5 research grade sensor chip (GE Healthcare Europe GmbH, Glattbrugg, Switzerland; BR-1000-14) with a human CD40 ligand polypeptide used as analyte. Other methods may include radioimmunoassays, and the Kinetic Exclusion Assay. The Kinetic Exclusion Assay is a general purpose immunoassay platform that is capable of measuring equilibrium dissociation constants, and association and dissociation rate constants for antigen/anti-body interactions.

[0034] Reference in the specification is made to percent identity between polypeptide or amino acid sequences. The percent identity between the two sequences is a function of the number of identical positions shared by the sequences, taking into account the number of gaps, and the length of each gap, which need to be introduced for optimal alignment of the two sequences. Identity can be measured as "local identity" or "global identity". Local identity refers the degree of sequence relatedness between polypeptides as determined by the match

between strings of such sequences. Global identity refers to the degree of sequence relatedness of a polypeptide compared to the full-length of a reference polypeptide. Unless specified otherwise, as used herein, identity means global identity. For the purposes of this disclosure and claims, the percentages for global identity are calculated using Needleman and Wunsch ((1970) J. Mol. Biol. 48:444-453) algorithm using a Blossum 62 scoring matrix with a gap penalty of 12, a gap extend penalty of 4, and a frameshift gap penalty of 5. There are many publically available software programs that incorporate the Needleman and Wunsch algorithm, e.g. the GAP program in the GCG software package.

[0035] One of ordinary skill in the art will appreciate that starting materials, biological and chemical materials, biological and chemical reagents, synthetic methods, purification methods, analytical methods, assay methods, and biological methods other than those specifically exemplified can be employed in the practice of the invention without resort to undue experimentation. All art-known functional equivalents, of any such materials and methods are intended to be included in this disclosure.

[0036] Amino acid substitutions are denoted by the convention in which the original amino acid, the position of the amino acid in the specified sequence and the replacement amino acid are identified, for example, C11S would indicate that the cysteine at position 11 of the polypeptide sequence is replaced with a serine.

[0037] Humanized antibodies are antibodies produced from non-human species whose protein sequences have been modified to increase their similarity to antibody variants produced naturally in humans. The process of "humanization" is usually applied to monoclonal antibodies developed for administration to humans (for example, antibodies developed as anti-cancer drugs).

[0038] Currently it is common to humanize a non-human antibody by insertion of relevant CDRs from antibodies created in a non-human animal into a human antibody "scaffold". "Direct" creation of a humanized antibody can be accomplished by inserting the appropriate CDR coding segments (responsible for the desired binding properties) into a human antibody "scaffold". This may be achieved through recombinant DNA methods using an appropriate vector and expression in mammalian cells. That is, after an antibody is developed to have the desired properties in a mouse (or other non-human), the DNA coding for that antibody can be isolated, cloned into a vector and sequenced. The DNA sequence corresponding to the antibody CDRs can then be determined. Once the precise sequence of the desired CDRs are known, a strategy can be devised for inserting these sequences appropriately into a construct containing the DNA for a human antibody variant. The CDRs may also be varied, e.g., to increase

specificity, prior to insertion into the scaffold.

[0039] The term "human" antibody refers to an antibody which possesses an amino acid sequence which corresponds to that of an antibody produced by a human and/or has been made using any technique for making human antibodies. This definition of a human antibody specifically excludes a humanized antibody comprising non-human antigen binding residues.

[0040] An "antigen binding antibody fragment" refers to a molecule other than an intact antibody that comprises a portion of an intact antibody that binds the antigen to which the intact antibody binds. Examples of antibody fragments include but are not limited to Fv, Fab, Fab', Fd fragments, dAb fragments, Fab'-SH, F(ab')₂; diabodies; triabodies; linear antibodies; single-chain antibody molecules (e.g., scFv); and multispecific antibodies formed from antibody fragments, minimal recognition units consisting of the amino acid residues that mimic the hypervariable region of an antibody (e.g., an isolated complementarity determining region (CDR) such as a CDR3 peptide). An antigen binding fragment as disclosed in the present application binds to the antigen CD40L.

[0041] An antigen-binding fragment of an antibody will typically comprise at least one variable domain. The variable domain may be of any size or amino acid composition and will generally comprise at least one CDR which is adjacent to or in frame with one or more framework sequences. In antigen-binding fragments having a VH domain associated with a VL domain, the VH and VL domains may be situated relative to one another in any suitable arrangement. For example, the variable region may be dimeric and contain VH-VH, VH-VL or VL-VL dimers. Alternatively, the antigen-binding fragment of an antibody may contain a monomeric VH or VL domain.

[0042] The isolated antibody includes bispecific antibodies in which each arm of the antibody or the antigen binding fragment binds to a different target or epitope.

[0043] The terms "full length antibody," "intact antibody," and "whole antibody" are used herein interchangeably to refer to an antibody having a structure substantially similar to a native antibody structure or having heavy chains that contain an Fc region.

[0044] "5c8" refers to the mouse anti-human antibody that binds CD40L and is produced by the hybridoma that is available from the ATCC having the accession number HB10916 and is described in U.S. Pat. No. 5,474,771. "hu5c8" refers to a humanized version of 5c8 the sequence of which is disclosed in Karpusas, et al., Structure vol. 9, pp 321-329, (2001).

[0045] The terms "subject" and "individual" and "patient" are used interchangeably herein, and refer to a human subject, individual or patient.

[0046] As referred to herein, all compositional percentages are by weight of the total

composition, unless otherwise specified. As used herein, the word "include," and its variants, is intended to be non-limiting, such that recitation of items in a list is not to the exclusion of other like items that may also be useful in the materials, compositions, devices, and methods of this technology. Similarly, the terms "may" and "may comprise" and their variants are intended to be non-limiting, such that recitation that an embodiment may or may comprise certain elements or features does not exclude other embodiments of the present technology that do not contain those elements or features

[0047] The term "isolated protein" or "isolated polypeptide" (e.g., an isolated antibody or isolated antigen binding fragment) is a protein or polypeptide that by virtue of its origin or source of derivation is not associated with naturally associated components that accompany it in its native state; is substantially free of other proteins from the same species; is expressed by a cell from a different species; or does not occur in nature. Thus, a polypeptide that is chemically synthesized or synthesized in a cellular system different from the cell from which it naturally originates will be "isolated" from its naturally associated components. A protein may also be rendered substantially free of naturally associated components by isolation, using protein purification techniques well known in the art.

[0048] The term "variant" as used herein is defined as a modified or altered form of a wildtype sequence, e.g. where one or more amino acids may be replaced by other amino acid(s) or non-amino acid(s) which do not substantially affect function. In some embodiments, the variant may contain an altered side chain for at least one amino acid residue.

[0049] The term "antigen" as used herein is defined as an entity that can stimulate the production of antibodies and specifically combine with them and/or an entity which elicits an immune system response. For example, a cell surface protein or a specific linear or non-linear portion thereof. The term herein may be abbreviated to "Ag."

[0050] The term "specifically binds," or the like, means that an antibody or antigen-binding fragment thereof forms a complex with an antigen that is relatively stable under physiological conditions. Specific binding may be characterized by an equilibrium dissociation constant (KD) of about 3000 nM or less (i.e., a smaller KD denotes a tighter binding), about 2000 nM or less, about 1000 nM or less; about 500 nM or less; about 300 nM or less; about 200 nM or less; about 100 nM or less; about 50 nM or less; about 1 nM or less; or about 0.5 nM.

[0051] Specific binding for a particular antigen or an epitope may be exhibited, for example, by an antibody having a KD for an antigen or epitope of at least about 1×10^{-4} M, at least about 1×10^{-5} M, at least about 1×10^{-6} M, at least about 1×10^{-7} M, at least about 1×10^{-8} M, at least about 1×10^{-9} M, alternatively at least about 1×10^{-10} M, at least about 1×10^{-11} M, at

least about 1×10^{-12} M, or greater, where K_D refers to an equilibrium dissociation constant of a particular antibody-antigen interaction. Typically, an antibody that specifically binds an antigen will have a K_D that is 20-, 50-, 100-, 500-, 1000-, 5,000-, 10,000- or more times greater for a control molecule relative to the antigen or epitope. Also, specific binding for a particular antigen or an epitope may be exhibited, for example, by an antibody having a K_a for an antigen or epitope of at least 20-, 50-, 100-, 500-, 1000-, 5,000-, 10,000- or more times greater for the epitope relative to a control, where K_a refers to an association rate of a particular antibody-antigen interaction.

[0052] The term "neutralizing antibody" includes an antibody that is capable of inhibiting and/or neutralizing the biological activity of CD40L, for example an anti-CD40L antibody or antigen fragment thereof that inhibits or prevents or diminishes the binding of CD40L to CD40, and thus inhibiting or reducing the signaling pathway triggered by CD40L and/or inhibiting or reducing the binding of CD40L to CD40.

[0053] The terms "antagonistic antibody" or "antagonist antibody" are used herein equivalently and include an antibody that is capable of inhibiting and/or neutralizing the biological signaling activity of CD40L, as described for a neutralizing antibody *supra*.

[0054] The terms and expressions which have been employed herein are used as terms of description and not of limitation, and there is no intention in the use of such terms and expressions of excluding any equivalents of the features shown and described or portions thereof, but it is recognized that various modifications are possible within the scope of the invention claimed. Thus, it should be understood that although aspects of the present invention have been specifically disclosed by various embodiments which may include preferred embodiments, exemplary embodiments and optional features, modifications and variations of the concepts herein disclosed may be resorted to by those skilled in the art. Such modifications and variations are considered to be within the scope of embodiments of the invention as described and as may be defined by the appended claims.

[0055] Pharmaceutical Compositions and methods of administration

[0056] Pharmaceutical compositions for use in accordance with the methods of the present disclosure may be formulated in a conventional manner using one or more physiologically acceptable carriers. Pharmaceutically acceptable carriers are determined in part by the particular composition being administered, as well as by the particular method used to administer the composition. Accordingly, there are a wide variety of suitable formulations of the compounds useful in the methods of the present disclosure (see, e.g., Remington: The Science and Practice of Pharmacy, 20th ed., Gennaro et al. Eds., Lippincott Williams and Wilkins, 2000).

[0057] Formulations suitable for parenteral administration include aqueous and non-aqueous, isotonic sterile injection solutions, which can contain antioxidants, buffers, bacteriostats, and solutes that render the formulation isotonic with the blood of the intended recipient, and aqueous and non-aqueous sterile suspensions that can include suspending agents, solubilizers, thickening agents, stabilizers, and preservatives. Exemplary injection or infusion excipients may include mannitol, citric acid monohydrate, dibasic sodium phosphate dihydrate, monobasic sodium phosphate dihydrate, polysorbate 80, sodium chloride, sodium citrate and water.

[0058] According to the present disclosure the compounds can be administered by any suitable means, which can vary, depending on the type of disorder being treated and on the nature of the compound itself. For example, for the antibodies and antigen binding fragments thereof, of the present invention, administration routes preferably include parenteral, e.g., intramuscular, intravenous, intraarterial, intraperitoneal, intracerebrospinal, intraspinal, epidural, subcutaneous or by sustained release systems or an implant. Preferably, the parenteral dosing is given by injection, most preferably intravenous, intramuscular or subcutaneous injection.

[0059] In some embodiments, the anti-CD40L antibodies or antigen-binding fragments thereof of the present disclosure are formulated for and may be lyophilized for storage and reconstituted in a suitable excipient prior to use according to art-known lyophilization and reconstitution techniques.

[0060] In one exemplary pharmaceutical composition containing the anti-CD40L antibody or antigen-binding fragment thereof, the composition is formulated as a sterile, preservative-free solution of the anti-CD40L antibody or antigen-binding fragment thereof for intravenous or subcutaneous administration. The formulation may be supplied as either a single-use, prefilled pen, as a single-use, for example containing about 1 mL prefilled glass syringe, or as a single-use institutional use vial. Preferably, the pharmaceutical composition containing the anti-CD40L antibody or antigen-binding fragment thereof is clear and colorless, with a pH of about 5.0 to about 6.9, preferably a pH of about 5.0 to about 6.5, and even more preferably a pH ranging from about 5.0 to about 6.0. In various embodiments, the formulations comprising the pharmaceutical compositions may contain from about 500 mg to about 1 mg, or from about 400 mg to about 10 mg, or from about 300 mg to about 30 mg or from about 200 mg to about 50 mg of the anti-CD40L antibody or antigen-binding fragment thereof per mL of solution when reconstituted and administered to the subject.

[0061] Selecting an administration regimen for a therapeutic depends on several factors, including the serum or tissue turnover rate of the entity, the level of symptoms, the

immunogenicity of the entity, and the accessibility of the target cells in the biological matrix, general health of the patient, the prior medical history of the patient, and the like. Preferably, an administration regimen maximizes the amount of therapeutic delivered to the patient consistent with an acceptable level of side effects. Accordingly, the amount of biologic delivered depends in part on the particular entity and the severity of the condition being treated. It should be appreciated that determination of proper dosage forms, dosage amounts, and routes of administration is within the level of ordinary skill in the pharmaceutical and medical arts.

[0062] Doses

[0063] The pharmaceutical formulations of the present disclosure may contain from about 0.001 to about 200 mg/kg of an anti-CD40L antibody or antigen binding fragment thereof, for example, from about 0.001 mg/kg to about 100 mg/kg, or from about 0.001 mg/kg to about 50 mg/kg, or from about 0.001 mg/kg to about 10 mg/kg intravenous injection of the anti- CD40L antibody, or antigen-binding fragment thereof, may be given as a bolus, and the rest of the antibody dose may be administered by intravenous injection. A predetermined dose of the anti-CD40L antibody, or antigen-binding fragment thereof, may be administered, for example, over a period of an hour to two hours to five hours.

