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(71) Applicant: DIANTHUS THERAPEUTICS, INC.

[US/US]; 203 Crescent Street, Bldg. #17, Suite #102B, Waltham, Massachusetts 02453 (US).

(72) Inventor: BEDIAN, Vahe; 203 Crescent Street, Bldg. #17,

Suite #102B, Waltham, Massachusetts 02453 (US).

(74) Agent: PALLADINO, Alicia M. et al.; 501 Grant Street,

Suite 300, Pittsburgh, Pennsylvania 15219 (US).

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(54) Title: ANTIBODIES THAT BIND TO C1S AND USES THEREOF

WiesLab CP 1% Human serum

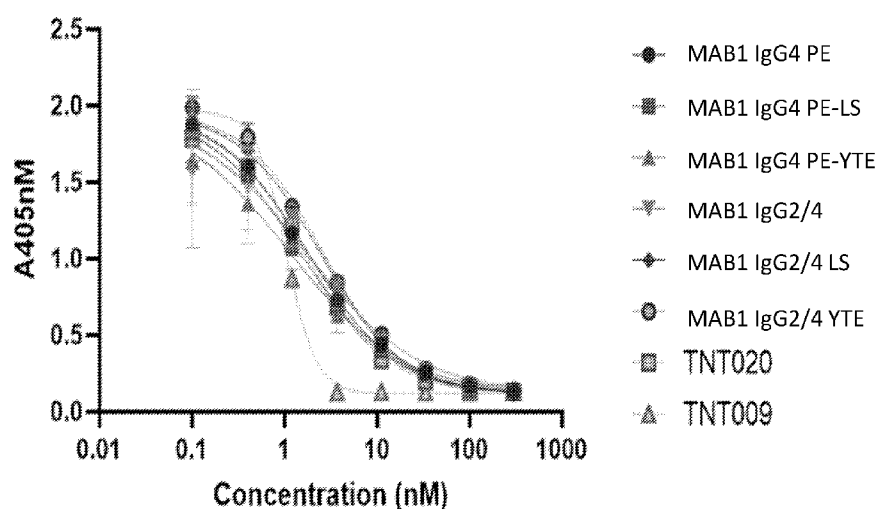


Figure 1

(57) Abstract: Embodiments that are provided for herein relate to antibodies and compositions that bind to C1s. Also provided are methods of producing the antibodies of the present disclosure, as well as uses of the provided antibodies and compositions for the treatment of C1s mediated diseases and disorders.

ANTIBODIES THAT BIND TO C1S AND USES THEREOF

Cross-Reference to Related Application

[0001] The present application claims priority to U.S. Provisional Application No. 63/201,952, filed May 20, 2021, which is hereby incorporated by reference in its entirety.

Field of the Invention

[0002] The field of the invention is immunology, in particular therapeutic antibodies, and treatment of disease with those antibodies.

Background

[0003] The complement system is a well-known effector mechanism of the innate immune response, providing not only protection against pathogens and other harmful agents but also recovery from injury. Complement activation due to autoantibodies and alloantibodies can lead to damage to normal cells or rejection of transplanted tissue. The complement pathway comprises a number of proteins that typically exist in the body in inactive form. The classical complement pathway is triggered by activation of the first component of complement, referred to as the C1 complex, which consists of C1q, C1r, and C1s proteins. Upon binding of C1 to an immune complex or other activator, the C1s component, a diisopropyl fluorophosphate (DFP)-sensitive serine protease, cleaves complement components C4 and C2 to initiate activation of the classical complement pathway. The classical complement pathway appears to play a role in many diseases and disorders. For example, sutimlimab, an antibody that inhibits C1s, is currently being investigated for treatment of hemolysis in adults with cold agglutinin disease, however, the dosing and lack of specificity for C1s, the active form, as opposed to the zymogen proC1s, and its physical properties, such as its lack of specificity, which requires a very high dose to be administered, may limit its use. Therefore, there is a need in the art for compounds that treat a complement classical pathway-mediated disease or disorder. The embodiments provided for here in satisfy these needs as well as others.

Summary

[0004] In some embodiments, antibodies, such as recombinant antibodies, or an antigen binding fragments thereof that binds to a C1s are provided. In some embodiments, the antibody

or antigen binding fragment thereof comprises an amino acid sequence, or a variant thereof, as provided for herein.

[0005] In some embodiments, isolated nucleic acid molecules encoding an antibody, or an antigen binding fragment thereof, a heavy chain variable region, a light chain variable region, heavy chain, or light chain as provided herein are provided.

[0006] In some embodiments, expression vectors comprising a nucleic acid molecule as provided for herein are provided.

[0007] In some embodiments, host cells comprising a nucleic acid molecule as provided for herein are provided.

[0008] In some embodiments, antibodies or antigen-binding fragments produced by the host cells are provided.

[0009] In some embodiments, methods of producing a polypeptide comprising a heavy chain variable region or light chain variable region as provided herein are provided. In some embodiments, the methods comprise growing a host cell under conditions so that the host cell expresses a polypeptide comprising the heavy chain variable region or the light chain variable region; and purifying the polypeptide comprising the heavy chain variable region and/or the light chain variable region.

[0010] In some embodiments, methods of treating a subject with a C1s mediated disorder are provided. In some embodiments, the methods comprise administering to the subject an antibody, or antigen binding fragment thereof, as provided herein or a pharmaceutical composition comprising the same. In some embodiments, the C1s mediated disorder is selected from hemolysis, Cold Agglutinin Disease, Immune Thrombocytopenia (ITP), Myasthenia Gravis, Glomerulopathies, Atypical Hemolytic uremic syndrome, antiphospholipid antibody syndrome, or transplant rejection.

[0011] In some embodiments, antibodies, or antigen binding fragments thereof, as provided herein, or or a pharmaceutical composition comprising the same, for use as a medicament are provided.

[0012] In some embodiments, use of the antibodies, or antigen binding fragments thereof, as provided for herein, or a pharmaceutical composition comprising the same are provided for the treatment of of a C1s mediated disorder, such as, but not limited to hemolysis, Cold Agglutinin

Disease, Immune Thrombocytopenia (ITP), Myasthenia Gravis, Glomerulopathies, Atypical Hemolytic uremic syndrome, antiphospholipid antibody syndrome, or transplant rejection. or as provided for herein.

[0013] In some embodiments, an antibody, or an antigen binding fragment thereof, is provided, wherein the antibody or antibody fragment comprises:

(a) a heavy chain variable region comprising heavy chain HCDR1, HCDR2, and HCDR3 sequences, wherein the heavy chain HCDR1 sequence has the amino acid sequence of SEQ ID NO: 9; the heavy chain HCDR2 has the amino acid sequence of SEQ ID NO: 10 and the heavy chain HCDR3 sequence has the amino acid sequence of SEQ ID NO: 11 or variants of any of the foregoing; and (ii) a light chain variable region comprising light chain LCDR1, LCDR2, and LCDR3 sequences, wherein the light chain LCDR1 sequence has the amino acid sequence SEQ ID NO: 12; the light chain LCDR2 sequence has the amino acid sequence of SEQ ID NO: 13; and the light chain LCDR3 sequence has the amino acid sequence of SEQ ID NO: 14; or variants of any of the foregoing;

(b) a heavy chain variable region comprising heavy chain HCDR1, HCDR2, and HCDR3 sequences, wherein the heavy chain HCDR1 sequence has the amino acid sequence of SEQ ID NO: 15; the heavy chain HCDR2 has the amino acid sequence of SEQ ID NO: 16 and the heavy chain HCDR3 sequence has the amino acid sequence of SEQ ID NO: 17 or variants of any of the foregoing; and (ii) a light chain variable region comprising light chain LCDR1, LCDR2, and LCDR3 sequences, wherein the light chain LCDR1 sequence has the amino acid sequence SEQ ID NO: 18; the light chain LCDR2 sequence has the amino acid sequence of SEQ ID NO: 19; and the light chain LCDR3 sequence has the amino acid sequence of SEQ ID NO: 20; or variants of any of the foregoing; or

(c) a heavy chain variable region comprising heavy chain HCDR1, HCDR2, and HCDR3 sequences, wherein the heavy chain HCDR1 sequence has the amino acid sequence of SEQ ID NO: 21; the heavy chain HCDR2 has the amino acid sequence of SEQ ID NO: 22 and the heavy chain HCDR3 sequence has the amino acid sequence of SEQ ID NO: 23 or variants of any of the foregoing; and (ii) a light chain variable region comprising light chain LCDR1, LCDR2, and LCDR3 sequences, wherein the light chain LCDR1 sequence has the amino acid sequence SEQ ID NO: 24; the light chain LCDR2 sequence has the amino acid sequence of SEQ ID NO: 25;

and the light chain LCDR3 sequence has the amino acid sequence of SEQ ID NO: 26; or variants of any of the foregoing.

[0014] In some embodiments, an antibody, or an antigen binding fragment thereof, is provided, wherein the antibody or antibody fragment comprises:

(a) a heavy chain variable region comprising heavy chain HCDR1, HCDR2, and HCDR3 sequences, wherein the heavy chain HCDR1 sequence has the amino acid sequence of SEQ ID NO: 27; the heavy chain HCDR2 has the amino acid sequence of SEQ ID NO: 28 and the heavy chain HCDR3 sequence has the amino acid sequence of SEQ ID NO: 11 or variants of any of the foregoing; and (ii) a light chain variable region comprising light chain LCDR1, LCDR2, and LCDR3 sequences, wherein the light chain LCDR1 sequence has the amino acid sequence SEQ ID NO: 29; the light chain LCDR2 sequence has the amino acid sequence of SEQ ID NO: 30; and the light chain LCDR3 sequence has the amino acid sequence of SEQ ID NO: 31; or variants of any of the foregoing;

(b) a heavy chain variable region comprising heavy chain HCDR1, HCDR2, and HCDR3 sequences, wherein the heavy chain HCDR1 sequence has the amino acid sequence of SEQ ID NO: 32; the heavy chain HCDR2 has the amino acid sequence of SEQ ID NO: 33 and the heavy chain HCDR3 sequence has the amino acid sequence of SEQ ID NO: 17 or variants of any of the foregoing; and (ii) a light chain variable region comprising light chain LCDR1, LCDR2, and LCDR3 sequences, wherein the light chain LCDR1 sequence has the amino acid sequence SEQ ID NO: 34; the light chain LCDR2 sequence has the amino acid sequence of SEQ ID NO: 35; and the light chain LCDR3 sequence has the amino acid sequence of SEQ ID NO: 36; or variants of any of the foregoing; or

(c) a heavy chain variable region comprising heavy chain HCDR1, HCDR2, and HCDR3 sequences, wherein the heavy chain HCDR1 sequence has the amino acid sequence of SEQ ID NO: 37; the heavy chain HCDR2 has the amino acid sequence of SEQ ID NO: 38 and the heavy chain HCDR3 sequence has the amino acid sequence of SEQ ID NO: 23 or variants of any of the foregoing; and (ii) a light chain variable region comprising light chain LCDR1, LCDR2, and LCDR3 sequences, wherein the light chain LCDR1 sequence has the amino acid sequence SEQ ID NO: 39; the light chain LCDR2 sequence has the amino acid sequence of SEQ ID NO: 40; and the light chain LCDR3 sequence has the amino acid sequence of SEQ ID NO: 41; or variants of any of the foregoing.