[0064] In a further embodiment, part of the dose is administered by a subcutaneous injection and/or infusion in the form of a bolus and the rest by infusion of the antibody formulation. In some exemplary doses, the antibody formulation may be administered subcutaneously in a dose ranging from about 0.001 to about 200 mg/kg, for example, from about 0.001 mg/kg to about 100 mg/kg, or from about 0.001 mg/kg to about 50 mg/kg, or from about 0.001 mg/kg to about 10 mg/kg intravenous injection of the anti- CD40L antibody, or antigen-binding fragment thereof. In some embodiments the dose may be given as a bolus, and the rest of the antibody dose may be administered by subcutaneous or intravenous injection. A predetermined dose of the anti- CD40L antibody, or antigen-binding fragment thereof, may be administered, for example, over a period of an hour, or a period of two hours, or a period of three hours, or a period of four hours or a period of five hours or longer.

[0065] Combination Therapies

[0066] The antibodies or antibody fragments thereof described herein can be administered alone (monotherapy) or in combination, i.e., combined with other agents. For example, in one embodiment the combination therapy may include one or more additional therapeutic agents. In another embodiment the combination therapy includes standard of care treatment that may, or may not, include additional therapeutic agents (consists essentially of the antibody or antibody fragment thereof).

[0067] Adjunctive or combined administration (co-administration) includes simultaneous administration of any of the antibodies or antigen binding fragments thereof, described herein and one or more agents in the same or different dosage form, or separate administration of the polypeptide and one or more agents (e.g., sequential administration). Such concurrent or sequential administration preferably results in both the polypeptide and the one or more agents being simultaneously present in treated patients.

[0068] Kits and Articles of Manufacture

[0069] Further provided are kits containing the antibody or antigen binding fragments thereof described herein and instructions for use. Kits typically include a packaged combination of reagents in predetermined amounts with instructions and a label indicating the intended use of the contents of the kit. The term label or instruction includes any writing, or recorded material supplied on or with the kit, or which otherwise accompanies the kit at any time during its manufacture, transport, sale or use. It can be in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of the manufacture, use or sale for administration to a human or for veterinary use. The label or instruction can also encompass advertising leaflets and brochures, packaging materials, and audio or video instructions.

[0070] Embodiments

[0071] All embodiments of the isolated antibodies or antigen binding fragments thereof, bind to CD40L and inhibit or block the binding of CD40L to CD40. As used herein, “block the binding of CD40L and CD40” and “block the interaction between CD40L and CD40” are used interchangeably. Inhibiting or blocking the binding can be direct or indirect. Generally the antibody or antigen binding fragment thereof, will interfere physically with the binding of CD40L to CD40 via direct specific competition with CD40 for the same binding site on CD40L or via steric hindrance caused by binding of the antibody or antigen binding fragment thereof in proximity to the CD40-binding site of CD40L. In other instances the effect is indirect, for example the antibody or antigen binding fragment thereof cause an allosteric change in the conformation of CD40L which inhibits or eliminates its binding to CD40.

[0072] One embodiment is an isolated antibody that binds to CD40L and that comprises a light chain and a heavy chain, wherein the light chain comprises a light chain variable region comprises an amino acid sequence having at least 90%, or at least 91%, or at least 92%, or at least 93%, or at least 94%, or at least 95%, or at least 96% or at least 97%, or at least 98% or at least 99% sequence identity with SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, or SEQ ID NO: 8, and the heavy chain comprises a variable heavy chain region wherein the heavy chain

variable region comprises an amino acid sequence having at least 90%, or at least 91%, or at least 92%, or at least 93%, or at least 94%, or at least 95%, or at least 96%, or at least 97%, or at least 98%, or at least 99% sequence identity with SEQ ID NO:1, SEQ ID NO: 2, SEQ ID NO: 3, or SEQ ID NO: 4.

[0073] In one embodiment the present disclosure provides an isolated antibody or antigen-binding fragment thereof that specifically binds to CD40L comprising: a) a heavy chain variable region (VH) comprising: i) a CDRH1 domain comprising the sequence set forth in SEQ ID NO: 9; ii) a CDRH2 domain comprising the sequence set forth in SEQ ID NO: 10, 11, 12, 13, or 14; iii) a CDRH3 domain comprising the sequence set forth in SEQ ID NO: 15; and (b) a light chain variable region (VL) comprising: i) a CDRL1 domain comprising the sequence set forth in SEQ ID NO: 16 or 17; ii) a CDRL2 domain comprising the sequence set forth in SEQ ID NO: 18 or 19; iii) a CDRL3 domain comprising the sequence set forth in SEQ ID NO: 20.

[0074] In aspect A the present disclosure provides an isolated antibody or antigen-binding fragment thereof that specifically binds to CD40 L comprising: a) a heavy chain variable region (VH) comprising: i) a CDRH1 domain consisting of the sequence set forth in SEQ ID NO: 9; ii) a CDRH2 domain consisting of the sequence set forth in SEQ ID NO: 10, 11, 12, 13, or 14; iii) a CDRH3 domain consisting of the sequence set forth in SEQ ID NO: 15; and (b) a light chain variable region (VL) comprising: i) a CDRL1 domain consisting of the sequence set forth in SEQ ID NO: 16 or 17; ii) a CDRL2 domain consisting of the sequence set forth in SEQ ID NO: 18 or 19; iii) a CDRL3 domain consisting of the sequence set forth in SEQ ID NO: 20.

[0075] One embodiment of aspect A is an isolated antibody or antigen-binding fragment thereof, comprising: (a) a heavy chain variable region (VH) comprising: i) a CDRH1 domain comprising the sequence set forth in SEQ ID NO: 9; ii) a CDRH2 domain comprising the sequence set forth in SEQ ID NO: 10; iii) a CDRH3 domain comprising the sequence set forth in SEQ ID NO: 15; and (b) a light chain variable region (VL) comprising: i) a CDRL1 domain comprising the sequence set forth in SEQ ID NO: 16; ii) a CDRL2 domain comprising the sequence set forth in SEQ ID NO: 18; iii) a CDRL3 domain comprising the sequence set forth in SEQ ID NO: 20. Another embodiment of aspect A is an isolated antibody or antigen-binding fragment thereof, comprising: (a) a heavy chain variable region (VH) comprising: i) a CDRH1 domain consisting of the sequence set forth in SEQ ID NO: 9; ii) a CDRH2 domain consisting of the sequence set forth in SEQ ID NO: 10; iii) a CDRH3 domain consisting of the sequence set forth in SEQ ID NO: 15; and (b) a light chain variable region (VL) comprising: i) a CDRL1 domain consisting of the sequence set forth in SEQ ID NO: 16; ii) a CDRL2 domain

consisting of the sequence set forth in SEQ ID NO: 18; iii) a CDRL3 domain consisting of the sequence set forth in SEQ ID NO: 20.

[0076] Yet another embodiment of aspect A is an isolated antibody or antigen-binding fragment thereof, comprising: (a) a heavy chain variable region (VH) comprising; i) a CDRH1 domain comprising the sequence set forth in SEQ ID NO: 9; ii) a CDRH2 domain comprising the sequence set forth in SEQ ID NO: 10; iii) a CDRH3 domain comprising the sequence set forth in SEQ ID NO: 15; and (b) a light chain variable region (VL) comprising: i) a CDRL1 domain comprising the sequence set forth in SEQ ID NO: 17; ii) a CDRL2 domain comprising the sequence set forth in SEQ ID NO: 18; iii) a CDRL3 domain comprising the sequence set forth in SEQ ID NO: 20. Still another embodiment of aspect A is an isolated antibody or antigen-binding fragment thereof, comprising: (a) a heavy chain variable region (VH) comprising; i) a CDRH1 domain consisting of the sequence set forth in SEQ ID NO: 9; ii) a CDRH2 domain consisting of the sequence set forth in SEQ ID NO: 10; iii) a CDRH3 domain consisting of the sequence set forth in SEQ ID NO: 15; and (b) a light chain variable region (VL) comprising: i) a CDRL1 domain consisting of the sequence set forth in SEQ ID NO: 17; ii) a CDRL2 domain consisting of the sequence set forth in SEQ ID NO: 18; iii) a CDRL3 domain consisting of the sequence set forth in SEQ ID NO: 20.

[0077] Still another embodiment of aspect A is an isolated antibody or antigen-binding fragment thereof, comprising: (a) a heavy chain variable region (VH) comprising; i) a CDRH1 domain comprising the sequence set forth in SEQ ID NO: 9; ii) a CDRH2 domain comprising the sequence set forth in SEQ ID NO: 10; iii) a CDRH3 domain comprising the sequence set forth in SEQ ID NO: 15; and (b) a light chain variable region (VL) comprising: i) a CDRL1 domain comprising the sequence set forth in SEQ ID NO: 16; ii) a CDRL2 domain comprising the sequence set forth in SEQ ID NO: 19; iii) a CDRL3 domain comprising the sequence set forth in SEQ ID NO: 20. Yet another embodiment of aspect A is an isolated antibody or antigen-binding fragment thereof, comprising: (a) a heavy chain variable region (VH) comprising; i) a CDRH1 domain consisting of the sequence set forth in SEQ ID NO: 9; ii) a CDRH2 domain consisting of the sequence set forth in SEQ ID NO: 10; iii) a CDRH3 domain consisting of the sequence set forth in SEQ ID NO: 15; and (b) a light chain variable region (VL) comprising: i) a CDRL1 domain consisting of the sequence set forth in SEQ ID NO: 16; ii) a CDRL2 domain consisting of the sequence set forth in SEQ ID NO: 19; iii) a CDRL3 domain consisting of the sequence set forth in SEQ ID NO: 20.

[0078] Another embodiment of aspect A is an isolated antibody or antigen-binding fragment thereof, comprising: (a) a heavy chain variable region (VH) comprising; i) a CDRH1 domain

comprising the sequence set forth in SEQ ID NO: 9; ii) a CDRH2 domain comprising the sequence set forth in SEQ ID NO: 10; iii) a CDRH3 domain comprising the sequence set forth in SEQ ID NO: 15; and (b) a light chain variable region (VL) comprising: i) a CDRL1 domain comprising the sequence set forth in SEQ ID NO: 17; ii) a CDRL2 domain comprising the sequence set forth in SEQ ID NO: 19; iii) a CDRL3 domain comprising the sequence set forth in SEQ ID NO: 20. Still another embodiment of aspect A is an isolated antibody or antigen-binding fragment thereof, comprising: (a) a heavy chain variable region (VH) comprising: i) a CDRH1 domain consisting of the sequence set forth in SEQ ID NO: 9; ii) a CDRH2 domain consisting of the sequence set forth in SEQ ID NO: 10; iii) a CDRH3 domain consisting of the sequence set forth in SEQ ID NO: 15; and (b) a light chain variable region (VL) comprising: i) a CDRL1 domain consisting of the sequence set forth in SEQ ID NO: 17; ii) a CDRL2 domain consisting of the sequence set forth in SEQ ID NO: 19; iii) a CDRL3 domain consisting of the sequence set forth in SEQ ID NO: 20

[0079] Yet another embodiment of aspect A is an isolated antibody or antigen-binding fragment thereof, comprising: (a) a heavy chain variable region (VH) comprising: i) a CDRH1 domain comprising the sequence set forth in SEQ ID NO: 9; ii) a CDRH2 domain comprising the sequence set forth in SEQ ID NO: 11; iii) a CDRH3 domain comprising the sequence set forth in SEQ ID NO: 15; and (b) a light chain variable region (VL) comprising: i) a CDRL1 domain comprising the sequence set forth in SEQ ID NO: 16; ii) a CDRL2 domain comprising the sequence set forth in SEQ ID NO: 18; iii) a CDRL3 domain comprising the sequence set forth in SEQ ID NO: 20. Still another embodiment of aspect A is an isolated antibody or antigen-binding fragment thereof, comprising: (a) a heavy chain variable region (VH) comprising: i) a CDRH1 domain consisting of the sequence set forth in SEQ ID NO: 9; ii) a CDRH2 domain consisting of the sequence set forth in SEQ ID NO: 11; iii) a CDRH3 domain consisting of the sequence set forth in SEQ ID NO: 15; and (b) a light chain variable region (VL) comprising: i) a CDRL1 domain consisting of the sequence set forth in SEQ ID NO: 16; ii) a CDRL2 domain consisting of the sequence set forth in SEQ ID NO: 18; iii) a CDRL3 domain consisting of the sequence set forth in SEQ ID NO: 20.

[0080] Yet another embodiment of aspect A is an isolated antibody or antigen-binding fragment thereof, comprising: (a) a heavy chain variable region (VH) comprising: i) a CDRH1 domain comprising the sequence set forth in SEQ ID NO: 9; ii) a CDRH2 domain comprising the sequence set forth in SEQ ID NO: 11; iii) a CDRH3 domain comprising the sequence set forth in SEQ ID NO: 15; and (b) a light chain variable region (VL) comprising: i) a CDRL1 domain comprising the sequence set forth in SEQ ID NO: 17; ii) a CDRL2 domain comprising

the sequence set forth in SEQ ID NO: 18; iii) a CDRL3 domain comprising the sequence set forth in SEQ ID NO: 20. Yet another embodiment of aspect A is an isolated antibody or antigen-binding fragment thereof, comprising: (a) a heavy chain variable region (VH) comprising: i) a CDRH1 domain consisting of the sequence set forth in SEQ ID NO: 9; ii) a CDRH2 domain consisting of the sequence set forth in SEQ ID NO: 11; iii) a CDRH3 domain consisting of the sequence set forth in SEQ ID NO: 15; and (b) a light chain variable region (VL) comprising: i) a CDRL1 domain consisting of the sequence set forth in SEQ ID NO: 17; ii) a CDRL2 domain consisting of the sequence set forth in SEQ ID NO: 18; iii) a CDRL3 domain consisting of the sequence set forth in SEQ ID NO: 20.

[0081] Another embodiment of aspect A is an isolated antibody or antigen-binding fragment thereof, comprising: (a) a heavy chain variable region (VH) comprising: i) a CDRH1 domain comprising the sequence set forth in SEQ ID NO: 9; ii) a CDRH2 domain comprising the sequence set forth in SEQ ID NO: 11; iii) a CDRH3 domain comprising the sequence set forth in SEQ ID NO: 15; and (b) a light chain variable region (VL) comprising: i) a CDRL1 domain comprising the sequence set forth in SEQ ID NO: 16; ii) a CDRL2 domain comprising the sequence set forth in SEQ ID NO: 19; iii) a CDRL3 domain comprising the sequence set forth in SEQ ID NO: 20. Yet another embodiment of aspect A is an isolated antibody or antigen-binding fragment thereof, comprising: (a) a heavy chain variable region (VH) comprising: i) a CDRH1 domain consisting of the sequence set forth in SEQ ID NO: 9; ii) a CDRH2 domain consisting of the sequence set forth in SEQ ID NO: 11; iii) a CDRH3 domain consisting of the sequence set forth in SEQ ID NO: 15; and (b) a light chain variable region (VL) comprising: i) a CDRL1 domain consisting of the sequence set forth in SEQ ID NO: 16; ii) a CDRL2 domain consisting of the sequence set forth in SEQ ID NO: 19; iii) a CDRL3 domain consisting of the sequence set forth in SEQ ID NO: 20.

[0082] Yet another embodiment of aspect A is an isolated antibody or antigen-binding fragment thereof, comprising: (a) a heavy chain variable region (VH) comprising: i) a CDRH1 domain comprising the sequence set forth in SEQ ID NO: 9; ii) a CDRH2 domain comprising the sequence set forth in SEQ ID NO: 11; iii) a CDRH3 domain comprising the sequence set forth in SEQ ID NO: 15; and (b) a light chain variable region (VL) comprising: i) a CDRL1 domain comprising the sequence set forth in SEQ ID NO: 17; ii) a CDRL2 domain comprising the sequence set forth in SEQ ID NO: 19; iii) a CDRL3 domain comprising the sequence set forth in SEQ ID NO: 20. Another embodiment of aspect A is an isolated antibody or antigen-binding fragment thereof, comprising: (a) a heavy chain variable region (VH) comprising: i) a CDRH1 domain consisting of the sequence set forth in SEQ ID NO: 9; ii) a CDRH2 domain

consisting of the sequence set forth in SEQ ID NO: 11; iii) a CDRH3 domain consisting of the sequence set forth in SEQ ID NO: 15; and (b) a light chain variable region (VL) comprising: i) a CDRL1 domain consisting of the sequence set forth in SEQ ID NO: 17; ii) a CDRL2 domain consisting of the sequence set forth in SEQ ID NO: 19; iii) a CDRL3 domain consisting of the sequence set forth in SEQ ID NO: 20.

[0083] Yet another embodiment of aspect A is an isolated antibody or antigen-binding fragment thereof, comprising: (a) a heavy chain variable region (VH) comprising: i) a CDRH1 domain comprising the sequence set forth in SEQ ID NO: 9; ii) a CDRH2 domain comprising the sequence set forth in SEQ ID NO: 12; iii) a CDRH3 domain comprising the sequence set forth in SEQ ID NO: 15; and (b) a light chain variable region (VL) comprising: i) a CDRL1 domain comprising the sequence set forth in SEQ ID NO: 16; ii) a CDRL2 domain comprising the sequence set forth in SEQ ID NO: 18; iii) a CDRL3 domain comprising the sequence set forth in SEQ ID NO: 20. Still another embodiment of aspect A is an isolated antibody or antigen-binding fragment thereof, comprising: (a) a heavy chain variable region (VH) comprising: i) a CDRH1 domain consisting of the sequence set forth in SEQ ID NO: 9; ii) a CDRH2 domain consisting of the sequence set forth in SEQ ID NO: 12; iii) a CDRH3 domain consisting of the sequence set forth in SEQ ID NO: 15; and (b) a light chain variable region (VL) comprising: i) a CDRL1 domain consisting of the sequence set forth in SEQ ID NO: 16; ii) a CDRL2 domain consisting of the sequence set forth in SEQ ID NO: 18; iii) a CDRL3 domain consisting of the sequence set forth in SEQ ID NO: 20.

[0084] Another embodiment of aspect A is an isolated antibody or antigen-binding fragment thereof, comprising: (a) a heavy chain variable region (VH) comprising: i) a CDRH1 domain comprising the sequence set forth in SEQ ID NO: 9; ii) a CDRH2 domain comprising the sequence set forth in SEQ ID NO: 12; iii) a CDRH3 domain comprising the sequence set forth in SEQ ID NO: 15; and (b) a light chain variable region (VL) comprising: i) a CDRL1 domain comprising the sequence set forth in SEQ ID NO: 17; ii) a CDRL2 domain comprising the sequence set forth in SEQ ID NO: 18; iii) a CDRL3 domain comprising the sequence set forth in SEQ ID NO: 20. Yet another embodiment of aspect A is an isolated antibody or antigen-binding fragment thereof, comprising: (a) a heavy chain variable region (VH) comprising: i) a CDRH1 domain consisting of the sequence set forth in SEQ ID NO: 9; ii) a CDRH2 domain consisting of the sequence set forth in SEQ ID NO: 12; iii) a CDRH3 domain consisting of the sequence set forth in SEQ ID NO: 15; and (b) a light chain variable region (VL) comprising: i) a CDRL1 domain consisting of the sequence set forth in SEQ ID NO: 17; ii) a CDRL2 domain consisting of the sequence set forth in SEQ ID NO: 18; iii) a CDRL3 domain consisting of the

sequence set forth in SEQ ID NO: 20.

[0085] Yet another embodiment of aspect A is an isolated antibody or antigen-binding fragment thereof, comprising: (a) a heavy chain variable region (VH) comprising: i) a CDRH1 domain comprising the sequence set forth in SEQ ID NO: 9; ii) a CDRH2 domain comprising the sequence set forth in SEQ ID NO: 12; iii) a CDRH3 domain comprising the sequence set forth in SEQ ID NO: 15; and (b) a light chain variable region (VL) comprising: i) a CDRL1 domain comprising the sequence set forth in SEQ ID NO: 16; ii) a CDRL2 domain comprising the sequence set forth in SEQ ID NO: 19; iii) a CDRL3 domain comprising the sequence set forth in SEQ ID NO: 20. Another embodiment of aspect A is an isolated antibody or antigen-binding fragment thereof, comprising: (a) a heavy chain variable region (VH) comprising: i) a CDRH1 domain consisting of the sequence set forth in SEQ ID NO: 9; ii) a CDRH2 domain consisting of the sequence set forth in SEQ ID NO: 12; iii) a CDRH3 domain consisting of the sequence set forth in SEQ ID NO: 15; and (b) a light chain variable region (VL) comprising: i) a CDRL1 domain consisting of the sequence set forth in SEQ ID NO: 16; ii) a CDRL2 domain consisting of the sequence set forth in SEQ ID NO: 19; iii) a CDRL3 domain consisting of the sequence set forth in SEQ ID NO: 20.

[0086] Still another embodiment of aspect A is an isolated antibody or antigen-binding fragment thereof, comprising: (a) a heavy chain variable region (VH) comprising: i) a CDRH1 domain comprising the sequence set forth in SEQ ID NO: 9; ii) a CDRH2 domain comprising the sequence set forth in SEQ ID NO: 12; iii) a CDRH3 domain comprising the sequence set forth in SEQ ID NO: 15; and (b) a light chain variable region (VL) comprising: i) a CDRL1 domain comprising the sequence set forth in SEQ ID NO: 17; ii) a CDRL2 domain comprising the sequence set forth in SEQ ID NO: 19; iii) a CDRL3 domain comprising the sequence set forth in SEQ ID NO: 20. Yet another embodiment of aspect A is an isolated antibody or antigen-binding fragment thereof, comprising: (a) a heavy chain variable region (VH) comprising: i) a CDRH1 domain consisting of the sequence set forth in SEQ ID NO: 9; ii) a CDRH2 domain consisting of the sequence set forth in SEQ ID NO: 12; iii) a CDRH3 domain consisting of the sequence set forth in SEQ ID NO: 15; and (b) a light chain variable region (VL) comprising: i) a CDRL1 domain consisting of the sequence set forth in SEQ ID NO: 17; ii) a CDRL2 domain consisting of the sequence set forth in SEQ ID NO: 19; iii) a CDRL3 domain consisting of the sequence set forth in SEQ ID NO: 20.

[0087] Another embodiment of aspect A is an isolated antibody or antigen-binding fragment thereof, comprising: (a) a heavy chain variable region (VH) comprising: i) a CDRH1 domain comprising the sequence set forth in SEQ ID NO: 9; ii) a CDRH2 domain comprising the

sequence set forth in SEQ ID NO: 13; iii) a CDRH3 domain comprising the sequence set forth in SEQ ID NO: 15; and (b) a light chain variable region (VL) comprising: i) a CDRL1 domain comprising the sequence set forth in SEQ ID NO: 16; ii) a CDRL2 domain comprising the sequence set forth in SEQ ID NO: 18; iii) a CDRL3 domain comprising the sequence set forth in SEQ ID NO: 20. Another embodiment of aspect A is an isolated antibody or antigen-binding fragment thereof, comprising: (a) a heavy chain variable region (VH) comprising: i) a CDRH1 domain consisting of the sequence set forth in SEQ ID NO: 9; ii) a CDRH2 domain consisting of the sequence set forth in SEQ ID NO: 13; iii) a CDRH3 domain consisting of the sequence set forth in SEQ ID NO: 15; and (b) a light chain variable region (VL) comprising: i) a CDRL1 domain consisting of the sequence set forth in SEQ ID NO: 16; ii) a CDRL2 domain consisting of the sequence set forth in SEQ ID NO: 18; iii) a CDRL3 domain consisting of the sequence set forth in SEQ ID NO: 20.

[0088] Another embodiment of aspect A is an isolated antibody or antigen-binding fragment thereof, comprising: (a) a heavy chain variable region (VH) comprising: i) a CDRH1 domain comprising the sequence set forth in SEQ ID NO: 9; ii) a CDRH2 domain comprising the sequence set forth in SEQ ID NO: 13; iii) a CDRH3 domain comprising the sequence set forth in SEQ ID NO: 15; and (b) a light chain variable region (VL) comprising: i) a CDRL1 domain comprising the sequence set forth in SEQ ID NO: 17; ii) a CDRL2 domain comprising the sequence set forth in SEQ ID NO: 18; iii) a CDRL3 domain comprising the sequence set forth in SEQ ID NO: 20. Still another embodiment of aspect A is an isolated antibody or antigen-binding fragment thereof, comprising: (a) a heavy chain variable region (VH) comprising: i) a CDRH1 domain consisting of the sequence set forth in SEQ ID NO: 9; ii) a CDRH2 domain consisting of the sequence set forth in SEQ ID NO: 13; iii) a CDRH3 domain consisting of the sequence set forth in SEQ ID NO: 15; and (b) a light chain variable region (VL) comprising: i) a CDRL1 domain consisting of the sequence set forth in SEQ ID NO: 17; ii) a CDRL2 domain consisting of the sequence set forth in SEQ ID NO: 18; iii) a CDRL3 domain consisting of the sequence set forth in SEQ ID NO: 20.

[0089] Still another embodiment of aspect A is an isolated antibody or antigen-binding fragment thereof, comprising: (a) a heavy chain variable region (VH) comprising: i) a CDRH1 domain comprising the sequence set forth in SEQ ID NO: 9; ii) a CDRH2 domain comprising the sequence set forth in SEQ ID NO: 13; iii) a CDRH3 domain comprising the sequence set forth in SEQ ID NO: 15; and (b) a light chain variable region (VL) comprising: i) a CDRL1 domain comprising the sequence set forth in SEQ ID NO: 17; ii) a CDRL2 domain comprising the sequence set forth in SEQ ID NO: 19; iii) a CDRL3 domain comprising the sequence set

forth in SEQ ID NO: 20. Yet another embodiment of aspect A is an isolated antibody or antigen-binding fragment thereof, comprising: (a) a heavy chain variable region (VH) comprising; i) a CDRH1 domain consisting of the sequence set forth in SEQ ID NO: 9; ii) a CDRH2 domain consisting of the sequence set forth in SEQ ID NO: 13; iii) a CDRH3 domain consisting of the sequence set forth in SEQ ID NO: 15; and (b) a light chain variable region (VL) comprising: i) a CDRL1 domain consisting of the sequence set forth in SEQ ID NO: 17; ii) a CDRL2 domain consisting of the sequence set forth in SEQ ID NO: 19; iii) a CDRL3 domain consisting of the sequence set forth in SEQ ID NO: 20.

[0090] Yet another embodiment of aspect A is an isolated antibody or antigen-binding fragment thereof, comprising: (a) a heavy chain variable region (VH) comprising; i) a CDRH1 domain comprising the sequence set forth in SEQ ID NO: 9; ii) a CDRH2 domain comprising the sequence set forth in SEQ ID NO: 14; iii) a CDRH3 domain comprising the sequence set forth in SEQ ID NO: 15; and (b) a light chain variable region (VL) comprising: i) a CDRL1 domain comprising the sequence set forth in SEQ ID NO: 16; ii) a CDRL2 domain comprising the sequence set forth in SEQ ID NO: 18; iii) a CDRL3 domain comprising the sequence set forth in SEQ ID NO: 20. Yet another embodiment of aspect A is an isolated antibody or antigen-binding fragment thereof, comprising: (a) a heavy chain variable region (VH) comprising; i) a CDRH1 domain consisting of the sequence set forth in SEQ ID NO: 9; ii) a CDRH2 domain consisting of the sequence set forth in SEQ ID NO: 14; iii) a CDRH3 domain consisting of the sequence set forth in SEQ ID NO: 15; and (b) a light chain variable region (VL) comprising: i) a CDRL1 domain consisting of the sequence set forth in SEQ ID NO: 16; ii) a CDRL2 domain consisting of the sequence set forth in SEQ ID NO: 18; iii) a CDRL3 domain consisting of the sequence set forth in SEQ ID NO: 20.