[0015] In some embodiments, an antibody, or an antigen binding fragment thereof, is provided, wherein the antibody or antibody fragment comprises:

(a) a heavy chain variable region comprising heavy chain HCDR1, HCDR2, and HCDR3 sequences, wherein the heavy chain HCDR1 sequence has the amino acid sequence of SEQ ID NO: 42; the heavy chain HCDR2 has the amino acid sequence of SEQ ID NO: 43 and the heavy chain HCDR3 sequence has the amino acid sequence of SEQ ID NO: 44 or variants of any of the foregoing; and (ii) a light chain variable region comprising light chain LCDR1, LCDR2, and LCDR3 sequences, wherein the light chain LCDR1 sequence has the amino acid sequence SEQ ID NO: 45; the light chain LCDR2 sequence has the amino acid sequence of SEQ ID NO: 30; and the light chain LCDR3 sequence has the amino acid sequence of SEQ ID NO: 14; or variants of any of the foregoing;

(b) a heavy chain variable region comprising heavy chain HCDR1, HCDR2, and HCDR3 sequences, wherein the heavy chain HCDR1 sequence has the amino acid sequence of SEQ ID NO: 46; the heavy chain HCDR2 has the amino acid sequence of SEQ ID NO: 47 and the heavy chain HCDR3 sequence has the amino acid sequence of SEQ ID NO: 48 or variants of any of the foregoing; and (ii) a light chain variable region comprising light chain LCDR1, LCDR2, and LCDR3 sequences, wherein the light chain LCDR1 sequence has the amino acid sequence SEQ ID NO: 49; the light chain LCDR2 sequence has the amino acid sequence of SEQ ID NO: 35; and the light chain LCDR3 sequence has the amino acid sequence of SEQ ID NO: 20; or variants of any of the foregoing; or

(c) a heavy chain variable region comprising heavy chain HCDR1, HCDR2, and HCDR3 sequences, wherein the heavy chain HCDR1 sequence has the amino acid sequence of SEQ ID NO: 50; the heavy chain HCDR2 has the amino acid sequence of SEQ ID NO: 51 and the heavy chain HCDR3 sequence has the amino acid sequence of SEQ ID NO: 52 or variants of any of the foregoing; and (ii) a light chain variable region comprising light chain LCDR1, LCDR2, and LCDR3 sequences, wherein the light chain LCDR1 sequence has the amino acid sequence SEQ ID NO: 53; the light chain LCDR2 sequence has the amino acid sequence of SEQ ID NO: 40; and the light chain LCDR3 sequence has the amino acid sequence of SEQ ID NO: 26; or variants of any of the foregoing.

[0016] In some embodiments, an antibody, or an antigen binding fragment thereof, is provided, wherein the antibody or antibody fragment comprises:

a. the HCDR1, HCDR2 and HCDR3 are selected from SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, respectively, from SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID NO: 11, respectively, and from SEQ ID NO: 42, SEQ ID NO: 43, SEQ ID NO: 44, respectively, and the LCDR1, LCDR2 and LCDR3 are selected from from SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, respectively, from SEQ ID NO: 29, SEQ ID NO: 30, SEQ ID NO: 31, respectively, and from SEQ ID NO: 45, SEQ ID NO: 30, SEQ ID NO: 14, respectively; or

b. the HCDR1, HCDR2 and HCDR3 are selected from SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, respectively, from SEQ ID NO: 32, SEQ ID NO: 33, SEQ ID NO: 17, respectively, and from SEQ ID NO: 46, SEQ ID NO: 47, SEQ ID NO: 48, respectively, and the LCDR1, LCDR2 and LCDR3 are selected from from SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 20, respectively, from SEQ ID NO: 34, SEQ ID NO: 35, SEQ ID NO: 36, respectively, and from SEQ ID NO: 49, SEQ ID NO: 35, SEQ ID NO: 20, respectively; or

c. the HCDR1, HCDR2 and HCDR3 are selected from SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO: 23, respectively, SEQ ID NO: 37, SEQ ID NO: 38, SEQ ID NO: 23, respectively, and SEQ ID NO: 50, SEQ ID NO: 51, SEQ ID NO: 52, respectively, and the LCDR1, LCDR2 and LCDR3 are selected from SEQ ID NO: 24, SEQ ID NO: 25, SEQ ID NO: 26, respectively, SEQ ID NO: 39, SEQ ID NO: 40, SEQ ID NO: 41, respectively, and SEQ ID NO: 53, SEQ ID NO: 40, SEQ ID NO: 26, respectively.

[0017] In some embodiments, a variant of an antibody or antigen binding fragment thereof is provided, wherein the variant has 1-10 substitutions, deletions, or insertions.

[0018] In some embodiments, a variant of an antibody or antigen binding fragment thereof is provided, wherein the variant has 1-10 conservative substitutions.

[0019] In some embodiments, a recombinant antibody or antigen binding fragment thereof is provided, wherein the recombinant antibody or antigen binding fragment thereof binds to a C1s. In some embodiments, the recombinant antibody or antigen binding fragment thereof is an antibody or antigen binding fragment thereof as provided for herein.

[0020] In some embodiments, an isolated nucleic acid molecule is provided. In some embodiments, the isolated nucleic acid molecule encodes an antibody or antigen binding fragment thereof, a heavy chain variable region, a light chain variable region, a heavy chain, a light chain, or a combination thereof. In some embodiments, the antibody or antigen binding

fragment thereof, a heavy chain variable region, a light chain variable region, a heavy chain, or light chain are as provided for herein.

[0021] In some embodiments, an expression vector is provided. In some embodiments, the expression vector comprises a nucleic acid molecule as provided for herein.

[0022] In some embodiments a host cell is provided. In some embodiments, the host cell comprises a nucleic acid molecule or expression vector as provided for herein. In some embodiments, the host cell comprises a nucleic acid molecule as provided for herein. In some embodiments, the host cell comprises an expression vector as provided for herein.

[0023] In some embodiments, an antibody or antigen binding fragment thereof is provided, wherein the antibody or antigen binding fragment thereof is produced by the host cell.

[0024] In some embodiments, a pharmaceutical composition is provided. In some embodiments, the pharmaceutical composition comprises an antibody or antigen binding fragment thereof as provided for herein.

[0025] In some embodiments, a method of producing a polypeptide comprising a heavy chain variable region or a light chain variable region is provided. In some embodiments, the method comprises (a) growing a host cell as provided for herein under conditions so that the host cell expresses the polypeptide comprising the heavy chain variable region or the light chain variable region; and (b) purifying the polypeptide comprising the heavy chain or the light chain variable regions. In some embodiments, the heavy chain variable region is as provided for herein. In some embodiments, the light chain variable region is as provided for herein.

[0026] In some embodiments, a method of producing an antibody or an antigen binding fragment of the antibody is provided. In some embodiments, the antibody or antigen binding fragment bind to human C1s. In some embodiments, the method comprises (a) growing a host cell as provided for herein under conditions so that the host cell expresses a polypeptide or polypeptides comprising the immunoglobulin heavy chain variable region and/or the immunoglobulin light chain variable region, thereby producing the antibody or the antigen binding fragment of the antibody; and (b) purifying the antibody or the antigen-binding fragment of the antibody.

[0027] In some embodiments, a method of treating a subject with a C1s mediated disorder is provided. In some embodiments, the method comprises administering to the subject an antibody

or antigen binding fragment thereof as provided for herein, or a pharmaceutical composition as provided for herein.

[0028] In some embodiments, an antibody or antigen binding fragment thereof or a pharmaceutical composition is provided, wherein the antibody or antigen binding fragment thereof or the pharmaceutical composition are for the use in the treatment of a C1s mediated disorder. In some embodiments, the antibody or antigen binding fragment thereof is as provided for herein. In some embodiments, the pharmaceutical composition is as provided for herein. In some embodiments, the C1s mediated disorder is as provided for herein. In some embodiments, the C1s mediated disorder is hemolysis or Cold Agglutinin Disease.

[0029] In some embodiments, an antibody or antigen binding fragment thereof or a pharmaceutical composition is provided, wherein the antibody or antigen binding fragment thereof or the pharmaceutical composition are for the use as a medicament. In some embodiments, the antibody or antigen binding fragment thereof is as provided for herein. In some embodiments, the pharmaceutical composition is as provided for herein.

[0030] In some embodiments, a use of an antibody or antigen binding fragment thereof or a pharmaceutical composition is provided, wherein the use is for the treatment of a C1s mediated disorder. In some embodiments, the antibody or antigen binding fragment thereof is as provided for herein. In some embodiments, the pharmaceutical composition is as provided for herein. In some embodiments, the C1s mediated disorder is as provided for herein.

Brief Description of the Drawings

[0031] **Figure 1** shows the dose response of six 4O11g antibodies that differ in their Fc regions, along with TNT009 and TNT020, in the Wieslab classical pathway kit used according to manufacturer's instruction.

[0032] **Figure 2** shows the dose response of four 4O11g variants along with TNT009, TNT020 and ravulizumab in C3b deposition in a FACS based assay using rabbit antibody sensitized human RBCs and 5% human serum

[0033] **Figure 3** shows the dose response of 4O11g antibody with TNT009, TNT020 and eculizumab in a human RBC lysis assay using 10% human serum

[0034] **Figure 4** depicts SPR sensograms where anti-Fc coated surfaces were used to capture test antibodies, and human C1s or proC1s_RQ was used as analyte.

Detailed Description

[0035] Provided herein are binding proteins, *e.g.*, antibodies, or fragments, thereof, that selectively bind to C1s and have low binding to the zymogen proC1s. In some embodiments, the antibodies inhibit activation of the classical complement pathway and can be used in methods to treat complement mediated disorders, such as, but not limited to those provided for herein. In some embodiments, the selectivity for C1s over proC1s can be used to reduce or prevent target mediated clearance of the therapeutic antibody, thus requiring lower doses and frequency of administration of the antibody.

[0036] Before the present compositions and methods are described, it is to be understood that the scope of the invention is not limited to the particular processes, compositions, or methodologies described herein, as these may vary. It is also to be understood that the terminology used in the description is for the purpose of describing the particular versions or embodiments only, and is not intended to limit the scope of the present invention. Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of embodiments of the methods and systems disclosed herein, the preferred methods, devices, and materials are now described.

[0037] The following explanations of terms and methods are provided to better describe the present disclosure and to guide those of ordinary skill in the art in the practice of the present disclosure.

[0038] As used herein, “comprising” means “including” and the singular forms “a” or “an” or “the” include plural references unless the context clearly dictates otherwise. For example, reference to “comprising a therapeutic agent” includes one or a plurality of such therapeutic agents. The term “or” refers to a single element of stated alternative elements, unless the context clearly indicates otherwise. For example, the phrase “A or B” refers to A alone or B alone. The phrase “A, B, or a combination thereof” refers to A alone, B alone, or a combination of A and B. Similarly, “one or more of A and B” refers to A, B, or a combination of both A and B. The phrase “A and B” refers to a combination of A and B. Furthermore, the various elements,

features and steps discussed herein, as well as other known equivalents for each such element, feature or step, can be mixed and matched by one of ordinary skill in this art to perform methods in accordance with principles described herein. Among the various elements, features, and steps some will be specifically included and others specifically excluded in particular examples.

[0039] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood to one of ordinary skill in the art. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present disclosure, suitable methods and materials are described below. The materials, methods, and examples are illustrative only and not intended to be limiting. All references cited herein are incorporated by reference in their entirety.

[0040] As used herein, the term “antibody” refers to any form of antibody that exhibits the desired biological activity. Thus, it is used in the broadest sense and specifically covers, but is not limited to, monoclonal antibodies (including full length monoclonal antibodies), polyclonal antibodies, multispecific antibodies (*e.g.*, bispecific antibodies), humanized, fully human antibodies, chimeric antibodies and camelized single domain antibodies. “Parental antibodies” are antibodies obtained by exposure of an immune system to an antigen prior to modification of the antibodies for an intended use, such as humanization of an antibody for use as a human therapeutic antibody.

[0041] As used herein, unless otherwise indicated, “antibody fragment” or “antigen binding fragment” refers to antigen binding fragments of antibodies, *i.e.* antibody fragments that retain the ability to bind specifically to the antigen bound by the full-length antibody, *e.g.* fragments that retain one or more CDR regions. Examples of antibody binding fragments include, but are not limited to, Fab, Fab', F(ab')₂, and Fv fragments; diabodies; linear antibodies; single-chain antibody molecules, *e.g.*, sc-Fv; nanobodies (single domain antibody) and multispecific antibodies formed from antibody fragments.

[0042] A “Fab fragment” is comprised of one light chain and the C_H1 and variable regions of one heavy chain. The heavy chain of a Fab molecule cannot form a disulfide bond with another heavy chain molecule.

[0043] An “Fc” region contains two heavy chain fragments comprising the C_H2 and C_H3 domains of an antibody. The two heavy chain fragments are held together by two or more disulfide bonds and by hydrophobic interactions of the C_H3 domains.

[0044] A “Fab' fragment” contains one light chain and a portion or fragment of one heavy chain that contains the V_H domain and the C_{H1} domain and also the region between the C_{H1} and C_{H2} domains, such that an interchain disulfide bond can be formed between the two heavy chains of two Fab' fragments to form a F(ab')₂ molecule.

[0045] A “F(ab')₂ fragment” contains two light chains and two heavy chains containing a portion of the constant region between the C_{H1} and C_{H2} domains, such that an interchain disulfide bond is formed between the two heavy chains. A F(ab')₂ fragment thus is composed of two Fab' fragments that are held together by a disulfide bond between the two heavy chains.

[0046] The “Fv region” comprises the variable regions from both the heavy and light chains, but lacks the constant regions.

[0047] The term “single-chain Fv” or “scFv” antibody refers to antibody fragments comprising the V_H and V_L domains of an antibody, wherein these domains are present in a single polypeptide chain. Generally, the Fv polypeptide further comprises a polypeptide linker between the V_H and V_L domains which enables the scFv to form the desired structure for antigen binding. For a review of scFv, see Pluckthun (1994) THE PHARMACOLOGY OF MONOCLONAL ANTIBODIES, vol. 113, Rosenberg and Moore eds. Springer-Verlag, New York, pp. 269-315. See also, International Patent Application Publication No. WO 88/01649 and U.S. Pat. Nos. 4,946, 778 and 5,260,203.

[0048] A “single-domain antibody” is an immunologically functional immunoglobulin fragment containing only the variable region of a heavy chain or the variable region of a light chain. In some instances, two or more V_H regions are covalently joined with a peptide linker to create a bivalent domain antibody. The two V_H regions of a bivalent domain antibody may target the same or different antigens.

[0049] A “bivalent antibody” comprises two antigen binding sites. In some instances, the two binding sites have the same antigen specificities. However, bivalent antibodies may be bispecific (see below).

[0050] In certain embodiments, monoclonal antibodies herein also include camelized single domain antibodies. See, e.g., Muyldermans *et al.* (2001) *Trends Biochem. Sci.* 26:230; Reichmann *et al.* (1999) *J. Immunol. Methods* 231:25; WO 94/04678; WO 94/25591; U.S. Pat. No. 6,005,079). In one embodiment, the present invention provides single domain antibodies comprising two V_H domains with modifications such that single domain antibodies are formed.

[0051] As used herein, the term “diabodies” refers to small antibody fragments with two antigen-binding sites, which fragments comprise a heavy chain variable domain (V_H) connected to a light chain variable domain (V_L) in the same polypeptide chain (V_H-V_L or V_L-V_H). By using a linker that is too short to allow pairing between the two domains on the same chain, the domains are forced to pair with the complementary domains of another chain and create two antigen-binding sites. Diabodies are described more fully in, *e.g.*, EP 404,097; WO 93/11161; and Holliger *et al.* (1993) *Proc. Natl. Acad. Sci. USA* 90: 6444-6448. For a review of engineered antibody variants generally see Holliger and Hudson (2005) *Nat. Biotechnol.* 23:1126-1136.

[0052] Typically, a variant antibody or antigen binding fragment of the antibodies provided herein retain at least 10% of its C1s binding activity (when compared to a parental antibody that is modified) when that activity is expressed on a molar basis. In some embodiments, a variant antibody (or antigen fragment thereof), or antigen binding fragment of an antibody provided herein, retains at least 20%, 50%, 70%, 80%, 90%, 95% or 100% or more of the C1s binding affinity as the parental antibody. As described herein, it is also intended that an antibody or antigen binding fragment of the invention can include conservative or non-conservative amino acid substitutions, which can also be referred to as “conservative variants” or “function conserved variants” of the antibody, that do not substantially alter its biologic activity.

[0053] “Isolated antibody” refers to the purification status of a binding compound and in such context means the molecule is substantially free of other biological molecules such as nucleic acids, proteins, lipids, carbohydrates, or other material such as cellular debris and growth media. Generally, the term “isolated” is not intended to refer to a complete absence of such material or to an absence of water, buffers, or salts, unless they are present in amounts that substantially interfere with experimental or therapeutic use of the binding compound as described herein.

[0054] The term “monoclonal antibody”, as used herein, refers to population of substantially homogeneous antibodies, *i.e.*, the antibody molecules comprising the population are identical in amino acid sequence except for possible naturally occurring mutations and/or post-translational modifications that may be present in minor amounts. In contrast, conventional (polyclonal) antibody preparations typically include a multitude of different antibodies having different amino acid sequences in their variable domains, particularly their CDRs, that are often specific for different epitopes. The modifier “monoclonal” indicates the character of the antibody as being obtained from a substantially homogeneous population of antibodies, and is not to be construed

as requiring production of the antibody by any particular method. For example, the monoclonal antibodies to be used in accordance with the present invention may be made by the hybridoma method first described by Kohler *et al.* (1975) *Nature* 256: 495, or may be made by recombinant DNA methods (*see, e.g.*, U.S. Pat. No. 4,816,567). The “monoclonal antibodies” may also be isolated from phage antibody libraries using the techniques described in Clackson *et al.* (1991) *Nature* 352: 624-628 and Marks *et al.* (1991) *J. Mol. Biol.* 222: 581-597, for example. *See also* Presta (2005) *J. Allergy Clin. Immunol.* 116:731.

[0055] As used herein, a “chimeric antibody” is an antibody having the variable domain from a first antibody and constant domain from a second antibody, where the first and second antibodies are from different species. (U.S. Pat. No. 4,816,567; and Morrison *et al.*, (1984) *Proc. Natl. Acad. Sci. USA* 81: 6851-6855). Typically, the variable domains are obtained from an antibody from an experimental animal (the “parental antibody”), such as a rodent, and the constant domain sequences are obtained from human antibodies, so that the resulting chimeric antibody will be less likely to elicit an adverse immune response in a human subject than the parental (*e.g.* rodent) antibody.

[0056] As used herein, the term “humanized antibody” refers to forms of antibodies that contain sequences from both human and non-human (*e.g.*, murine, rat) antibodies. In general, the humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the hypervariable loops correspond to those of a non-human immunoglobulin, and all or substantially all of the framework (FR) regions are those of a human immunoglobulin sequence. The humanized antibody may optionally comprise at least a portion of a human immunoglobulin constant region (Fc).

[0057] The term “fully human antibody” refers to an antibody that comprises human immunoglobulin protein sequences only. A fully human antibody may contain murine carbohydrate chains if produced in a mouse, in a mouse cell, or in a hybridoma derived from a mouse cell. Similarly, “mouse antibody” refers to an antibody that comprises mouse immunoglobulin sequences only. Alternatively, a fully human antibody may contain rat carbohydrate chains if produced in a rat, in a rat cell, or in a hybridoma derived from a rat cell. Similarly, “rat antibody” refers to an antibody that comprises rat immunoglobulin sequences only.

[0058] In some embodiments, the basic antibody structural unit comprises a tetramer. Each tetramer includes two identical pairs of polypeptide chains, each pair having one “light” (about 25 kDa) and one “heavy” chain (about 50-70 kDa). The amino-terminal portion of each chain includes a variable region of about 100 to 110 or more amino acids primarily responsible for antigen recognition. The carboxy-terminal portion of the heavy chain may define a constant region primarily responsible for effector function. Typically, human light chains are classified as kappa and lambda light chains. Furthermore, human heavy chains are typically classified as mu, delta, gamma, alpha, or epsilon, and define the antibody's isotype as IgM, IgD, IgG, IgA, and IgE, respectively. Within light and heavy chains, the variable and constant regions are joined by a “J” region of about 12 or more amino acids, with the heavy chain also including a “D” region of about 10 more amino acids. See generally, *Fundamental Immunology* Ch. 7 (Paul, W., ed., 2nd ed. Raven Press, N.Y. (1989).

[0059] The variable regions of each light/heavy chain pair form the antibody binding site. Thus, in general, an intact antibody has two binding sites. However, in bifunctional or bispecific antibodies, the two binding sites are, in general, not the same.