[0091] Another embodiment of aspect A is an isolated antibody or antigen-binding fragment thereof, comprising: (a) a heavy chain variable region (VH) comprising; i) a CDRH1 domain comprising the sequence set forth in SEQ ID NO: 9; ii) a CDRH2 domain comprising the sequence set forth in SEQ ID NO: 14; iii) a CDRH3 domain comprising the sequence set forth in SEQ ID NO: 15; and (b) a light chain variable region (VL) comprising: i) a CDRL1 domain comprising the sequence set forth in SEQ ID NO: 17; ii) a CDRL2 domain comprising the sequence set forth in SEQ ID NO: 18; iii) a CDRL3 domain comprising the sequence set forth in SEQ ID NO: 20. Another embodiment of aspect A is an isolated antibody or antigen-binding fragment thereof, comprising: (a) a heavy chain variable region (VH) comprising; i) a CDRH1 domain consisting of the sequence set forth in SEQ ID NO: 9; ii) a CDRH2 domain consisting of the sequence set forth in SEQ ID NO: 14; iii) a CDRH3 domain consisting of the sequence

set forth in SEQ ID NO: 15; and (b) a light chain variable region (VL) comprising: i) a CDRL1 domain consisting of the sequence set forth in SEQ ID NO: 17; ii) a CDRL2 domain consisting of the sequence set forth in SEQ ID NO: 18; iii) a CDRL3 domain consisting of the sequence set forth in SEQ ID NO: 20.

[0092] Yet another embodiment of aspect A is an isolated antibody or antigen-binding fragment thereof, comprising: (a) a heavy chain variable region (VH) comprising: i) a CDRH1 domain comprising the sequence set forth in SEQ ID NO: 9; ii) a CDRH2 domain comprising the sequence set forth in SEQ ID NO: 14; iii) a CDRH3 domain comprising the sequence set forth in SEQ ID NO: 15; and (b) a light chain variable region (VL) comprising: i) a CDRL1 domain comprising the sequence set forth in SEQ ID NO: 17; ii) a CDRL2 domain comprising the sequence set forth in SEQ ID NO: 19; iii) a CDRL3 domain comprising the sequence set forth in SEQ ID NO: 20. Yet another embodiment of aspect A is an isolated antibody or antigen-binding fragment thereof, comprising: (a) a heavy chain variable region (VH) comprising: i) a CDRH1 domain consisting of the sequence set forth in SEQ ID NO: 9; ii) a CDRH2 domain consisting of the sequence set forth in SEQ ID NO: 14; iii) a CDRH3 domain consisting of the sequence set forth in SEQ ID NO: 15; and (b) a light chain variable region (VL) comprising: i) a CDRL1 domain consisting of the sequence set forth in SEQ ID NO: 17; ii) a CDRL2 domain consisting of the sequence set forth in SEQ ID NO: 19; iii) a CDRL3 domain consisting of the sequence set forth in SEQ ID NO: 20.

[0093] In aspect B the present disclosure provides isolated antibodies or an antigen-binding fragment thereof that specifically binds to CD40 L comprising: (a) a heavy chain variable region (VH) having the amino acid sequence as set forth in SEQ ID NOs: 1, 2, 3, or 4; and (b) a light chain variable region (VL) having the amino acid sequence as set forth in SEQ ID NOs: 5, 6, 7, or 8.

[0094] An embodiment of aspect B is an isolated antibody or antigen-binding fragment thereof comprising a heavy chain variable region (VH) having the amino acid sequence as set forth in SEQ ID NO: 1 and the light chain variable region (VL) having the amino acid sequence as set forth in SEQ ID NO: 5.

[0095] Another embodiment of aspect B is an isolated antibody or antigen-binding fragment thereof, comprising a heavy chain variable region (VH) having the amino acid sequence as set forth in SEQ ID NO: 1 and the light chain variable region (VL) having the amino acid sequence as set forth in SEQ ID NO: 6.

[0096] Yet another embodiment of aspect B is an isolated antibody or antigen-binding fragment thereof, comprising a heavy chain variable region (VH) having the amino acid

sequence as set forth in SEQ ID NO: 1 and the light chain variable region (VL) having the amino acid sequence as set forth in SEQ ID NO: 7.

[0097] Another embodiment of aspect B is an isolated antibody or antigen-binding fragment thereof, comprising a heavy chain variable region (VH) having the amino acid sequence as set forth in SEQ ID NO: 1 and the light chain variable region (VL) having the amino acid sequence as set forth in SEQ ID NO: 8.

[0098] Yet another embodiment of aspect B is an isolated antibody or antigen-binding fragment thereof, comprising a heavy chain variable region (VH) having the amino acid sequence as set forth in SEQ ID NO: 1 and the light chain variable region (VL) having the amino acid sequence as set forth in SEQ ID NO: 5.

[0099] Still another embodiment of aspect B is an isolated antibody or antigen-binding fragment thereof, comprising a heavy chain variable region (VH) having the amino acid sequence as set forth in SEQ ID NO: 1 and the light chain variable region (VL) having the amino acid sequence as set forth in SEQ ID NO: 6.

[00100] Another embodiment of aspect B is an isolated antibody or antigen-binding fragment thereof, comprising a heavy chain variable region (VH) having the amino acid sequence as set forth in SEQ ID NO: 1 and the light chain variable region (VL) having the amino acid sequence as set forth in SEQ ID NO: 7.

[00101] Yet another embodiment of aspect B is an isolated antibody or antigen-binding fragment thereof, comprising a heavy chain variable region (VH) having the amino acid sequence as set forth in SEQ ID NO: 1 and the light chain variable region (VL) having the amino acid sequence as set forth in SEQ ID NO: 8.

[00102] Another embodiment of aspect B is an isolated antibody or antigen-binding fragment thereof, comprising a heavy chain variable region (VH) having the amino acid sequence as set forth in SEQ ID NO: 3 and the light chain variable region (VL) having the amino acid sequence as set forth in SEQ ID NO: 5.

[00103] Yet another embodiment of aspect B is an isolated antibody or antigen-binding fragment thereof, comprising a heavy chain variable region (VH) having the amino acid sequence as set forth in SEQ ID NO: 3 and the light chain variable region (VL) having the amino acid sequence as set forth in SEQ ID NO: 6.

[00104] Another embodiment of aspect B is an isolated antibody or antigen-binding fragment thereof, comprising a heavy chain variable region (VH) having the amino acid sequence as set forth in SEQ ID NO: 3 and the light chain variable region (VL) having the amino acid sequence as set forth in SEQ ID NO: 7.

[00105] Still another embodiment of aspect B is an isolated antibody or antigen-binding fragment thereof, comprising a heavy chain variable region (VH) having the amino acid sequence as set forth in SEQ ID NO: 3 and the light chain variable region (VL) having the amino acid sequence as set forth in SEQ ID NO: 8.

[00106] Yet another embodiment of aspect B is an isolated antibody or antigen-binding fragment thereof, comprising a heavy chain variable region (VH) having the amino acid sequence as set forth in SEQ ID NO: 4 and the light chain variable region (VL) having the amino acid sequence as set forth in SEQ ID NO: 5.

[00107] Still another embodiment of aspect B is an isolated antibody or antigen-binding fragment thereof, comprising a heavy chain variable region (VH) having the amino acid sequence as set forth in SEQ ID NO: 4 and the light chain variable region (VL) having the amino acid sequence as set forth in SEQ ID NO: 6.

[00108] Another embodiment of aspect B is an isolated antibody or antigen-binding fragment thereof, comprising a heavy chain variable region (VH) having the amino acid sequence as set forth in SEQ ID NO: 4 and the light chain variable region (VL) having the amino acid sequence as set forth in SEQ ID NO: 7.

[00109] Yet another embodiment of aspect B is an isolated antibody or antigen-binding fragment thereof, comprising a heavy chain variable region (VH) having the amino acid sequence as set forth in SEQ ID NO: 4 and the light chain variable region (VL) having the amino acid sequence as set forth in SEQ ID NO: 8.

[00110] Aspect C provides isolated antibodies of any of the embodiments described in the present application wherein the antibody comprises an Fc region and the Fc region has been engineered to reduce or eliminate one or more Fc effector function.

[00111] One embodiment of aspect C is where the Fc region is engineered such that the Fc region has reduced or eliminated binding to an Fc Receptor (FcR) or reduced or eliminated binding to C1q. In a particular embodiment of aspect C the FcR is FC γ RIa (CD64), FC γ RIIa (CD32), FC γ RIIIa (CD16a), or FC γ RIIIb (CD16b). In another embodiment of aspect C the FcR is Fc γ RIIa.

[00112] An embodiment of aspect C is an isolated antibody according to any one of the embodiments of the present invention, wherein the antibody is of the IgG1, IgG2, IgG3 or IgG4 isotype or any combination or hybrid version thereof. Another embodiment of aspect C is an isolated antibody according to any one of the embodiments of the present invention, wherein the antibody is of the IgG1 isotype, and wherein the heavy chain constant region comprises the amino acid sequence as set forth in SEQ ID NO: 21. (P238S and N297G) As shown in

Experiment 3, none of the antibody clones provided in the present disclosure that were engineered with the Fc of SEQ ID NO: 21, bound to FC γ RIa, FC γ RIIa, FC γ RIIIa, or FC γ RIIIb. As shown in Experiment 4, none of the antibody clones provided in the present disclosure that were engineered with the Fc of SEQ ID NO: 21, bound to C1q.

[00113] A mutation of the IgG backbone Fc at position 297 (N297A) has been shown to abrogate IgG glycosylation and Fc gamma receptor binding. A mutation of the IgG backbone Fc at position 265 (D265A) has been shown to abrogate Fc gamma receptor binding. Accordingly embodiments of the present invention were prepared that comprised these mutations in the Fc region. One embodiment of aspect C is an isolated antibody according to any one the embodiments of the present disclosure which comprises a heavy chain constant region wherein the heavy chain constant region comprises the amino acid sequence as set forth in SEQ ID NO: 22. (D265A and N297A)

[00114] United States Patent Application publication number 2014/0294834 discloses a mutation of the heavy chain constant region. Thus, another embodiment is an isolated antibody according to any one of the embodiments having an Fc region that are disclosed in the present application, comprising a heavy chain constant region wherein the heavy chain constant region comprises the amino acid sequence as set forth in SEQ ID NO: 23. (T299K –MM131)

[00115] Another embodiment is an isolated antibody according to any one of the embodiments having an Fc region that are disclosed in the present application, comprising a heavy chain constant region wherein the heavy chain constant region comprises the amino acid sequence as set forth in SEQ ID NO: 24. (N299K)

[00116] In a particular embodiment the isolated antibody is the heavy chain variable region connected to the heavy chain constant region. In one embodiment the heavy chain variable region VH1 is connected directly to the heavy chain constant region having the P238S and N297G and the isolated antibody heavy chain consists of the amino acid sequence as provided in SEQ ID NO: 42. In another embodiment the heavy chain variable region VH2 is connected directly to the heavy chain constant region having the P238S and N297G and the isolated antibody heavy chain consists of the amino acid sequence as provided in SEQ ID NO: 43. In yet another embodiment the heavy chain variable region VH3 is connected directly to the heavy chain constant region having the P238S and N297G and the isolated antibody heavy chain consists of the amino acid sequence as provided in SEQ ID NO: 44. In still another embodiment the heavy chain variable region VH4 is connected directly to the heavy chain constant region having the P238S and N297G and the isolated antibody heavy chain consists of the amino acid sequence as provided in SEQ ID NO: 45.

[00117] In one embodiment the heavy chain variable region VH1 is connected directly to the heavy chain constant region having the D265A/N297A and the isolated antibody heavy chain consists of the amino acid sequence as provided in SEQ ID NO: 46. In yet another embodiment the heavy chain variable region VH2 is connected directly to the heavy chain constant region having the D265A/N297A and the isolated antibody heavy chain consists of the amino acid sequence as provided in SEQ ID NO: 47. In still another embodiment the heavy chain variable region VH3 is connected directly to the heavy chain constant region having the 265A/N297A and the isolated antibody heavy chain consists of the amino acid sequence as provided in SEQ ID NO: 48. In yet another embodiment the heavy chain variable region V4 is connected directly to the heavy chain constant region having the 265A/N297A and the isolated antibody heavy chain consists of the amino acid sequence as provided in SEQ ID NO: 49.

[00118] In still another embodiment the heavy chain variable region VH1 is connected directly to the heavy chain constant region having the IgG1/IgG4 hybrid and the isolated antibody heavy chain consists of the amino acid sequence as provided in SEQ ID NO: 50. In yet another embodiment the heavy chain variable region VH2 is connected directly to the heavy chain constant region having the IgG1/IgG4 hybrid and the isolated antibody heavy chain consists of the amino acid sequence as provided in SEQ ID NO: 51. In yet another embodiment the heavy chain variable region VH3 is connected directly to the heavy chain constant region having the IgG1/IgG4 hybrid and the isolated antibody heavy chain consists of the amino acid sequence as provided in SEQ ID NO: 51. In another embodiment the heavy chain variable region VH4 is connected directly to the heavy chain constant region having the IgG1/IgG4 hybrid and the isolated antibody heavy chain consists of the amino acid sequence as provided in SEQ ID NO: 53.