[0060] Typically, the variable domains of both the heavy and light chains comprise three hypervariable regions, also called complementarity determining regions (CDRs), located within relatively conserved framework regions (FR). The CDRs are usually aligned by the framework regions, enabling binding to a specific epitope. In general, from N-terminal to C-terminal, both light and heavy chains variable domains comprise FR1, CDR1, FR2, CDR2, FR3, CDR3 and FR4. The assignment of amino acids to each domain is, generally, in accordance with the definitions of *Sequences of Proteins of Immunological Interest*, Kabat, *et al.*; National Institutes of Health, Bethesda, Md.; 5th ed.; NIH Publ. No. 91-3242 (1991); Kabat (1978) Adv. Prot. Chem. 32:1-75; Kabat, *et al.*, (1977) J. Biol. Chem. 252:6609-6616; Chothia, *et al.*, (1987) J Mol. Biol. 196:901-917 or Chothia, *et al.*, (1989) Nature 342:878-883.

[0061] As used herein, the term “hypervariable region” refers to the amino acid residues of an antibody that are responsible for antigen-binding. The hypervariable region comprises amino acid residues from a “complementarity determining region” or “CDR” (*i.e.* residues 24-34 (CDRL1), 50-56 (CDRL2) and 89-97 (CDRL3) in the light chain variable domain and residues 31-35 (CDRH1), 50-65 (CDRH2) and 95-102 (CDRH3) in the heavy chain variable domain; Kabat *et al.* (1991) Sequences of Proteins of Immunological Interest, 5th Ed. Public Health

Service, National Institutes of Health, Bethesda, Md.) and/or those residues from a “hypervariable loop” (*i.e.* residues 26-32 (CDRL1), 50-52 (CDRL2) and 91-96 (CDRL3) in the light chain variable domain and 26-32 (CDRH1), 53-55 (CDRH2) and 96-101 (CDRH3) in the heavy chain variable domain; Chothia and Lesk (1987) *J. Mol. Biol.* 196: 901-917). The CDRs can also be referenced according to the IMGT system for the identification of CDRs, which is described in Lefranc MP. Unique database numbering system for immunogenetic analysis. *Immunol Today* (1997) 18:509. As used herein, the term “framework” or “FR” residues refers to those variable domain residues other than the hypervariable region residues defined herein as CDR residues. CDRs provide the majority of contact residues for the binding of the antibody to the antigen or epitope. CDRs of interest can be derived from donor antibody variable heavy and light chain sequences, and include analogs of the naturally occurring CDRs, which analogs also share or retain the same antigen binding specificity and/or neutralizing ability as the donor antibody from which they were derived.

[0062] As used herein, “specific binding” or “immunospecific binding” or “binds immunospecifically” refer to antibody binding to a predetermined antigen at a much higher affinity than for another antigen(s) (*e.g.* selectively binds the active form of complement component C1s as compared to inactive C1s, which can also be referred to as proC1s zymogen). In some embodiments, the antibody binds the predetermined antigen with a dissociation constant (K_D) of 10^{-7} M or less, and such K_D is at least two-fold less than its K_D for binding to a non-specific antigen (*e.g.*, BSA, casein, or another non-specific polypeptide).

[0063] The phrases “an antibody recognizing C1s” and “an antibody specific for C1s” are used interchangeably herein with the term “an antibody which binds immunospecifically to C1s.” In some embodiments, the antibody binds specifically or preferentially to C1s, such as the active form of C1s over other proteins, such as, but not limited to, the inactive form of C1s (proC1s). The degree of specificity necessary for an anti-C1s antibody may depend on the intended use of the antibody, and at any rate is defined by its suitability for use for an intended purpose. In some embodiments, the antibody, or binding compound derived from the antigen-binding site of an antibody, of the contemplated method binds to its antigen (active form of C1s), with an affinity that is at least two fold greater, at least ten times greater, at least 20-times greater, or at least 100-times greater than the affinity with any other antigen, including, but not limited to inactive C1s.

[0064] Methods for determining mAb specificity and affinity by competitive inhibition can be found in Harlow, et al., *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1988), Colligan et al., eds., *Current Protocols in Immunology*, Greene Publishing Assoc. and Wiley Interscience, N.Y., (1992, 1993), and Muller, *Meth. Enzymol.* 92:589 601 (1983), which references are entirely incorporated herein by reference.

[0065] The term “homolog” means protein sequences having between 40% and 100% sequence identity to a reference sequence. Percent identity between two peptide chains can be determined by pair wise alignment using the default settings of the AlignX module of Vector NTI v.9.0.0 (Invitrogen Corp., Carlsbad, Calif.) or other suitable alignment software, such as BLAST. In some embodiments, the antibody, or antigen binding fragment thereof has, at least 50, 60, 70, 80, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99% homology or identity to a sequence described herein. In some embodiments, the antibody has conservative substitutions as compared to a sequence described herein. Exemplary conservative substitutions are illustrated in Table 1 and are encompassed within the scope of the disclosed subject matter. The conservative substitution may reside in the framework regions, or in antigen-binding sites, as long they do not adversely affect the properties of the antibody. Substitutions may be made to improve antibody properties, for example stability or affinity. Conservative substitutions will produce molecules having functional and chemical characteristics similar to those molecules into which such modifications are made. Exemplary amino acid substitutions are shown in the table below.

Table 1

Table: Exemplary Conservative Substitutions:	
Original Residue	Exemplary Conservative Substitutions
Ala	Val, Leu, Ile
Arg	Lys, Gln, Asn
Asn	Gln
Asp	Glu
Cys	Ser, Ala
Gln	Asn
Gly	Pro, Ala
His	Asn, Gln, Lys, Arg
Ile	Leu, Val, Met, Ala, Phe
Leu	Ile, Val, Met, Ala, Phe
Lys	Arg, Gln, Asn
Met	Leu, Phe, Ile
Phe	Leu, Val, Ile, Ala, Tyr
Pro	Ala

Ser	Thr, Ala, Cys
Thr	Ser
Trp	Tyr, Phe
Tyr	Trp, Phe, Thr, Ser
Val	Ile, Met, Leu, Phe, Ala

[0066] In some embodiments, variants of the proteins and peptides provided herein are provided. In some embodiments, a variant comprises a substitution, deletions, or insertion. In some embodiments, the variant comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 (*e.g.*, 1-10) substitutions. As described herein, the substitutions can be conservative substitutions. In some embodiments, the substitution is non-conservative. In some embodiments, the variant comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 (*e.g.*, 1-10) deletions. In some embodiments, the variant comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 (*e.g.*, 1-10) insertions. In some embodiments, the substitutions, deletions, or insertions are present in the CDRs provided for herein. In some embodiments, the substitutions, deletions, or insertions are not present in the CDRs provided for herein.

[0067] The term “in combination with” as used herein means that the described agents can be administered to an animal or subject together in a mixture, concurrently as single agents or sequentially as single agents in any order.

[0068] The term “epitope” is meant to refer to that portion of any molecule capable of being recognized by and bound by an antibody at one or more of the Ab’s antigen binding regions. Epitopes usually consist of chemically active surface groupings of molecules such as amino acids or sugar side chains and have specific three dimensional structural characteristics as well as specific charge characteristics

[0069] “Expression vector” refers to a vector comprising a recombinant polynucleotide comprising expression control sequences operatively linked to a nucleotide sequence to be expressed. An expression vector comprises sufficient cis-acting elements for expression; other elements for expression can be supplied by the host cell or in an *in vitro* expression system. Expression vectors include all those known in the art, such as cosmids, plasmids (*e.g.*, naked or contained in liposomes) and viruses (*e.g.*, Sendai viruses, lentiviruses, retroviruses, adenoviruses, and adeno-associated viruses) that incorporate the recombinant polynucleotide.

[0070] In some embodiments, the antibody is a monoclonal antibody which binds to C1s. The sequence of active C1s is as follows (SEQ ID NO: 56): Residues 1-15 (SEQ ID NO: 75)

constitute the signal peptide which is cleaved during translation, and residues 16-688 (SEQ ID NO: 76) constitute the mature protein.

MWCIVLFSLLAWVYA EPTMYGEILSPNYPQAYPSEVEKSWDIEVPEGYGIHL YFTHLDIE
LSENCAYDSVQIISGDTEEGRLCGQRSSNNPHSPIVEEFQVPYNKLQVIFKSDFSNEERFT
GFAAYYVATDINECTDFVDVPCSHFCNNFIGGYFCSCPPEYFLHDDMKNCGVNCSGDVFT
TALIGEIASPNYPKPY PENSRC EYQIRLEKGFQVVVTLRREDFDVEAADSAGNCLDSL VF
VAGDRQFGPYCGHGFPGPLNIETKSNALDIIFQTDLTGQKKGWKLRYHGDPMPCPKEDT
PNSVWEPAAKAKYVFRD VVQITCLDGFVEVVEGRVGATSFYSTCQSNGKWSNSKLK CQPV
DCGIPESIEGKVEDPESTLFGSVIRYTCEEPY YMMENGGGGGEYHCAGNGSWVNEVLGP
ELPKCVPVCGVPREPFE EKQRIIGGSDADIKNFPWQVFFDNPWAGGALINEYWVL TAAH
VVEGNREPTMYVGSTSVQTSRLAKSKMLTPEHVFIHPGWKLLEVPEGR TNFDNDIALVR
LKDPVKMGPTVSPICLP GTSSDYNLMDGDLGLISGWGRTEKRDRAVRLKAARLPVAPL
RKCKEVKVEKPTADAEAYVFTPNMICAGGEKGMDSCCKGDSGGAF AVQDPNDKTKFYA
AGL VSWGPQCGTYGLYTRVKNYVDWIMKTMQENSTPRED (SEQ ID NO: 56)

MWCIVLFSLLAWVYA (SEQ ID NO: 75)

EPTMYGEILSPNYPQAYPSEVEKSWDIEVPEGYGIHL YFTHLDIE LSENCAYDSVQIISGD
TEEGRLCGQRSSNNPHSPIVEEFQVPYNKLQVIFKSDFSNEERFTGFAAYYVATDINECT
DFVDVPCSHFCNNFIGGYFCSCPPEYFLHDDMKNCGVNCSGDVFTALIGEIASPNYPKPY
PENSRC EYQIRLEKGFQVVVTLRREDFDVEAADSAGNCLDSL VFVAGDRQFGPYCGHGF
FPGPLNIETKSNALDIIFQTDLTGQKKGWKLRYHGDPMPCPKEDTPNSVWEPAAKAKYVFR
D VVQITCLDGFVEVVEGRVGATSFYSTCQSNGKWSNSKLK CQPVDCGIPESIEGKVED
PESTLFGSVIRYTCEEPY YMMENGGGGGEYHCAGNGSWVNEVLGP ELPKCVPVCGVPRE
PFE EKQRIIGGSDADIKNFPWQVFFDNPWAGGALINEYWVL TAAHVVEGNREPTMYVG
STSVQTSRLAKSKMLTPEHVFIHPGWKLLEVPEGR TNFDNDIALVRLKDPVKMGPTVSPIC
LP GTSSDYNLMDGDLGLISGWGRTEKRDRAVRLKAARLPVAPLRKCKEVKVEKPTAD
AEAYVFTPNMICAGGEKGMDSCCKGDSGGAF AVQDPNDKTKFYAAGL VSWGPQCGTY
GLYTRVKNYVDWIMKTMQENSTPRED (SEQ ID NO: 76)