[00119] In another embodiment the heavy chain variable region VH1 is connected directly to the heavy chain constant region having the IgG4 and the isolated antibody heavy chain consists of the amino acid sequence as provided in SEQ ID NO: 54. In still another embodiment the heavy chain variable region VH2 is connected directly to the heavy chain constant region having the IgG4 and the isolated antibody heavy chain consists of the amino acid sequence as provided in SEQ ID NO: 55. In yet another embodiment the heavy chain variable region VH3 is connected directly to the heavy chain constant region having the IgG4 and the isolated antibody heavy chain consists of the amino acid sequence as provided in SEQ ID NO: 56. In another embodiment the heavy chain variable region VH4 is connected directly to the heavy chain constant region having the IgG4 and the isolated antibody heavy chain consists of the amino acid sequence as provided in SEQ ID NO: 57.

[00120] Yet another embodiment is an isolated antibody according to any one of the embodiments having a variable light chain and a light chain constant region wherein the light chain constant region comprises the sequence set forth in SEQ ID NO: 25. Another embodiment is a variable light chain 1 with the constant light chain region wherein the amino acid sequence is provided in SEQ ID NO: 38. Yet another embodiment is the variable light chain 2 with the constant light chain region wherein the amino acid sequence is provided in SEQ ID NO: 39. In still another embodiment the variable light chain 3 with the constant light chain region wherein the amino acid sequence is provided in SEQ ID NO: 40. In yet another embodiment the variable light chain 4 with the constant light chain region wherein the amino acid sequence is provided in SEQ ID NO: 41.

[00121] Another embodiment is a method for treating a subject with a CD40L-associated disease or disorder comprising administering to the subject a therapeutically effective amount of an antibody or antigen binding fragment thereof, disclosed in the present application.

[00122] Another embodiment is an isolated antibody having a heavy chain with the amino acid sequence as provided in SEQ ID NO: 42 and a light chain sequence as provided in SEQ ID NO: 38. Another embodiment is an isolated antibody having a heavy chain with the amino acid sequence as provided in SEQ ID NO: 43 and a light chain sequence as provided in SEQ ID NO: 38. Another embodiment is an isolated antibody having a heavy chain with the amino acid sequence as provided in SEQ ID NO: 44 and a light chain sequence as provided in SEQ ID NO: 38. Another embodiment is an isolated antibody having a heavy chain with the amino acid sequence as provided in SEQ ID NO: 45 and a light chain sequence as provided in SEQ ID NO: 38. Another embodiment is an isolated antibody having a heavy chain with the amino acid sequence as provided in SEQ ID NO: 42 and a light chain sequence as provided in SEQ ID NO: 39. Another embodiment is an isolated antibody having a heavy chain with the amino acid sequence as provided in SEQ ID NO: 43 and a light chain sequence as provided in SEQ ID NO: 39. Another embodiment is an isolated antibody having a heavy chain with the amino acid sequence as provided in SEQ ID NO: 44 and a light chain sequence as provided in SEQ ID NO: 39. Another embodiment is an isolated antibody having a heavy chain with the amino acid sequence as provided in SEQ ID NO: 45 and a light chain sequence as provided in SEQ ID NO: 39. Another embodiment is an isolated antibody having a heavy chain with the amino acid sequence as provided in SEQ ID NO: 42 and a light chain sequence as provided in SEQ ID NO: 40. Another embodiment is an isolated antibody having a heavy chain with the amino acid sequence as provided in SEQ ID NO: 43 and a light chain sequence as provided in SEQ ID NO: 40. Another embodiment is an isolated antibody having a heavy chain with the amino acid

with the amino acid sequence as provided in SEQ ID NO: 55 and a light chain amino acid sequence as provided in SEQ ID NO: 40. Another embodiment is an isolated antibody having a heavy chain with the amino acid sequence as provided in SEQ ID NO: 56 and a light chain amino acid sequence as provided in SEQ ID NO: 40. Another embodiment is an isolated antibody having a heavy chain with the amino acid sequence as provided in SEQ ID NO: 57 and a light chain amino acid sequence as provided in SEQ ID NO: 40. Another embodiment is an isolated antibody having a heavy chain with the amino acid sequence as provided in SEQ ID NO: 54 and a light chain amino acid sequence as provided in SEQ ID NO: 41. Another embodiment is an isolated antibody having a heavy chain with the amino acid sequence as provided in SEQ ID NO: 55 and a light chain amino acid sequence as provided in SEQ ID NO: 41. Another embodiment is an isolated antibody having a heavy chain with the amino acid sequence as provided in SEQ ID NO: 56 and a light chain amino acid sequence as provided in SEQ ID NO: 41. Another embodiment is an isolated antibody having a heavy chain with the amino acid sequence as provided in SEQ ID NO: 57 and a light chain amino acid sequence as provided in SEQ ID NO: 41.

[00126] Yet another embodiment is a method for treating a subject with a neurodegenerative or a neuromuscular disease or disorder; an inflammatory or immune disease or disorder; or an autoimmune disease, comprising administering to the subject a therapeutically effective amount of an antibody or antigen binding fragment thereof, disclosed in the present application.

[00127] Another embodiment is a method for treating a subject with a an autoimmune disease, selected from the group consisting of systemic lupus erythematosus, type-1 diabetes, Myasthenia gravis, psoriasis, Addison's disease, Crohn's disease, uveitis, multiple sclerosis, hemolytic anemia, inflammatory bowel disease, immune thrombocytopenic purpura, Graves' disease, and rheumatoid arthritis, comprising administering to the subject a therapeutically effective amount of an antibody or antigen binding fragment thereof, disclosed in the present application.

[00128] Still another embodiment is a method for treating a subject having a neurodegenerative disorder or a neuromuscular disorder selected from the group consisting of Alzheimer's Disease, Parkinson's Disease, Amyotrophic Lateral Sclerosis, Multifocal Motor Neuropathy, Primary Lateral Sclerosis, Spinal Muscular Atrophy, Kennedy's Disease, and Spinocerebellar Ataxia comprising administering to the subject a therapeutically effective amount of an antibody or antigen binding fragment thereof disclosed in the present application.

[00129] Yet another embodiment is a method for treating a subject having Amyotrophic Lateral Sclerosis comprising administering to the subject a therapeutically effective amount of

an antibody or antigen binding fragment thereof, disclosed in the present application.

[00130] Another embodiment is a method for inhibiting an immune response in a subject comprising administering to the subject a therapeutically effective amount of an antibody or antigen binding fragment thereof, disclosed in the present application.

[00131] Another embodiment is a method of inhibiting an immune response in a subject comprising administering to the subject a therapeutically effective amount of an antibody or antigen binding fragment thereof, wherein the immune response is graft vs. host disease, or organ transplant rejection.

[00132] Yet another embodiment is a method according to any of the methods of the present disclosure, wherein the antibody or antibody fragment is administered in combination with another therapeutic agent. One embodiment is a method according to any of the methods of the present disclosure, wherein the antibody or antibody fragment is administered in combination with a compound that blocks the interaction between CD28 and CD86 or between CD28 and CD80.

[00133] Still another embodiment is a method according to any of the methods of the present disclosure, wherein the antibody or antibody fragment is administered in combination with compound that blocks the interaction between CD28 and CD86 or between CD28 and CD80 is a CTLA4-Ig fusion protein.

[00134] Yet another embodiment is a method according to any of the methods of the present disclosure, wherein the antibody or antibody fragment is administered in combination with compound that blocks the interaction between CD28 and CD86 or between CD28 and CD80 is abatacept or belatacept or galiximab.

Table 1. Sequences

Description	Sequence	SEQ ID NO:
Heavy chain 1 (VH1)	EVQLVQSGAEVKKPGASVKVSCKASGYTFTSYMYWVRQ APGQGLEWMGEINPSNGDTNYAQKFQGRVTMTVDSTST VYMEISSLRSED ¹ TAVYYCARSDGRNDMDSWGQGLTVTS S	1
Heavy chain 2 (VH2)	EVQLVQSGAEVKKPGASVKVSCKASGYIFTSYMYWVRQ APGQGLEWMGEINPSNGDTNYAEKFKGRVTMTVDSTST VYMEISSLRSED ² TAVYYCTRSDGRNDMDSWGQGLTVTS S	2
Heavy chain 3 (VH3)	EVQLVQSGAEVKKPGASVKVSCKASGYIFTSYMYWVRQ APGQGLEWIGEINPSNGDTNYAEKFKGRATLTVDSTST VYMEISSLRSED ³ TAVYYCTRSDGRNDMDSWGQGLTVTS S	3

Description	Sequence	SEQ ID NO:
Heavy chain 4 (VH4)	QVQLVQSGAEVKKPGASVKVSCKASGYIFTSYYMYWVRQ APGQGLEWIGEINPSNGDTNFAEKFKGRATLTVDSTST VYME LSSLR SEDTAVYYCTRSDGRNDMDSWGQGT LV TVS S	4
Light chain 1 (VL1)	EIVLTQSPATLSLSPGERATLSCRASQRVSSSTYSYMHW YQQKPGQAPRLLIYDASNRATGIPARFSGSGSGTDFTLT ISSLEPEDFAVYYCQHSWEIPPTFGQG TKLEIK	5
Light chain 2 (VL2)	EIVLTQSPATLSLSPGERATLSCRADERVSSSTYSYMHW YQQKPGQAPRLLIYDASNRATGIPARFSGSGSGTDFTLT ISSLEPEDFAVYYCQHSWEIPPTFGQG TKLEIK	6
Light chain 3 (VL3)	EIVLTQSPATLSLSPGERATLSCRASQRVSSSTYSYMHW YQQKPGQAPRLLIYASNRETGIPARFSGSGSGTDFTLT ISSLEPEDFAVYYCQHSWEIPPTFGQG TKLEIK	7
Light chain 4 (VL4)	EIVLTQSPATLSLSPGERATLSCRADERVSSSTYSYMHW YQQKPGQAPRLLIYASNRETGIPARFSGSGSGTDFTLT ISSLEPEDFAVYYCQHSWEIPPTFGQG TKLEIK	8
Heavy chain CDR1	SYMY	9
Heavy chain H1 CDR2	EINPSNGDTNYAQKFQG	10
Heavy chain H2 CDR2A (CDR2 and flanking region RV)	EINPSNGDTNYAEKFKGRV	11
Heavy chain H3 CDR2B (CDR2 and flanking region RA)	EINPSNGDTNYAEKFKGRA	12
Heavy chain H4 CDR2	EINPSNGDTNFAEKFKG	13
Heavy chain H2 and H3 CDR2	EINPSNGDTNYAEKFKG	14
Heavy Chain CDR3	SDGRNDMDS	15
Light Chain CDR1 L1 and L4	RASQRVSSSTYSYMH	16
Light Chain CDR1 L2 and L4	RADERVSSSTYSYMH	17
Light Chain CDR2 L1 and L2	DASNRAT	18
Light Chain CDR2 L3 and L4	YASNRET	19
Light Chain CDR3	QHSWEIPPT	20
Engineered effectorless IgG1 Fc with P238S and N297G mutations (underlined)	EPKSCDKTHTCPPCPAPELLGGSSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGK	21

Description	Sequence	SEQ ID NO:
Engineered D265A/N297A effectorless IgG1 constant heavy chain	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWN SGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICN VNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLF PPKPKDTLMISRTPEVTCVVDVAVSHEDPEVKFNWYVDGVEVH NAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKA LPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLV KGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLT VDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG	22
Engineered effectorless IgG1/IgG4 hybrid constant heavy chain sequence	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWN SGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICN VNHKPSNTKVDKKVEPKSCDKTHTCPSCPAPEFLGGPSVFLF PPKPKDTLMISRTPEVTCVVDVVSQEDPEVQFNWYVDGVEVH NAKTKPREEQFNSKYRVVSVLTVLHQDWLNGKEYKCKVSNKG LPSSIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLSCAV KGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLVSKLT VDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG	23
Engineered effectorless IgG4 constant heavy chain sequence	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWN SGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICN VDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPK PKDTLMISRTPEVTCVVDVVSQEDPEVQFNWYVDGVEVHNAK TKPREEQFNSKYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPS SIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGF YPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSRLTVDK SRWQEGNVFSCSVMHEALHNHYTQKSLSLSLG	24
Constant light chain sequence	RTVAAPSVEIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWK VDNALQSGNSQESVTEQDSKSTYLSSTLTLSKADYEEKHKV YACEVTHQGLSSPVTKSFNRGEC	25
Heavy chain 1 (VH1) DNA	GAGGTGCAGCTGGTGCAGTCCGGCGCCGAGGTGAAGAAGCCC GGCGCCTCCGTGAAGGTGTCTGCAAGGCCTCCGGCTACACC TTCACCTCCTACTACATGTACTGGGTGAGGCAGGCCCCCGGC CAGGGCCTGGAGTGGATGGGCGAGATCAACCCCTCCAACGGC GACACCAACTACGCACAGAAGTTCCAGGGTAGGGTCACCATG ACCGTGGACACGTCCACCTCCACCGTCTACATGGAGCTGTCC TCCCTGAGGTCCGAGGACACCGCCGTGTACTACTGCGCCAGG TCCGACGGCAGGAACGACATGGACTCCTGGGGCCAGGGCACC CTGGTGACCGTGTCTCTCC	26
Heavy chain 2 (VH2) DNA	GAGGTGCAGCTGGTGCAGTCCGGCGCCGAGGTGAAGAAGCCC GGCGCCTCCGTGAAGGTGTCTGCAAGGCCTCCGGCTACATC TTCACCTCCTACTACATGTACTGGGTGAGGCAGGCCCCCGGC CAGGGCCTGGAGTGGATGGGCGAGATCAACCCCTCCAACGGC GACACCAACTACGCAGAGAAGTTCAAGGGTAGGGTCACCATG ACCGTGGACACGTCCACCTCCACCGTCTACATGGAGCTGTCC TCCCTGAGGTCCGAGGACACCGCCGTGTACTACTGCACCAGG TCCGACGGCAGGAACGACATGGACTCCTGGGGCCAGGGCACC CTGGTGACCGTGTCTCTCC	27