[0071] The difference between inactive C1s and active C1s is that inactive proC1s is cleaved at the peptide bond between R437 and I438 and undergoes a conformational change. The two fragments generated by this cleavage remain associated by a disulfide bond. Without wishing to be bound by a particular theory, proC1s is a single chain 86,000 Da protein that is the native form of C1s proteins (e.g. serine protease). C1s is a subunit of the C1 complex which is the first complement component in the cascade referred to as the classical pathway of complement. ProC1s is an inactive zymogen until C1 is activated. C1 complex binds to and is activated by antigen-antibody complexes (immune complexes) yielding C1r enzyme. C1r enzyme in the C1 complex activates proC1s generating C1s enzyme. C1 complex is a non-covalent calcium-dependent complex of one C1q, two C1r and two C1s molecules. C1q binds through two or more

of its six arms to the Fc domains of IgG or IgM. The binding of multiple arms to immune complexes causes the two C1r proteins in the complex (protease zymogens) to activate producing two proteases that cleave and activate the two proC1s in the complex (Morikis, D. and Lambris, J.D. (2005)). This activation of proC1s is caused by cleavage into the two chain C1s enzyme with 58,000 and 28,000 dalton fragments.

[0072] In some embodiments, the antibody comprises a Fc domain. The Fc domain can be linked to the heavy or light chain of the antibody. In some embodiments, the Fc domain comprises a mutation to extend the half-life of the antibody. In some embodiments, the Fc domain comprises a mutation such as those described in U.S. Patent No. 7,670,600, which is hereby incorporated by reference in its entirety. In some embodiment, the constant region comprises a mutation at position at amino acid residue 428 relative to a wild-type human IgG constant domain, numbered according to the EU numbering index of Kabat. Without being bound to any particular theory, an antibody comprising a mutation that corresponds to residue 428 can have an increased half-life compared to the half-life of an IgG having the wild-type human IgG constant domain. In some embodiments, the mutation is a substitution of the native residue with a threonine, leucine, phenylalanine or serine. In some embodiments, the antibody further comprises one or more amino acid substitutions relative to the corresponding wild-type human IgG constant domain at one or more of amino acid residues 251-256, 285-290, 308-314, 385-389, and 429-436, numbered according to the Kabat EU numbering index. The specific mutations or substitutions at these positions are described in U.S. Patent No. 7,670,600, which is hereby incorporated by reference in its entirety.

[0073] Other mutations can be used in the Fc domain, such as those provided for in U.S. Patent No. 8,394,925, which is hereby incorporated by reference in its entirety. In some embodiments, the Fc region is a variant Fc region comprising amino acid substitutions at positions 428 and 434, wherein the amino acid substitutions are a leucine that is not the wild-type amino acid at position 428 and a serine that is not the wild-type amino acid at position 434, wherein the polypeptide is an antibody and wherein numbering is according to the EU Index in Kabat et al. In some embodiments, the Fc region comprises a S228P, L235E, M428L, or N434S substitution. In some embodiments, the Fc region comprises a M428L substitution. In some embodiments, the Fc region comprises a N434S substitution. In some embodiments, the Fc region comprises a

M428L and a N434S substitution. In some embodiments, the Fc region comprises a M252Y, S254T, and/or T256E substitution.

[0074] In some embodiments, the antibody comprises a constant region as set forth below with or without the mutations provided for the list below.

>IgG4 S228P L235E LS

ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS
GLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSV
FLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNST
YRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEM
TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSRLTVDKSRW
QEGNVFSCSVLHEALHSHYTQKSLSLSLGK (SEQ ID NO: 7)

>IgG4 S228P L235E YTE

ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS
GLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSV
FLFPPKPKDTLYITREPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNST
YRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEM
TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSRLTVDKSRW
QEGNVFSCSVMEALHNHYTQKSLSLSLGK (SEQ ID NO: 8)

[0075] In some embodiments, the antibody comprises a constant region as provided herein, wherein the C-terminal lysine (K) amino acid has been deleted. In some embodiments, the antibody comprises a constant region as set follows:

>IgG4 S228P L235E LS-trunc

ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS
GLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSV
FLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNST
YRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEM
TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSRLTVDKSRW
QEGNVFSCSVLHEALHSHYTQKSLSLSLG (SEQ ID NO: 57)

>IgG4 S228P L235E YTE-trunc

ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS
GLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSV
FLFPPKPKDTLYITREPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNST
YRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEM
TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSRLTVDKSRW
QEGNVFSCSVMEALHNHYTQKSLSLSLG (SEQ ID NO: 58)

[0076] In some embodiments, the antibody, such as the light chain, comprises a kappa constant region, such as the human constant domain, which can comprise a sequence of:

>Human kappa constant domain

RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQ
DSKDSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 65)

[0077] As used herein and unless otherwise indicated, the term “about” is intended to mean $\pm$ 5% of the value it modifies. Thus, about 100 means 95 to 105.

[0078] In some embodiments, the antibodies described herein are used to detect the presence of the antigen. The present antibody can be used in any device or method to detect the presence of the antigen. In some embodiments, the antibodies are used to detect the active form of C1s. In some embodiments, the antibodies are used to detect the active form preferentially (specifically) over the inactive form of C1s.

[0079] The term “purified” with referenced to an antibody refers to an antibody that is substantially free of other material that associates with the molecule in its natural environment. For instance, a purified protein is substantially free of the cellular material or other proteins from the cell or tissue from which it is derived. The term refers to preparations where the isolated protein is sufficiently pure to be analyzed, or at least 70% to 80% (w/w) pure, at least 80%-90% (w/w) pure, 90-95% pure; and, at least 95%, 96%, 97%, 98%, 99%, or 100% (w/w) pure. In some embodiments, the antibody is purified.

Antibody Conjugates

[0080] The antibodies provided for herein may also be conjugated to a chemical moiety. The chemical moiety may be, *inter alia*, a polymer, a radionuclide or a cytotoxic factor. In some embodiments, this can be referred to as an antibody drug conjugate. In some embodiments, the chemical moiety is a polymer which increases the half-life of the antibody molecule in the body of a subject. Suitable polymers include, but are not limited to, polyethylene glycol (PEG) (*e.g.*, PEG with a molecular weight of 2kDa, 5 kDa, 10 kDa, 12kDa, 20 kDa, 30kDa or 40kDa), dextran and monomethoxypolyethylene glycol (mPEG). Lee, *et al.*, (1999) (Bioconj. Chem. 10:973-981) discloses PEG conjugated single-chain antibodies. Wen, *et al.*, (2001) (Bioconj. Chem. 12:545-553) disclose conjugating antibodies with PEG which is attached to a radiometal chelator (diethylenetriaminopentaacetic acid (DTPA)). Examples of chemical moieties include, but are not limited to, anti-mitotics, such as calicheamicins (*e.g.* ozogamicin), monomethyl auristatin E, mertansine, and the like. Other examples include, but are not limited to, biologically active anti-microtubule agents, alkylating agents and DNA minor groove binding

agents. Other examples of are provided herein and below. The chemical moiety can be linked to the antibody through a linking group (maleimide), a cleavable linker, such as a cathepsin cleavable linkers (valine-citrulline), and in some embodiments, one or more spacers (e.g. para-aminobenzylcarbamate).

[0081] The antibodies and antibody fragments of the invention may also be conjugated with labels such as ^{99}Tc , ^{90}Y , ^{111}In , ^{32}P , ^{14}C , ^{125}I , ^3H , ^{131}I , ^{11}C , ^{15}O , ^{13}N , ^{18}F , ^{35}S , ^{51}Cr , ^{57}To , ^{226}Ra , ^{60}Co , ^{59}Fe , ^{57}Se , ^{152}Eu , ^{67}Cu , ^{217}Ci , ^{211}At , ^{212}Pb , ^{47}Sc , ^{109}Pd , ^{234}Th , and ^{40}K , ^{157}Gd , ^{55}Mn , ^{52}Tr and ^{56}Fe .

[0082] The antibodies and antibody fragments may also be conjugated with fluorescent or chemiluminescent labels, including fluorophores such as rare earth chelates, fluorescein and its derivatives, rhodamine and its derivatives, isothiocyanate, phycoerythrin, phycocyanin, allophycocyanin, o-phthalaldehyde, fluorescamine, ^{152}Eu , dansyl, umbelliferone, luciferin, luminal label, isoluminal label, an aromatic acridinium ester label, an imidazole label, an acridinium salt label, an oxalate ester label, an aequorin label, 2,3-dihydrophthalazinediones, biotin/avidin, spin labels and stable free radicals.

[0083] The antibody molecules may also be conjugated to a cytotoxic factor such as diphtheria toxin, *Pseudomonas aeruginosa* exotoxin A chain, ricin A chain, abrin A chain, modeccin A chain, alpha-sarcin, *Aleurites fordii* proteins and compounds (e.g., fatty acids), dianthin proteins, *Phytolacca americana* proteins PAPI, PAPII, and PAP-S, *momordica charantia* inhibitor, curcin, crotin, *saponaria officinalis* inhibitor, mitogellin, restrictocin, phenomycin, and enomycin.

[0084] Any method known in the art for conjugating the antibody molecules of the invention to the various moieties may be employed, including those methods described by Hunter, *et al.*, (1962) Nature 144:945; David, *et al.*, (1974) Biochemistry 13:1014; Pain, *et al.*, (1981) J. Immunol. Meth. 40:219; and Nygren, J., (1982) Histochem. and Cytochem. 30:407. Methods for conjugating antibodies are conventional and very well known in the art.

[0085] In some embodiments, antibodies (e.g. an anti-C1s antibody) are provided herein. In some embodiments, the antibody is a recombinant antibody that binds to C1s. In some embodiments, the antibody binds to the active form of C1s. In some embodiments, the antibody binds to active form preferentially over the inactive form of C1s. In some embodiments, the antibody binds to the active form with an affinity that is at least 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, or 200% higher as compared to its affinity for the inactive form of C1s. In some embodiments, the C1s protein is a human C1s protein, such as the active form of C1s. In some

embodiments, the antibody does not specifically bind to the inactive form of the C1s protein. As used herein, the term “recombinant antibody” refers to an antibody that is not naturally occurring. In some embodiments, the term “recombinant antibody” refers to an antibody that is not isolated from a human subject. In some embodiments, the antibody binds with at least 100X more affinity to the active form of C1s as compared to proC1s.

[0086] In some embodiments, an antibody, or antigen binding fragment thereof is provided, wherein the antibody or antibody fragment comprises a peptide selected from the following table, which illustrate the CDRs based on Kabat numbering.

Table 2:

Kabat CDRs						
Ab ID No	HCDR1	HCDR2	HCDR3	LCDR1	LCDR2	LCDR3
MAb1	ELSMH (SEQ ID NO: 9)	TFDPEEGET IYAQKFQG (SEQ ID NO: 10)	EGLAGRPFDS (SEQ ID NO: 11)	RASQSISSW LA (SEQ ID NO: 12)	KASSLES (SEQ ID NO: 13)	QQYNSYSWT (SEQ ID NO: 14)
MAb2	DYYMS (SEQ ID NO: 15)	YISRSGSTKY YADSVKG (SEQ ID NO: 16)	DETDYALDY (SEQ ID NO: 17)	QASQDISNY LN (SEQ ID NO: 18)	DASNLET (SEQ ID NO: 19)	QQYEDLPLT (SEQ ID NO: 20)
MAb3	DYGMS (SEQ ID NO: 21)	GINWEGGST GYADSVKG (SEQ ID NO: 22)	DEQLGGNYY YYYYMDV (SEQ ID NO: 23)	RASQGIRN DLG (SEQ ID NO: 24)	TASNLS (SEQ ID NO: 25)	LQYNSYPLT (SEQ ID NO: 26)

[0087] The CDRs in the above-identified table can also be referred to according to Chothia CDRs or IMGT CDRs. These are illustrated in the following tables for the different antibodies.

Table 3:

CHOTHIA CDRS						
Ab ID No	HCDR1	HCDR2	HCDR3	LCDR1	LCDR2	LCDR3
MAb1	GDTLTEL (SEQ ID NO: 27)	DPEEGE (SEQ ID NO: 28)	EGLAGRPFDS (SEQ ID NO: 11)	SQSISSW (SEQ ID NO: 29)	KAS (SEQ ID NO: 30)	YNSYSW (SEQ ID NO: 31)
MAb2	GFTFSDY (SEQ ID NO: 32)	SRSGST (SEQ ID NO: 33)	DETDYALDY (SEQ ID NO: 17)	SQDISNY (SEQ ID NO: 34)	DAS (SEQ ID NO: 35)	YEDLPL (SEQ ID NO: 36)
MAb3	GFTFDDY (SEQ ID NO: 37)	NWEGGS (SEQ ID NO: 38)	DEQLGGNYY YYYYMDV (SEQ ID NO: 23)	SQGIRND (SEQ ID NO: 39)	TAS (SEQ ID NO: 40)	YNSYPL (SEQ ID NO: 41)

Table 4:

IMGT CDRS						
Ab ID No	HCDR1	HCDR2	HCDR3	LCDR1	LCDR2	LCDR3
MAb1	GDTLTEL S (SEQ ID NO: 42)	FDPEEGET (SEQ ID NO: 43)	VTEGLAGRPF DS (SEQ ID NO: 44)	QSISSW (SEQ ID NO: 45)	KAS (SEQ ID NO: 30)	QQYNSYSWT (SEQ ID NO: 14)
MAb2	GFTFSDY Y (SEQ ID NO: 46)	ISRSGSTK (SEQ ID NO: 47)	ARDETDYAL DY (SEQ ID NO: 48)	QDISNY (SEQ ID NO: 49)	DAS (SEQ ID NO: 35)	QQYEDLPLT (SEQ ID NO: 20)
MAb3	GFTFDDY G (SEQ ID NO: 50)	INWEGGST (SEQ ID NO: 51)	ARDEQLGGN YYYYYYMDV (SEQ ID NO: 52)	QGIRND (SEQ ID NO: 53)	TAS (SEQ ID NO: 40)	LQYNSYPLT (SEQ ID NO: 26)

[0088] In some embodiments, an antibody, or antibody binding fragment thereof, comprises a heavy or light chain CDR as provided in the tables above. In some embodiments, an antibody, or antibody binding fragment thereof, comprises a light chain LCDR having a sequence of SEQ ID NO: 12, 13, 14, 18, 19, 20, 24, 25, 26, 29, 30, 31, 34, 35, 36, 39, 40, 41, 45, , , 49, , , 53, , , or a combination thereof. In some embodiments, the light chain LCDR comprises a sequence of SEQ ID NO: 12. In some embodiments, the light chain LCDR comprises a sequence of SEQ ID NO: 13. In some embodiments, the light chain LCDR comprises a sequence of SEQ ID NO: 14. In some embodiments, the light chain LCDR comprises a sequence of SEQ ID NO: 18. In some embodiments, the light chain LCDR comprises a sequence of SEQ ID NO: 19. In some embodiments, the light chain LCDR comprises a sequence of SEQ ID NO: 20. In some embodiments, the light chain LCDR comprises a sequence of SEQ ID NO: 24. In some embodiments, the light chain LCDR comprises a sequence of SEQ ID NO: 25. In some embodiments, the light chain LCDR comprises a sequence of SEQ ID NO: 26. In some embodiments, the light chain LCDR comprises a sequence of SEQ ID NO: 29. In some embodiments, the light chain LCDR comprises a sequence of SEQ ID NO: 30. In some embodiments, the light chain LCDR comprises a sequence of SEQ ID NO: 31. In some embodiments, the light chain LCDR comprises a sequence of SEQ ID NO: 34. In some embodiments, the light chain LCDR comprises a sequence of SEQ ID NO: 35. In some embodiments, the light chain LCDR comprises a sequence of SEQ ID NO: 36. In some embodiments, the light chain LCDR comprises a sequence of SEQ ID NO: 39. In some embodiments, the light chain LCDR comprises a sequence of SEQ ID NO: 40. In some embodiments, the light chain LCDR comprises a sequence of SEQ ID NO: 41. In some

embodiments, the light chain LCDR comprises a sequence of SEQ ID NO: 45. In some embodiments, the light chain LCDR comprises a sequence of SEQ ID NO: 49. In some embodiments, the light chain LCDR comprises a sequence of SEQ ID NO: 53. In some embodiments, the light chain LCDR comprises a sequence that is a combination of one or more of SEQ ID NO: 12, 13, 14, 18, 19, 20, 24, 25, 26, 29, 30, 31, 34, 35, 36, 39, 40, 41, 45, 49, and 53. In some embodiments, an antibody, or antibody binding fragment thereof, comprises a heavy chain HCDR having a sequence of SEQ ID NO: 9, 10, 11, 15, 16, 17, 21, 22, 23, 27, 28, 32, 33, , 37, 38, , 42, 43, 44, 46, 47, 48, 50, 51, or 52. In some embodiments, the heavy chain HCDR comprises a sequence of SEQ ID NO: 9. In some embodiments, the heavy chain HCDR comprises a sequence of SEQ ID NO: 10. In some embodiments, the heavy chain HCDR comprises a sequence of SEQ ID NO: 11. In some embodiments, the heavy chain HCDR comprises a sequence of SEQ ID NO: 15. In some embodiments, the heavy chain HCDR comprises a sequence of SEQ ID NO: 16. In some embodiments, the heavy chain HCDR comprises a sequence of SEQ ID NO: 17. In some embodiments, the heavy chain HCDR comprises a sequence of SEQ ID NO: 21. In some embodiments, the heavy chain HCDR comprises a sequence of SEQ ID NO: 22. In some embodiments, the heavy chain HCDR comprises a sequence of SEQ ID NO: 23. In some embodiments, the heavy chain HCDR comprises a sequence of SEQ ID NO: 27. In some embodiments, the heavy chain HCDR comprises a sequence of SEQ ID NO: 28. In some embodiments, the heavy chain HCDR comprises a sequence of SEQ ID NO: 32. In some embodiments, the heavy chain HCDR comprises a sequence of SEQ ID NO: 33. In some embodiments, the heavy chain HCDR comprises a sequence of SEQ ID NO: 37. In some embodiments, the heavy chain HCDR comprises a sequence of SEQ ID NO: 38. In some embodiments, the heavy chain HCDR comprises a sequence of SEQ ID NO: 42. In some embodiments, the heavy chain HCDR comprises a sequence of SEQ ID NO: 43. In some embodiments, the heavy chain HCDR comprises a sequence of SEQ ID NO: 44. In some embodiments, the heavy chain HCDR comprises a sequence of SEQ ID NO: 46. In some embodiments, the heavy chain HCDR comprises a sequence of SEQ ID NO: 47. In some embodiments, the heavy chain HCDR comprises a sequence of SEQ ID NO: 48. In some embodiments, the heavy chain HCDR comprises a sequence of SEQ ID NO: 50. In some embodiments, the heavy chain HCDR comprises a sequence of SEQ ID NO: 51. In some embodiments, the heavy chain HCDR

comprises a sequence of SEQ ID NO: 52. In some embodiments, the heavy chain HCDR comprises a sequence that is a combination of one or more of SEQ ID NO: 9, 10, 11, 15, 16, 17, 21, 22, 23, 27, 28, 32, 33, 37, 38, 42, 43, 44, 46, 47, 48, 50, 51, and 52. It is to be understood that the CDRs referenced in the embodiments throughout the present specification can be interchanged with the CDRs that are characterized by different formats, such as Chothia and IMGT, which are illustrated in the tables above.

[0089] In some embodiments, an antibody, or antibody binding fragment thereof, comprises a light chain variable region having a LCDR1, a LCDR2, and a LCDR3, wherein the LCDR1 has a sequence of SEQ ID NO: 12, the LCDR2 has a sequence of SEQ ID NO: 13, and the LCDR3 has a sequence of SEQ ID NO: 14.

[0090] In some embodiments, an antibody, or antibody binding fragment thereof, comprises a light chain variable region having a LCDR1, a LCDR2, and a LCDR3, wherein the LCDR1 has a sequence of SEQ ID NO: 12, the LCDR2 has a sequence of SEQ ID NO: 13, and the LCDR3 has a sequence of SEQ ID NO: 20.

[0091] In some embodiments, an antibody, or antibody binding fragment thereof, comprises a light chain variable region having a LCDR1, a LCDR2, and a LCDR3, wherein the LCDR1 has a sequence of SEQ ID NO: 12, the LCDR2 has a sequence of SEQ ID NO: 13, and the LCDR3 has a sequence of SEQ ID NO: 26.

[0092] In some embodiments, an antibody, or antibody binding fragment thereof, comprises a light chain variable region having a LCDR1, a LCDR2, and a LCDR3, wherein the LCDR1 has a sequence of SEQ ID NO: 12, the LCDR2 has a sequence of SEQ ID NO: 19, and the LCDR3 has a sequence of SEQ ID NO: 14.