Description	Sequence	SEQ ID NO:
Heavy chain 3 (VH3) DNA	GAGGTGCAGCTGGTGCAGTCCGGCGCCGAGGTGAAGAAGCCC GGCGCCTCCGTGAAGGTGTCCTGCAAGGCCTCCGGCTACATC TTCACCTCCTACTACATGTACTGGGTGAGGCAGGCCCCCGGC CAGGGCCTGGAGTGGATCGGCGAGATCAACCCCTCCAACGGC GACACCAACTACGCAGAGAAGTTCAAGGGTAGGGCCACCCTG ACCGTGGACACGTCCACCTCCACCGTCTACATGGAGCTGTCC TCCCTGAGGTCCGAGGACACCGCCGTGTACTACTGCACCAGG TCCGACGGCAGGAACGACATGGACTCCTGGGGCCAGGGCACC CTGGTGACCGTGTCTCC	28
Heavy chain 4 (VH4) DNA	CAGGTGCAGCTGGTGCAGTCCGGCGCCGAGGTGAAGAAGCCC GGCGCCTCCGTGAAGGTGTCCTGCAAGGCCTCCGGCTACATC TTCACCTCCTACTACATGTACTGGGTGAGGCAGGCCCCCGGC CAGGGCCTGGAGTGGATCGGCGAGATCAACCCCTCCAACGGC GACACCAACTTCGCAGAGAAGTTCAAGGGTAGGGCCACCCTG ACCGTGGACACGTCCACCTCCACCGTCTACATGGAGCTGTCC TCCCTGAGGTCCGAGGACACCGCCGTGTACTACTGCACCAGG TCCGACGGCAGGAACGACATGGACTCCTGGGGCCAGGGCACC CTGGTGACCGTGTCTCC	29
Light chain 1 (VL1) DNA	GAGATCGTGCTGACCCAGTCACCTGCCACCCTGTCCCTGTCA CCTGGAGAGAGAGCCACCCTCTCCTGCAGAGCCTCCCAGAGG GTGTCCTCCTCCACCTACTCCTACATGCACTGGTACCAGCAG AAGCCTGGACAGGCACCTAGGCTGCTGATCTACGACGCCTCC AACAGGGCGACCGGTATACCAGCCAGGTTCTCAGGCTCAGGC TCAGGCACCGACTTCACCCTGACCATCTCCTCCCTGGAGCCA GAGGACTTCGCCGTCTACTACTGCCAGCACTCCTGGGAGATC CCACCTACCTTCGGACAAGGCACCAAGCTGGAAATCAAA	30
Light chain 2 (VL2) DNA	GAGATCGTGCTGACCCAGTCACCTGCCACCCTGTCCCTGTCA CCTGGAGAGAGAGCCACCCTCTCCTGCAGAGCCGATGAGAGG GTGTCCTCCTCCACCTACTCCTACATGCACTGGTACCAGCAG AAGCCTGGACAGGCACCTAGGCTGCTGATCTACGACGCCTCC AACAGGGCGACCGGTATACCAGCCAGGTTCTCAGGCTCAGGC TCAGGCACCGACTTCACCCTGACCATCTCCTCCCTGGAGCCA GAGGACTTCGCCGTCTACTACTGCCAGCACTCCTGGGAGATC CCACCTACCTTCGGACAAGGCACCAAGCTGGAAATCAAA	31
Light chain 3 (VL3) DNA	GAGATCGTGCTGACCCAGTCACCTGCCACCCTGTCCCTGTCA CCTGGAGAGAGAGCCACCCTCTCCTGCAGAGCCTCCCAGAGG GTGTCCTCCTCCACCTACTCCTACATGCACTGGTACCAGCAG AAGCCTGGACAGGCACCTAGGCTGCTGATCAAGTACGCCTCC AACAGGGAGACCGGTATACCAGCCAGGTTCTCAGGCTCAGGC TCAGGCACCGACTTCACCCTGACCATCTCCTCCCTGGAGCCA GAGGACTTCGCCGTCTACTACTGCCAGCACTCCTGGGAGATC CCACCTACCTTCGGACAAGGCACCAAGCTGGAAATCAAA	32
Light chain 4 (VL4) DNA	GAGATCGTGCTGACCCAGTCACCTGCCACCCTGTCCCTGTCA CCTGGAGAGAGAGCCACCCTCTCCTGCAGAGCCGATGAGAGG GTGTCCTCCTCCACCTACTCCTACATGCACTGGTACCAGCAG AAGCCTGGACAGGCACCTAGGCTGCTGATCAAGTACGCCTCC AACAGGGAGACCGGTATACCAGCCAGGTTCTCAGGCTCAGGC TCAGGCACCGACTTCACCCTGACCATCTCCTCCCTGGAGCCA GAGGACTTCGCCGTCTACTACTGCCAGCACTCCTGGGAGATC CCACCTACCTTCGGACAAGGCACCAAGCTGGAAATCAAA	33

Description	Sequence	SEQ ID NO:
Fc fragment of IgG, high affinity Ia, receptor (CD64) (FC γ RIa)	MWFLTTLLLWVPVDGQVDTTKAVITLQPPWVSVFQEETVTLH CEVLHLPGSSSTQWFLNGTATQTSTPSYRITSASVNDSEYR CQRGLSGRSDPIQLEIHRGWLLLQVSSRVFTEGEPLALRCHA WKDKLVYNVLYYRNGKAFKFFHWNNSNLTILKTNISHNGTYHC SGMGKHRYTSAGISVTVKELFPAPVLNASVTSPLLEGNLVTL SCETKLLLQRPGLQLYFSFYMGSKTLRGRNTSSEYQILTARR EDSGLYWCEAATEDGNVLKRSPELELQVLGLQLPTPVWFHVL FYLAVGIMFLVNTVLWVTIRKELKRKKKWDLEISLDSGHEKK VISSLQEDRHLEELKCQEKEEQLEQEGVHRKEPQGAT	34
Low affinity immunoglobulin gamma Fc region acceptor IIa (FC γ RIIa) (CD32)	MTMETQMSQNVCPRNLWLLQPLTVLALLLASADSQAAPPKAVL KLEPPWINVLQEDSVTLTCQGARSPESDSIQWFHNGNLIPTH TQPSYRFKANNNDSEYTCQTGQTSLSDPVHLTVLSEWLVLO TPHLEFQEGETIMLRCHSWKDKPLVKVTFQNGKSQKFSLD PTFSIPQANHSHSGDYHCTGNIGYTLFSSKPVTITVQVPMSG SSSPMGVIVAVVIATAVAIAVAVALIYCRKKRISANSTDP VKAAQFEPPGRQMIAIRKRQLEETNNDYETADGGYMTLNPR PTDDDKNIYLTLPNDHVNNSN	35
low affinity immunoglobulin gamma Fc region receptor IIIa (FC γ RIIIa) (CD16a)	MGGGAGERLFTSSCLVGLVPLGLRISLVTCPQLQCGIMWQLLL PTALLLLVSAGMRTEDLPAKAVVFLEPQWYRVLEKDSVTLKCQ GAYSPEDNSTQWFHNESLISSQASSYFIDAATVDDSGEYRCQ TNLSTLSDPVQLEVHIGWLLLQAPRWVFKEEDPIHLRCHSWK NTALHKVTYLQNGKGRKYFHHNSDFYIPKATLKDSGSYFCRG LVGSKNVSSSETVNITITQGLAVSTISSFFPPGYQVSFCLVMV LLFAVDTGLYFSVKTNISSSTRDWKDHKFKWRKDPQDK	36
Low affinity immunoglobulin gamma Fc region receptor IIIb (FC γ RIIIb) (CD16b))	MWQLLLPTALLLLVSAGMRTEDLPAKAVVFLEPQWYSVLEKDS VTLKCQGAYSPEDNSTQWFHNESLISSQASSYFIDAATVNDS GEYRCQTNLSTLSDPVQLEVHIGWLLLQAPRWVFKEEDPIHL RCHSWKNTALHKVTYLQNGKDRKYFHHNSDFHIPKATLKDSG SYFCRGLVGSKNVSSSETVNITITQGLAVSTISSFFPPGYQVS FCLVMVLLFAVDTGLYFSVKTNI	37
Light chain 1 with constant light chain (VL1-C)	EIVLTQSPATLSLSPGERATLSCRASQRVSSSTYSYMHYQQ KPGQAPRLLIYDASNRATGIPARFSGSGSGTDFTLTISSLEP EDFAVYYCQHSWEIPPTFGQGTEKLEIKRTVAAPSVFIFPPSD EQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVT EQDSKDSTYSLSSSTLTLSKADYEKHKVYACEVTHQGLSSPVT KSFNRGEC	38
Light chain 2 with constant light chain (VL2-C)	EIVLTQSPATLSLSPGERATLSCRADERVSSSTYSYMHW YQQKPGQAPRLLIYDASNRATGIPARFSGSGSGTDFTLT ISSLEPEDFAVYYCQHSWEIPPTFGQGTEKLEIKRTVAAP SVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQ SGNSQESVTEQDSKDSTYSLSSSTLTLSKADYEKHKVYACEVT HQGLSSPVTKSFNRGEC	39
Light chain 3 with constant light chain (VL3-C)	EIVLTQSPATLSLSPGERATLSCRASQRVSSSTYSYMHW YQQKPGQAPRLLIYASNRETGIPARFSGSGSGTDFTLT ISSLEPEDFAVYYCQHSWEIPPTFGQGTEKLEIKRTVAAP SVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQ SGNSQESVTEQDSKDSTYSLSSSTLTLSKADYEKHKVYACEVT HQGLSSPVTKSFNRGEC	40

Description	Sequence	SEQ ID NO:
Light chain 4 with constant light chain (VL4-C)	EIVLTQSPATLSLSPGERATLSCRADERVSSSTYSYMHWYQQKPGQAPRLLIKYASNRETGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQHSWEIPPTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	41
Heavy chain 1- IgG1 Fc with P238S and N297G mutations (VH1-Fc-P238/N297)	EPKSCDKTHTCPPCPAPELLGGSSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSSVMHEALHNHYTQKSLSLSPGK	42
Heavy chain 2- IgG1 Fc with P238S and N297G mutations (VH2- Fc-P238/N297)	EPKSCDKTHTCPPCPAPELLGGSSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSSVMHEALHNHYTQKSLSLSPGK	43
Heavy chain 3- IgG1 Fc with P238S and N297G mutations (VH3-Fc-P238/N297)	EPKSCDKTHTCPPCPAPELLGGSSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSSVMHEALHNHYTQKSLSLSPGK	44
Heavy chain 4- IgG1 Fc with P238S and N297G mutations (VH4 – Fc-P238/N297)	EPKSCDKTHTCPPCPAPELLGGSSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSSVMHEALHNHYTQKSLSLSPGK	45
Heavy chain 1-Fc D265A/N297A effectorless IgG1 (VH1-Fc-D265A/N297A)	EVQLVQSGAEVKKPGASVKVSCKASGYTFTSYMYWVRQAPGQGLEWMGEINPSNGDTNYAQKFQGRVTMTVDTSTSTVYMELSSLRSEDTAVYYCARSDGRNDMDSWGQGTLTVTSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVAVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSSVMHEALHNHYTQKSLSLSPG	46
Heavy chain 2-Fc D265A/N297A effectorless IgG1 (VH2-Fc-D265A/N297A)	EVQLVQSGAEVKKPGASVKVSCKASGYIFTSYMYWVRQAPGQGLEWMGEINPSNGDTNYAEKFKGRVTMTVDTSTSTVYMELSSLRSEDTAVYYCTRSDGRNDMDSWGQGTLTVTSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVAVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSSVMHEALHNHYTQKSLSLSPG	47