[0093] In some embodiments, an antibody, or antibody binding fragment thereof, comprises a light chain variable region having a LCDR1, a LCDR2, and a LCDR3, wherein the LCDR1 has a sequence of SEQ ID NO: 12, the LCDR2 has a sequence of SEQ ID NO: 19, and the LCDR3 has a sequence of SEQ ID NO: 20.

[0094] In some embodiments, an antibody, or antibody binding fragment thereof, comprises a light chain variable region having a LCDR1, a LCDR2, and a LCDR3, wherein the LCDR1 has a sequence of SEQ ID NO: 12, the LCDR2 has a sequence of SEQ ID NO: 19, and the LCDR3 has a sequence of SEQ ID NO: 26.

[0095] In some embodiments, an antibody, or antibody binding fragment thereof, comprises a light chain variable region having a LCDR1, a LCDR2, and a LCDR3, wherein the LCDR1 has a sequence of SEQ ID NO: 12, the LCDR2 has a sequence of SEQ ID NO: 25, and the LCDR3 has a sequence of SEQ ID NO: 14.

[0096] In some embodiments, an antibody, or antibody binding fragment thereof, comprises a light chain variable region having a LCDR1, a LCDR2, and a LCDR3, wherein the LCDR1 has a sequence of SEQ ID NO: 12, the LCDR2 has a sequence of SEQ ID NO: 25, and the LCDR3 has a sequence of SEQ ID NO: 20.

[0097] In some embodiments, an antibody, or antibody binding fragment thereof, comprises a light chain variable region having a LCDR1, a LCDR2, and a LCDR3, wherein the LCDR1 has a sequence of SEQ ID NO: 12, the LCDR2 has a sequence of SEQ ID NO: 25, and the LCDR3 has a sequence of SEQ ID NO: 26.

[0098] In some embodiments, an antibody, or antibody binding fragment thereof, comprises a light chain variable region having a LCDR1, a LCDR2, and a LCDR3, wherein the LCDR1 has a sequence of SEQ ID NO: 18, the LCDR2 has a sequence of SEQ ID NO: 13, and the LCDR3 has a sequence of SEQ ID NO: 14.

[0099] In some embodiments, an antibody, or antibody binding fragment thereof, comprises a light chain variable region having a LCDR1, a LCDR2, and a LCDR3, wherein the LCDR1 has a sequence of SEQ ID NO: 18, the LCDR2 has a sequence of SEQ ID NO: 13, and the LCDR3 has a sequence of SEQ ID NO: 20.

[00100] In some embodiments, an antibody, or antibody binding fragment thereof, comprises a light chain variable region having a LCDR1, a LCDR2, and a LCDR3, wherein the LCDR1 has a sequence of SEQ ID NO: 18, the LCDR2 has a sequence of SEQ ID NO: 13, and the LCDR3 has a sequence of SEQ ID NO: 26.

[00101] In some embodiments, an antibody, or antibody binding fragment thereof, comprises a light chain variable region having a LCDR1, a LCDR2, and a LCDR3, wherein the LCDR1 has a sequence of SEQ ID NO: 18, the LCDR2 has a sequence of SEQ ID NO: 19, and the LCDR3 has a sequence of SEQ ID NO: 14.

[00102] In some embodiments, an antibody, or antibody binding fragment thereof, comprises a light chain variable region having a LCDR1, a LCDR2, and a LCDR3, wherein the LCDR1 has a

sequence of SEQ ID NO: 18, the LCDR2 has a sequence of SEQ ID NO: 19, and the LCDR3 has a sequence of SEQ ID NO: 20.

[00103] In some embodiments, an antibody, or antibody binding fragment thereof, comprises a light chain variable region having a LCDR1, a LCDR2, and a LCDR3, wherein the LCDR1 has a sequence of SEQ ID NO: 18, the LCDR2 has a sequence of SEQ ID NO: 19, and the LCDR3 has a sequence of SEQ ID NO: 26.

[00104] In some embodiments, an antibody, or antibody binding fragment thereof, comprises a light chain variable region having a LCDR1, a LCDR2, and a LCDR3, wherein the LCDR1 has a sequence of SEQ ID NO: 18, the LCDR2 has a sequence of SEQ ID NO: 25, and the LCDR3 has a sequence of SEQ ID NO: 14.

[00105] In some embodiments, an antibody, or antibody binding fragment thereof, comprises a light chain variable region having a LCDR1, a LCDR2, and a LCDR3, wherein the LCDR1 has a sequence of SEQ ID NO: 18, the LCDR2 has a sequence of SEQ ID NO: 25, and the LCDR3 has a sequence of SEQ ID NO: 20.

[00106] In some embodiments, an antibody, or antibody binding fragment thereof, comprises a light chain variable region having a LCDR1, a LCDR2, and a LCDR3, wherein the LCDR1 has a sequence of SEQ ID NO: 18, the LCDR2 has a sequence of SEQ ID NO: 25, and the LCDR3 has a sequence of SEQ ID NO: 26.

[00107] In some embodiments, an antibody, or antibody binding fragment thereof, comprises a light chain variable region having a LCDR1, a LCDR2, and a LCDR3, wherein the LCDR1 has a sequence of SEQ ID NO: 24, the LCDR2 has a sequence of SEQ ID NO: 13, and the LCDR3 has a sequence of SEQ ID NO: 14.

[00108] In some embodiments, an antibody, or antibody binding fragment thereof, comprises a light chain variable region having a LCDR1, a LCDR2, and a LCDR3, wherein the LCDR1 has a sequence of SEQ ID NO: 24, the LCDR2 has a sequence of SEQ ID NO: 13, and the LCDR3 has a sequence of SEQ ID NO: 20.

[00109] In some embodiments, an antibody, or antibody binding fragment thereof, comprises a light chain variable region having a LCDR1, a LCDR2, and a LCDR3, wherein the LCDR1 has a sequence of SEQ ID NO: 24, the LCDR2 has a sequence of SEQ ID NO: 13, and the LCDR3 has a sequence of SEQ ID NO: 26.

[00110] In some embodiments, an antibody, or antibody binding fragment thereof, comprises a light chain variable region having a LCDR1, a LCDR2, and a LCDR3, wherein the LCDR1 has a sequence of SEQ ID NO: 24, the LCDR2 has a sequence of SEQ ID NO: 19, and the LCDR3 has a sequence of SEQ ID NO: 14.

[00111] In some embodiments, an antibody, or antibody binding fragment thereof, comprises a light chain variable region having a LCDR1, a LCDR2, and a LCDR3, wherein the LCDR1 has a sequence of SEQ ID NO: 24, the LCDR2 has a sequence of SEQ ID NO: 19, and the LCDR3 has a sequence of SEQ ID NO: 20.

[00112] In some embodiments, an antibody, or antibody binding fragment thereof, comprises a light chain variable region having a LCDR1, a LCDR2, and a LCDR3, wherein the LCDR1 has a sequence of SEQ ID NO: 24, the LCDR2 has a sequence of SEQ ID NO: 19, and the LCDR3 has a sequence of SEQ ID NO: 26.

[00113] In some embodiments, an antibody, or antibody binding fragment thereof, comprises a light chain variable region having a LCDR1, a LCDR2, and a LCDR3, wherein the LCDR1 has a sequence of SEQ ID NO: 24, the LCDR2 has a sequence of SEQ ID NO: 25, and the LCDR3 has a sequence of SEQ ID NO: 14.

[00114] In some embodiments, an antibody, or antibody binding fragment thereof, comprises a light chain variable region having a LCDR1, a LCDR2, and a LCDR3, wherein the LCDR1 has a sequence of SEQ ID NO: 24, the LCDR2 has a sequence of SEQ ID NO: 25, and the LCDR3 has a sequence of SEQ ID NO: 20.

[00115] In some embodiments, an antibody, or antibody binding fragment thereof, comprises a light chain variable region having a LCDR1, a LCDR2, and a LCDR3, wherein the LCDR1 has a sequence of SEQ ID NO: 24, the LCDR2 has a sequence of SEQ ID NO: 25, and the LCDR3 has a sequence of SEQ ID NO: 26.

[00116] In some embodiments, an antibody, or antibody binding fragment thereof, comprises a heavy chain variable region having a HCDR1, a HCDR2, and a HCDR3, wherein the HCDR1 has a sequence of SEQ ID NO: 9, the HCDR2 has a sequence of SEQ ID NO: 10, and the HCDR3 has a sequence of SEQ ID NO: 11.

[00117] In some embodiments, an antibody, or antibody binding fragment thereof, comprises a heavy chain variable region having a HCDR1, a HCDR2, and a HCDR3, wherein the HCDR1

has a sequence of SEQ ID NO: 9, the HCDR2 has a sequence of SEQ ID NO: 10, and the HCDR3 has a sequence of SEQ ID NO: 17.

[00118] In some embodiments, an antibody, or antibody binding fragment thereof, comprises a heavy chain variable region having a HCDR1, a HCDR2, and a HCDR3, wherein the HCDR1 has a sequence of SEQ ID NO: 9, the HCDR2 has a sequence of SEQ ID NO: 10, and the HCDR3 has a sequence of SEQ ID NO: 23.

[00119] In some embodiments, an antibody, or antibody binding fragment thereof, comprises a heavy chain variable region having a HCDR1, a HCDR2, and a HCDR3, wherein the HCDR1 has a sequence of SEQ ID NO: 9, the HCDR2 has a sequence of SEQ ID NO: 16, and the HCDR3 has a sequence of SEQ ID NO: 11.

[00120] In some embodiments, an antibody, or antibody binding fragment thereof, comprises a heavy chain variable region having a HCDR1, a HCDR2, and a HCDR3, wherein the HCDR1 has a sequence of SEQ ID NO: 9, the HCDR2 has a sequence of SEQ ID NO: 16, and the HCDR3 has a sequence of SEQ ID NO: 17.

[00121] In some embodiments, an antibody, or antibody binding fragment thereof, comprises a heavy chain variable region having a HCDR1, a HCDR2, and a HCDR3, wherein the HCDR1 has a sequence of SEQ ID NO: 9, the HCDR2 has a sequence of SEQ ID NO: 16, and the HCDR3 has a sequence of SEQ ID NO: 23.

[00122] In some embodiments, an antibody, or antibody binding fragment thereof, comprises a heavy chain variable region having a HCDR1, a HCDR2, and a HCDR3, wherein the HCDR1 has a sequence of SEQ ID NO: 9, the HCDR2 has a sequence of SEQ ID NO: 22, and the HCDR3 has a sequence of SEQ ID NO: 11.

[00123] In some embodiments, an antibody, or antibody binding fragment thereof, comprises a heavy chain variable region having a HCDR1, a HCDR2, and a HCDR3, wherein the HCDR1 has a sequence of SEQ ID NO: 9, the HCDR2 has a sequence of SEQ ID NO: 22, and the HCDR3 has a sequence of SEQ ID NO: 17.