Description	Sequence	SEQ ID NO:
Heavy chain 3-Fc D265A/N297A effectorless IgG1 (VH3-Fc- D265A/N297A)	EVQLVQSGAEVKKPGASVKVSCKASGYIFTSYYMYWVRQ APGQGLEWIGEINPSNGDTNYAEKFKGRATLTVDSTST VYME LSSLRSEDTAVYYCTRS DGRNDMDSWGQGT LVTVS SASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVT VSW NSGALTSGVHTFPAVLQSSGLYSLSSVTV PSSLGTQTYIC NVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFL FPPKPKDTLMISRTPEVTCV VAVSHEDPEVKFNWYVDGVEV HNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCL VKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKL TVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG	48
Heavy chain 4-Fc D265A/N297A effectorless IgG1 (VH4-Fc- D265A/N297A)	QVQLVQSGAEVKKPGASVKVSCKASGYIFTSYYMYWVRQ APGQGLEWIGEINPSNGDTNF AEKFKGRATLTVDSTST VYME LSSLRSEDTAVYYCTRS DGRNDMDSWGQGT LVTVS SASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVT VSW NSGALTSGVHTFPAVLQSSGLYSLSSVTV PSSLGTQTYIC NVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFL FPPKPKDTLMISRTPEVTCV VAVSHEDPEVKFNWYVDGVEV HNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCL VKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKL TVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG	49
Heavy chain 1-Fc effectorless IgG1/IgG4 hybrid (VH1-Fc-IgG1/IgG4 hybrid)	EVQLVQSGAEVKKPGASVKVSCKASGYTFTSYMYWVRQ APGQGLEWMGEINPSNGDTNYAQKFQGRVTMTVDSTST VYME LSSLRSEDTAVYYCARSDGRNDMDSWGQGT LVTVS SASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVT VSW NSGALTSGVHTFPAVLQSSGLYSLSSVTV PSSLGTQTYIC NVNHKPSNTKVDKKVEPKSCDKTHTCPSCPAPEFLGGPSVFL FPPKPKDTLMISRTPEVTCVVDVVSQEDPEVQFNWYVDGVEV HNAKTKPREEQFNSKYRVVSVLTVLHQDWLNGKEYKCKVSNK GLPSSIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLSCA VKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLVSKL TVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG	50
Heavy chain 2-Fc effectorless IgG1/IgG4 hybrid (VH2-Fc-IgG1/IgG4 hybrid)	EVQLVQSGAEVKKPGASVKVSCKASGYIFTSYYMYWVRQ APGQGLEWMGEINPSNGDTNYAEKFKGRVTMTVDSTST VYME LSSLRSEDTAVYYCTRS DGRNDMDSWGQGT LVTVS SASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVT VSW NSGALTSGVHTFPAVLQSSGLYSLSSVTV PSSLGTQTYIC NVNHKPSNTKVDKKVEPKSCDKTHTCPSCPAPEFLGGPSVFL FPPKPKDTLMISRTPEVTCVVDVVSQEDPEVQFNWYVDGVEV HNAKTKPREEQFNSKYRVVSVLTVLHQDWLNGKEYKCKVSNK GLPSSIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLSCA VKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLVSKL TVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG	51

Description	Sequence	SEQ ID NO:
Heavy chain 3-Fc effectorless IgG1/IgG4 hybrid (VH3-Fc-IgG1/IgG4 hybrid)	EVQLVQSGAEVKKPGASVKVSCKASGYIFTSYYMYWVRQ APGQGLEWIGEINPSNGDTNYAEKFKGRATLTVDSTST VYME LSSLRSEDTAVYYCTRS DGRNDMDSWGQGT LVTVS SASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVT VSW NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYIC NVNHKPSNTKVDKKVEPKSCDKTHTCPSCPAPEFLGGPSVFL FPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEV HNAKTKPREEQFNSKYRVVSVLTVLHQDWLNGKEYKCKVSNK GLPSSIEKTIKAKGQPREPQVYTLPPSREEMTKNQVSLSCA VKGFPYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLVSKL TVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG	52
Heavy chain 4-Fc effectorless IgG1/IgG4 hybrid (VH4-Fc-IgG1/IgG4 hybrid)	QVQLVQSGAEVKKPGASVKVSCKASGYIFTSYYMYWVRQ APGQGLEWIGEINPSNGDTNFAEKFKGRATLTVDSTST VYME LSSLRSEDTAVYYCTRS DGRNDMDSWGQGT LVTVS SASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVT VSW NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYIC NVNHKPSNTKVDKKVEPKSCDKTHTCPSCPAPEFLGGPSVFL FPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEV HNAKTKPREEQFNSKYRVVSVLTVLHQDWLNGKEYKCKVSNK GLPSSIEKTIKAKGQPREPQVYTLPPSREEMTKNQVSLSCA VKGFPYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLVSKL TVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG	53
Heavy chain 1-Fc effectorless IgG4 constant heavy chain (VH1-Fc- IgG4)	EVQLVQSGAEVKKPGASVKVSCKASGYTFTSYMYWVRQ APGQGLEWMGEINPSNGDTNYAQKFQGRVTMTVDSTST VYME LSSLRSEDTAVYYCARSDGRNDMDSWGQGT LVTVS SASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVT VSW NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYTC NVDHKPSNTKVDKRVESKYGPCCPPCPAPEFLGGPSVFLFPP KPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNA KTKPREEQFNSKYRVVSVLTVLHQDWLNGKEYKCKVSNKGLP SSIEKTIKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKG FYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSRLTVD KSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLG	54
Heavy chain 2-Fc effectorless IgG4 constant heavy chain (VH2-Fc- IgG4)	EVQLVQSGAEVKKPGASVKVSCKASGYIFTSYYMYWVRQ APGQGLEWMGEINPSNGDTNYAEKFKGRVTMTVDSTST VYME LSSLRSEDTAVYYCTRS DGRNDMDSWGQGT LVTVS SASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVT VSW NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYTC NVDHKPSNTKVDKRVESKYGPCCPPCPAPEFLGGPSVFLFPP KPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNA KTKPREEQFNSKYRVVSVLTVLHQDWLNGKEYKCKVSNKGLP SSIEKTIKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKG FYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSRLTVD KSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLG	55

Description	Sequence	SEQ ID NO:
Heavy chain 3-Fc effectorless IgG4 constant heavy chain (VH3-Fc- IgG4)	EVQLVQSGAEVKKPGASVKVSCKASGYIFTSYYMYWVRQ APGQGLEWIGEINPSNGDTNYAEKFKGRATLTVDSTST VYME LSSLRSEDTAVYYCTRS DGRNDMDSWGQGT LVTVS SASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVT VSW NSGALTSGVHTFPAVLQSSGLYSLSSVTV PSSLGTKTYTC NVDHKPSNTKVDKRVESKYGPCCPPCPAPEFLGGPSVFLFPP KPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNA KTKPREEQFNSKYRVVSVLT VLVHQLDNLNGKEYKCKVSNKGLP SSIIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKG FYPSDIAVEWESNGQPENNYKTT PPVLDSDGSFFFLYSRLTVD KSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLG	56
Heavy chain 4-Fc effectorless IgG4 constant heavy chain (VH4-Fc- IgG4)	QVQLVQSGAEVKKPGASVKVSCKASGYIFTSYYMYWVRQ APGQGLEWIGEINPSNGDTNFAEKFKGRATLTVDSTST VYME LSSLRSEDTAVYYCTRS DGRNDMDSWGQGT LVTVS SASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVT VSW NSGALTSGVHTFPAVLQSSGLYSLSSVTV PSSLGTKTYTC NVDHKPSNTKVDKRVESKYGPCCPPCPAPEFLGGPSVFLFPP KPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNA KTKPREEQFNSKYRVVSVLT VLVHQLDNLNGKEYKCKVSNKGLP SSIIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKG FYPSDIAVEWESNGQPENNYKTT PPVLDSDGSFFFLYSRLTVD KSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLG	57

EXAMPLES

[00135] Example 1 CD40L binding assay

[00136] In order to make a comparison of CD40L binding of antibodies from all 16 clones versus 5c8 or AT-1501 a binding assay was run using 2 clones with 5c8 and AT-1501 run on the same 96-well assay plate. A three part sandwich ELISA assay was used to determine the level of binding of the antibodies of the present disclosure in comparison to reference antibodies 5c8-19 and AT1501. 96-well polystyrene plates were coated with recombinant human CD40L (BioLegend Cat. # 591706) using 2 ug/ml in PBS and 50 ul/well was added to Costar 96-well ½ area high binding assay plates (Corning 3690) and incubated overnight at 4°C. Plates were blocked with (1X) PBS/1.0%BSA (140 ul/well) for 1 hour at room temperature to prevent background binding. Binding curves of 5C8 or AT1501 (from 2 ug/ml out serial 2-fold dilutions) were added (50 ul/well) and incubated for 1 hour at room temperature. Plates are washed and incubated with HRP-(Fab2) donkey anti-human IgG (Fc specific) (Jackson Immuno. 709-036-098) at a 1:10,000 dilution (50 ul/well) for 1 hour at room temperature. Plates were washed and TMB substrate (Surmodics BioFX TMBW-1000-01) was added (50ul/well). Color development is stopped after 5 minutes at room temperature with 25 ul 2NH₂SO₄. Plates are read on Molecular Devices SpectraMax M5 plate reader using SoftMax Pro 6.2.2 program to

determine absorbance at 450 nm.

[00137] Relative CD40L binding potency was calculated as follows: $[\text{IC}_{50}(\text{clone}) / \text{IC}_{50}(\text{5c8 or AT-1501}) \times 100\%]$. The ranked potency of the 16 clones versus 5c8 is shown in Figure 1A and the ranked potency versus AT-1501 is shown in Figure 1B. The resulting binding curves are shown in Figures 2A-2Q (comparison of 16 clones versus 5c8, Figure 2H shows the comparison between AT-1501 and 5c8) and Figures 3A-3Q (comparison of the 16 clones versus AT-1501, Figure 3H shows the comparison between AT-1501 and 5c8). The IC_{50} , LCL, UCL and Relative Potency for each clone are shown in Table 2 (comparison with 5c8) and Table 3 (comparison with AT-1501).

Table 2

Fig. No.	Clone	IC ₅₀	LCL	UCL	Rel. Pot.
2A	16-3	0.022	0.017	0.026	46
	5c8	0.047	0.040	0.054	
2B	8-3	0.036	0.028	0.043	51
	5c8	0.070	0.062	0.078	
2C	12-4	0.020	0.013	0.027	47
	5c8	0.042	0.038	0.046	
2D	8-4	0.036	0.030	0.041	51
	5c8	0.070	0.062	0.078	
2E	13-2	0.020	0.013	0.027	48
	5c8	0.041	0.038	0.045	
2F	4-4	0.037	0.029	0.045	51
	5c8	0.072	0.064	0.081	
2G	17-1	0.028	0.023	0.033	63
	5c8	0.044	0.036	0.053	
2H	AT-1501	0.049	0.043	0.056	95
	5c8	0.052	0.046	0.058	
2I	5-3	0.055	0.047	0.063	76
	5c8	0.072	0.064	0.081	
2J	6-6	0.065	0.059	0.070	106
	5c8	0.061	0.054	0.068	
2K	18-2	0.041	0.036	0.046	92
	5c8	0.044	0.036	0.053	
2L	10-4	0.075	0.065	0.086	113
	5c8	0.067	0.058	0.076	
2M	10-1	0.079	0.070	0.089	119
	5c8	0.067	0.058	0.076	
2N	7-5	0.102	0.094	0.111	168
	5c8	0.061	0.054	0.068	

Fig. No.	Clone	IC50	LCL	UCL	Rel. Pot.
2O	15-4	0.063	0.056	0.069	133
	5c8	0.047	0.040	0.054	
2P	11-5	0.092	0.071	0.112	177
	5c8	0.052	0.046	0.058	
2Q	15-1	0.081	0.073	0.089	163
	5c8	0.050	0.046	0.053	

Table 3

Fig. No.	Clone	IC50	LCL	UCL	Rel. Pot.
3A	12-4	0.020	0.013	0.027	45
	AT-1501	0.044	0.039	0.049	
3B	8-3	0.036	0.028	0.043	59
	AT-1501	0.060	0.053	0.068	
3C	13-2	0.020	0.013	0.027	45
	AT-1501	0.044	0.038	0.049	
3D	8-4	0.036	0.030	0.041	59
	AT-1501	0.060	0.053	0.068	
3E	16-3	0.022	0.017	0.026	48
	AT-1501	0.045	0.039	0.051	
3F	4-4	0.037	0.029	0.045	60
	AT-1501	0.062	0.054	0.070	
3G	17-1	0.028	0.023	0.033	66
	AT-1501	0.042	0.035	0.050	
3H	5c8	0.052	0.046	0.058	105
	AT-1501	0.049	0.043	0.056	
3I	5-3	0.055	0.047	0.063	89
	AT-1501	0.062	0.054	0.070	
3J	10-4	0.075	0.065	0.086	115
	AT-1501	0.066	0.056	0.076	
3K	18-2	0.041	0.036	0.046	96
	AT-1501	0.042	0.035	0.050	
3L	10-1	0.079	0.070	0.089	121
	AT-1501	0.066	0.056	0.076	
3M	6-6	0.065	0.059	0.070	132
	AT-1501	0.049	0.047	0.051	
3N	11-5	0.092	0.071	0.112	174
	AT-1501	0.053	0.050	0.056	
3O	15-4	0.063	0.056	0.069	139
	AT-1501	0.045	0.039	0.051	
3P	7-5	0.102	0.094	0.111	210

Fig. No.	Clone	IC50	LCL	UCL	Rel. Pot.
	AT-1501	0.049	0.047	0.051	
3Q	15-1	0.081	0.073	0.089	159
	AT-1501	0.051	0.046	0.055	

[00138] Example 2 Binding activity to human FcγRI, FcγRIIa, FcγRIIIa and FcγRIIIb

[00139] The 16 VH/VL antibody clones constructed with an IgG1 Fc having two mutations P238S and N297G (SEQ ID NO: 21). These antibody clones were assayed for Fc effector function for binding to human FcγRI, FcγRIIa and FcγRIIIa.

[00140] Anti-CD40L antibodies (Abatacept included as negative control) are diluted to 2ug/ml in (1X) PBS and 50 ul/well was added to Costar 96-well ½ area high binding assay plates (Corning 3690) for overnight incubation at 4°C. Plates were blocked with (1X) PBS/1.0% BSA (140 ul/well) for 1 hour at room temperature to prevent background binding. Binding curves of recombinant human FcγRI, Ila, IIIa and IIIb (from 5 ug/ml out serial 2-fold dilutions) were added (50 ul/well) and incubated for 1 hour at room temperature. Plates were washed and incubated with mouse anti-human CD16 (anti-FcRIII); CD32 (anti-FcRIIa) or CD64 (anti-FcRI) (eBioSciences/Invitrogen 14-0168-82; 16-0329-81; 14-0649-82) at 2 ug/ml (50 ul/well) for 1 hour at room temperature. Plates were washed and incubated with HRP-(Fab₂) goat anti-mouse IgG (Fc specific) (Jackson Immuno. 116-036-071) at a 1:10,000 dilution (50 ul/well) for 1 hour at room temperature. Plates were washed and TMB substrate (Surmodics BioFX TMBW-1000-01) was added (50 ul/well). Color development was stopped after 5 mins at room temperature with (25 ul/well) 2NH₂SO₄. Plates were read on Molecular Devices SpectraMax M5 plate reader using SoftMax Pro 6.2.2 program to determine absorbance at 450nm.

[00141] As can be seen in the figures, the clones disclosed in this application were negative for binding to the three Fc receptors while 5c8 bound to FcγRI, FcγRIIa but not to FcγRIIIa or FcγRIIIb. Each of Figures 4A and 4B show the binding to FcγRIa for eight antibody clones compared with the binding curves of 5c8, AT-1501 and Abatacept. Each of Figures 5A and 5B show the binding to FcγRIIa for eight antibody clones compared with the binding curve of 5c8, AT-1501 and Abatacept. Each of Figures 6A and 6B show the binding to FcγRIIIa for eight antibody clones compared with the binding curves of 5c8, AT-1501 and Abatacept. Each of Figures 6C and 6D show the binding to FcγRIIIb for eight antibody clones compared with the binding curves of 5c8, AT-1501 and Abatacept. (Figures 4A, 5A, 6A and 6A show results from antibody clones 4-4, 5-3, 6-6, 7-5, 8-3, 8-4, 10-1 and 10-4, Figures 4B, 5B, 6C and 6D

show results from antibody clones 11-5, 12-4, 13-2, 15-1, 15-4, 16-3, 17-1 and 18-2).

[00142] Example 4 Binding Activity to C1q

[00143] Anti-CD40L antibodies (Abatacept included as negative control) were diluted to 2 ug/ml in (1X) PBS and 50 ul/well was added to Costar 96-well ½ area high binding assay plates (Corning 3690) for overnight incubation at 4°C. Plates were blocked with (1X) PBS/1.0% BSA (140 ul/well) for 1 hour at room temperature to prevent background binding. Binding curves of natural human C1q protein (Abcam ab96363) from 10ug/ml out serial 2-fold dilutions were added (50 ul/well) for 1 hour at room temperature. Plates were washed and HRP-sheep anti-human C1q (Abcam ab46191) is added at a 1:400 dilution (50 ul/well) and incubated for 1 hour at room temperature. Plates were washed and TMB substrate (Surmodics BioFX TMBW-1000-01) is added (50 ul/well). Color development was stopped after 5 minutes at room temperature with (25 ul/well) 2NH₂SO₄. Plates were read on Molecular Devices SpectraMax M5 plate reader using SoftMax Pro 6.2.2 program to determine absorbance at 450nm.

[00144] As can be seen in the figures, the antibody from all sixteen antibody clones disclosed in this application were negative for binding to C1q while 5c8 showed significant binding. Each of Figures 7A and 7B show the binding to C1q for eight antibody clones compared with the binding curves of 5c8, AT-1501 and Abatacept. Figure 7A shows results from antibody clones 4-4, 5-3, 6-6, 7-5, 8-3, 8-4, 10-1 and 10-4 and 7B shows results from antibody clones 11-5, 12-4, 13-2, 15-1, 15-4, 16-3, 17-1 and 18-2.

CLAIMS

1. An isolated antibody or antigen-binding fragment thereof, comprising:
 - (a) a heavy chain variable region (VH) having the amino acid sequence as set forth in SEQ ID NO: 1 and the light chain variable region (VL) having the amino acid sequence as set forth in SEQ ID NO: 5; or
 - (b) a heavy chain variable region (VH) having the amino acid sequence as set forth in SEQ ID NO: 1 and the light chain variable region (VL) having the amino acid sequence as set forth in SEQ ID NO: 6; or
 - (c) a heavy chain variable region (VH) having the amino acid sequence as set forth in SEQ ID NO: 1 and the light chain variable region (VL) having the amino acid sequence as set forth in SEQ ID NO: 7; or
 - (d) a heavy chain variable region (VH) having the amino acid sequence as set forth in SEQ ID NO: 1 and the light chain variable region (VL) having the amino acid sequence as set forth in SEQ ID NO: 8; or
 - (e) a heavy chain variable region (VH) having the amino acid sequence as set forth in SEQ ID NO: 2 and the light chain variable region (VL) having the amino acid sequence as set forth in SEQ ID NO: 5; or
 - (f) a heavy chain variable region (VH) having the amino acid sequence as set forth in SEQ ID NO: 2 and the light chain variable region (VL) having the amino acid sequence as set forth in SEQ ID NO: 6; or
 - (g) a heavy chain variable region (VH) having the amino acid sequence as set forth in SEQ ID NO: 2 and the light chain variable region (VL) having the amino acid sequence as set forth in SEQ ID NO: 7; or
 - (h) a heavy chain variable region (VH) having the amino acid sequence as set forth in SEQ ID NO: 2 and the light chain variable region (VL) having the amino acid sequence as set forth in SEQ ID NO: 8; or
 - (i) a heavy chain variable region (VH) having the amino acid sequence as set forth in SEQ ID NO: 3 and the light chain variable region (VL) having the amino acid sequence as set forth in SEQ ID NO: 5; or

j) a heavy chain variable region (VH) having the amino acid sequence as set forth in SEQ ID NO: 3 and the light chain variable region (VL) having the amino acid sequence as set forth in SEQ ID NO: 6; or

(k) a heavy chain variable region (VH) having the amino acid sequence as set forth in SEQ ID NO: 3 and the light chain variable region (VL) having the amino acid sequence as set forth in SEQ ID NO: 7; or

(l) a heavy chain variable region (VH) having the amino acid sequence as set forth in SEQ ID NO: 3 and the light chain variable region (VL) having the amino acid sequence as set forth in SEQ ID NO: 8; or

(m) a heavy chain variable region (VH) having the amino acid sequence as set forth in SEQ ID NO: 4 and the light chain variable region (VL) having the amino acid sequence as set forth in SEQ ID NO: 5; or

(n) a heavy chain variable region (VH) having the amino acid sequence as set forth in SEQ ID NO: 4 and the light chain variable region (VL) having the amino acid sequence as set forth in SEQ ID NO: 6; or

(o) a heavy chain variable region (VH) having the amino acid sequence as set forth in SEQ ID NO: 4 and the light chain variable region (VL) having the amino acid sequence as set forth in SEQ ID NO: 7; or

(p) a heavy chain variable region (VH) having the amino acid sequence as set forth in SEQ ID NO: 4 and the light chain variable region (VL) having the amino acid sequence as set forth in SEQ ID NO: 8.

2. The isolated antibody or antigen-binding fragment thereof, comprising the heavy chain variable region (VH) having the amino acid sequence as set forth in SEQ ID NO: 1 and the light chain variable region (VL) having the amino acid sequence as set forth in SEQ ID NO: 5.

3. The isolated antibody or antigen-binding fragment thereof, comprising the heavy chain variable region (VH) having the amino acid sequence as set forth in SEQ ID NO: 1 and the light chain variable region (VL) having the amino acid sequence as set forth in SEQ ID NO: 6.

4. The isolated antibody or antigen-binding fragment thereof, comprising the heavy chain variable region (VH) having the amino acid sequence as set forth in SEQ ID NO: 1 and the light chain variable region (VL) having the amino acid sequence as set forth in SEQ ID NO: 7.

5. The isolated antibody or antigen-binding fragment thereof, comprising the heavy chain variable region (VH) having the amino acid sequence as set forth in SEQ ID NO: 1 and the light chain variable region (VL) having the amino acid sequence as set forth in SEQ ID NO: 8.

6. The isolated antibody or antigen-binding fragment thereof, comprising the heavy chain variable region (VH) having the amino acid sequence as set forth in SEQ ID NO: 2 and the light chain variable region (VL) having the amino acid sequence as set forth in SEQ ID NO: 5.

7. The isolated antibody or antigen-binding fragment thereof, comprising the heavy chain variable region (VH) having the amino acid sequence as set forth in SEQ ID NO: 2 and the light chain variable region (VL) having the amino acid sequence as set forth in SEQ ID NO: 6.

8. The isolated antibody or antigen-binding fragment thereof, comprising the heavy chain variable region (VH) having the amino acid sequence as set forth in SEQ ID NO: 2 and the light chain variable region (VL) having the amino acid sequence as set forth in SEQ ID NO: 7.

9. The isolated antibody or antigen-binding fragment thereof, comprising the heavy chain variable region (VH) having the amino acid sequence as set forth in SEQ ID NO: 2 and the light chain variable region (VL) having the amino acid sequence as set forth in SEQ ID NO: 8.

10. The isolated antibody or antigen-binding fragment thereof, comprising the heavy chain variable region (VH) having the amino acid sequence as set forth in SEQ ID NO: 3 and the light chain variable region (VL) having the amino acid sequence as set forth in SEQ ID NO: 5.

11. The isolated antibody or antigen-binding fragment thereof, comprising the heavy chain variable region (VH) having the amino acid sequence as set forth in SEQ ID NO: 3 and the light chain variable region (VL) having the amino acid sequence as set forth in SEQ ID NO: 6.

12. The isolated antibody or antigen-binding fragment thereof, comprising the heavy chain variable region (VH) having the amino acid sequence as set forth in SEQ ID NO: 3 and the light chain variable region (VL) having the amino acid sequence as set forth in SEQ ID NO: 7.

13. The isolated antibody or antigen-binding fragment thereof, comprising the heavy chain variable region (VH) having the amino acid sequence as set forth in SEQ ID NO: 3 and the light chain variable region (VL) having the amino acid sequence as set forth in SEQ ID NO: 8.

14. The isolated antibody or antigen-binding fragment thereof, comprising the heavy chain variable region (VH) having the amino acid sequence as set forth in SEQ ID NO: 4 and the light chain variable region (VL) having the amino acid sequence as set forth in SEQ ID NO: 5.

15. The isolated antibody or antigen-binding fragment thereof, comprising the heavy chain variable region (VH) having the amino acid sequence as set forth in SEQ ID NO: 4 and the light chain variable region (VL) having the amino acid sequence as set forth in SEQ ID NO: 6.

16. The isolated antibody or antigen-binding fragment thereof, comprising the heavy chain variable region (VH) having the amino acid sequence as set forth in SEQ ID NO: 4 and the light chain variable region (VL) having the amino acid sequence as set forth in SEQ ID NO: 7.

17. The isolated antibody or antigen-binding fragment thereof, comprising the heavy chain variable region (VH) having the amino acid sequence as set forth in SEQ ID NO: 4 and the light chain variable region (VL) having the amino acid sequence as set forth in SEQ ID NO: 8.

18. The isolated antibody or antigen binding fragment thereof, according to any one of claims 1 to 17, wherein the antibody is of the IgG1 isotype, and wherein the heavy chain constant region comprises the amino acid sequence as set forth in SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO: 23, or SEQ ID NO: 24.

19. The isolated antibody according to claim 18, wherein the antibody further comprises a light chain constant region wherein the light chain constant region comprises the amino acid sequence set forth in SEQ ID NO: 25.

20. The isolated antibody according to claim 1, wherein the antibody comprises:

(a) a heavy chain having the amino acid sequence as set forth in SEQ ID NO: 42 and the light chain having the amino acid sequence as set forth in SEQ ID NO: 38; or

(b) a heavy chain having the amino acid sequence as set forth in SEQ ID NO: 42 and the light chain having the amino acid sequence as set forth in SEQ ID NO: 39; or

(c) a heavy chain having the amino acid sequence as set forth in SEQ ID NO: 42 and the light chain having the amino acid sequence as set forth in SEQ ID NO: 40; or

(d) a heavy chain having the amino acid sequence as set forth in SEQ ID NO: 42 and the light chain having the amino acid sequence as set forth in SEQ ID NO: 41; or

(e) a heavy chain having the amino acid sequence as set forth in SEQ ID NO: 43 and the light chain having the amino acid sequence as set forth in SEQ ID NO: 38; or

(f) a heavy chain having the amino acid sequence as set forth in SEQ ID NO: 43 and the light chain having the amino acid sequence as set forth in SEQ ID NO: 39; or

(g) a heavy chain having the amino acid sequence as set forth in SEQ ID NO: 43 and the light chain having the amino acid sequence as set forth in SEQ ID NO: 40; or

(h) a heavy chain having the amino acid sequence as set forth in SEQ ID NO: 43 and the light chain having the amino acid sequence as set forth in SEQ ID NO: 41; or

(i) a heavy chain having the amino acid sequence as set forth in SEQ ID NO: 44 and the light chain having the amino acid sequence as set forth in SEQ ID NO: 38; or

j) a heavy chain having the amino acid sequence as set forth in SEQ ID NO: 44 and the light chain having the amino acid sequence as set forth in SEQ ID NO: 39; or

(k) a heavy chain having the amino acid sequence as set forth in SEQ ID NO: 44 and the light chain having the amino acid sequence as set forth in SEQ ID NO: 40; or

(l) a heavy chain having the amino acid sequence as set forth in SEQ ID NO: 44 and the light chain having the amino acid sequence as set forth in SEQ ID NO: 41; or

(m) a heavy chain having the amino acid sequence as set forth in SEQ ID NO: 45 and the light chain having the amino acid sequence as set forth in SEQ ID NO: 38; or

(n) a heavy chain having the amino acid sequence as set forth in SEQ ID NO: 45 and the light chain having the amino acid sequence as set forth in SEQ ID NO: 39; or

(o) a heavy chain having the amino acid sequence as set forth in SEQ ID NO: 45 and the light chain having the amino acid sequence as set forth in SEQ ID NO: 40; or

(p) a heavy chain having the amino acid sequence as set forth in SEQ ID NO: 45 and the light chain having the amino acid sequence as set forth in SEQ ID NO: 41.