[00124] In some embodiments, an antibody, or antibody binding fragment thereof, comprises a heavy chain variable region having a HCDR1, a HCDR2, and a HCDR3, wherein the HCDR1 has a sequence of SEQ ID NO: 9, the HCDR2 has a sequence of SEQ ID NO: 22, and the HCDR3 has a sequence of SEQ ID NO: 23.

[00125] In some embodiments, an antibody, or antibody binding fragment thereof, comprises a heavy chain variable region having a HCDR1, a HCDR2, and a HCDR3, wherein the HCDR1 has a sequence of SEQ ID NO: 15, the HCDR2 has a sequence of SEQ ID NO: 10, and the HCDR3 has a sequence of SEQ ID NO: 11.

[00126] In some embodiments, an antibody, or antibody binding fragment thereof, comprises a heavy chain variable region having a HCDR1, a HCDR2, and a HCDR3, wherein the HCDR1 has a sequence of SEQ ID NO: 15, the HCDR2 has a sequence of SEQ ID NO: 10, and the HCDR3 has a sequence of SEQ ID NO: 17.

[00127] In some embodiments, an antibody, or antibody binding fragment thereof, comprises a heavy chain variable region having a HCDR1, a HCDR2, and a HCDR3, wherein the HCDR1 has a sequence of SEQ ID NO: 15, the HCDR2 has a sequence of SEQ ID NO: 10, and the HCDR3 has a sequence of SEQ ID NO: 23.

[00128] In some embodiments, an antibody, or antibody binding fragment thereof, comprises a heavy chain variable region having a HCDR1, a HCDR2, and a HCDR3, wherein the HCDR1 has a sequence of SEQ ID NO: 15, the HCDR2 has a sequence of SEQ ID NO: 16, and the HCDR3 has a sequence of SEQ ID NO: 11.

[00129] In some embodiments, an antibody, or antibody binding fragment thereof, comprises a heavy chain variable region having a HCDR1, a HCDR2, and a HCDR3, wherein the HCDR1 has a sequence of SEQ ID NO: 15, the HCDR2 has a sequence of SEQ ID NO: 16, and the HCDR3 has a sequence of SEQ ID NO: 17.

[00130] In some embodiments, an antibody, or antibody binding fragment thereof, comprises a heavy chain variable region having a HCDR1, a HCDR2, and a HCDR3, wherein the HCDR1 has a sequence of SEQ ID NO: 15, the HCDR2 has a sequence of SEQ ID NO: 16, and the HCDR3 has a sequence of SEQ ID NO: 23.

[00131] In some embodiments, an antibody, or antibody binding fragment thereof, comprises a heavy chain variable region having a HCDR1, a HCDR2, and a HCDR3, wherein the HCDR1 has a sequence of SEQ ID NO: 15, the HCDR2 has a sequence of SEQ ID NO: 22, and the HCDR3 has a sequence of SEQ ID NO: 11.

[00132] In some embodiments, an antibody, or antibody binding fragment thereof, comprises a heavy chain variable region having a HCDR1, a HCDR2, and a HCDR3, wherein the HCDR1

has a sequence of SEQ ID NO: 15, the HCDR2 has a sequence of SEQ ID NO: 22, and the HCDR3 has a sequence of SEQ ID NO: 17.

[00133] In some embodiments, an antibody, or antibody binding fragment thereof, comprises a heavy chain variable region having a HCDR1, a HCDR2, and a HCDR3, wherein the HCDR1 has a sequence of SEQ ID NO: 15, the HCDR2 has a sequence of SEQ ID NO: 22, and the HCDR3 has a sequence of SEQ ID NO: 23.

[00134] In some embodiments, an antibody, or antibody binding fragment thereof, comprises a heavy chain variable region having a HCDR1, a HCDR2, and a HCDR3, wherein the HCDR1 has a sequence of SEQ ID NO: 21, the HCDR2 has a sequence of SEQ ID NO: 10, and the HCDR3 has a sequence of SEQ ID NO: 11.

[00135] In some embodiments, an antibody, or antibody binding fragment thereof, comprises a heavy chain variable region having a HCDR1, a HCDR2, and a HCDR3, wherein the HCDR1 has a sequence of SEQ ID NO: 21, the HCDR2 has a sequence of SEQ ID NO: 10, and the HCDR3 has a sequence of SEQ ID NO: 17.

[00136] In some embodiments, an antibody, or antibody binding fragment thereof, comprises a heavy chain variable region having a HCDR1, a HCDR2, and a HCDR3, wherein the HCDR1 has a sequence of SEQ ID NO: 21, the HCDR2 has a sequence of SEQ ID NO: 10, and the HCDR3 has a sequence of SEQ ID NO: 23.

[00137] In some embodiments, an antibody, or antibody binding fragment thereof, comprises a heavy chain variable region having a HCDR1, a HCDR2, and a HCDR3, wherein the HCDR1 has a sequence of SEQ ID NO: 21, the HCDR2 has a sequence of SEQ ID NO: 16, and the HCDR3 has a sequence of SEQ ID NO: 11.

[00138] In some embodiments, an antibody, or antibody binding fragment thereof, comprises a heavy chain variable region having a HCDR1, a HCDR2, and a HCDR3, wherein the HCDR1 has a sequence of SEQ ID NO: 21, the HCDR2 has a sequence of SEQ ID NO: 16, and the HCDR3 has a sequence of SEQ ID NO: 17.

[00139] In some embodiments, an antibody, or antibody binding fragment thereof, comprises a heavy chain variable region having a HCDR1, a HCDR2, and a HCDR3, wherein the HCDR1 has a sequence of SEQ ID NO: 21, the HCDR2 has a sequence of SEQ ID NO: 16, and the HCDR3 has a sequence of SEQ ID NO: 23.

[00140] In some embodiments, an antibody, or antibody binding fragment thereof, comprises a heavy chain variable region having a HCDR1, a HCDR2, and a HCDR3, wherein the HCDR1 has a sequence of SEQ ID NO: 21, the HCDR2 has a sequence of SEQ ID NO: 22, and the HCDR3 has a sequence of SEQ ID NO: 11.

[00141] In some embodiments, an antibody, or antibody binding fragment thereof, comprises a heavy chain variable region having a HCDR1, a HCDR2, and a HCDR3, wherein the HCDR1 has a sequence of SEQ ID NO: 21, the HCDR2 has a sequence of SEQ ID NO: 22, and the HCDR3 has a sequence of SEQ ID NO: 17.

[00142] In some embodiments, an antibody, or antibody binding fragment thereof, comprises a heavy chain variable region having a HCDR1, a HCDR2, and a HCDR3, wherein the HCDR1 has a sequence of SEQ ID NO: 21, the HCDR2 has a sequence of SEQ ID NO: 22, and the HCDR3 has a sequence of SEQ ID NO: 23.

[00143] For clarity, the following tables are provided depicting non-limiting exemplary combinations of light chain (Table 5) and heavy chain (Table 6) CDRs.

Table 5:

	LCDR1	LCDR2	LCDR3
V _{LA}	SEQ ID NO: 12	SEQ ID NO: 13	SEQ ID NO: 14
V _{LB}	SEQ ID NO: 12	SEQ ID NO: 13	SEQ ID NO: 20
V _{LC}	SEQ ID NO: 12	SEQ ID NO: 13	SEQ ID NO: 26
V _{LD}	SEQ ID NO: 12	SEQ ID NO: 19	SEQ ID NO: 14
V _{LE}	SEQ ID NO: 12	SEQ ID NO: 19	SEQ ID NO: 20
V _{LF}	SEQ ID NO: 12	SEQ ID NO: 19	SEQ ID NO: 26
V _{LG}	SEQ ID NO: 12	SEQ ID NO: 25	SEQ ID NO: 14
V _{LH}	SEQ ID NO: 12	SEQ ID NO: 25	SEQ ID NO: 20
V _{LI}	SEQ ID NO: 12	SEQ ID NO: 25	SEQ ID NO: 26
V _{LJ}	SEQ ID NO: 18	SEQ ID NO: 13	SEQ ID NO: 14
V _{LK}	SEQ ID NO: 18	SEQ ID NO: 13	SEQ ID NO: 20
V _{LL}	SEQ ID NO: 18	SEQ ID NO: 13	SEQ ID NO: 26
V _{LM}	SEQ ID NO: 18	SEQ ID NO: 19	SEQ ID NO: 14
V _{LN}	SEQ ID NO: 18	SEQ ID NO: 19	SEQ ID NO: 20

V _{LO}	SEQ ID NO: 18	SEQ ID NO: 19	SEQ ID NO: 26
V _{LP}	SEQ ID NO: 18	SEQ ID NO: 25	SEQ ID NO: 14
V _{LQ}	SEQ ID NO: 18	SEQ ID NO: 25	SEQ ID NO: 20
V _{LR}	SEQ ID NO: 18	SEQ ID NO: 25	SEQ ID NO: 26
V _{LS}	SEQ ID NO: 24	SEQ ID NO: 13	SEQ ID NO: 14
V _{LT}	SEQ ID NO: 24	SEQ ID NO: 13	SEQ ID NO: 20
V _{LU}	SEQ ID NO: 24	SEQ ID NO: 13	SEQ ID NO: 26
V _{LV}	SEQ ID NO: 24	SEQ ID NO: 19	SEQ ID NO: 14
V _{LW}	SEQ ID NO: 24	SEQ ID NO: 19	SEQ ID NO: 20
V _{LX}	SEQ ID NO: 24	SEQ ID NO: 19	SEQ ID NO: 26
V _{LY}	SEQ ID NO: 24	SEQ ID NO: 25	SEQ ID NO: 14
V _{LZ}	SEQ ID NO: 24	SEQ ID NO: 25	SEQ ID NO: 20
V _{LAB}	SEQ ID NO: 24	SEQ ID NO: 25	SEQ ID NO: 26

Table 6:

	HCDR1	HCDR2	HCDR3
V _{HA}	SEQ ID NO: 9	SEQ ID NO: 10	SEQ ID NO: 11
V _{HB}	SEQ ID NO: 9	SEQ ID NO: 10	SEQ ID NO: 17
V _{HC}	SEQ ID NO: 9	SEQ ID NO: 10	SEQ ID NO: 23
V _{HD}	SEQ ID NO: 9	SEQ ID NO: 16	SEQ ID NO: 11
V _{HE}	SEQ ID NO: 9	SEQ ID NO: 16	SEQ ID NO: 17
V _{HF}	SEQ ID NO: 9	SEQ ID NO: 16	SEQ ID NO: 23
V _{HG}	SEQ ID NO: 9	SEQ ID NO: 22	SEQ ID NO: 11
V _{HH}	SEQ ID NO: 9	SEQ ID NO: 22	SEQ ID NO: 17
V _{HI}	SEQ ID NO: 9	SEQ ID NO: 22	SEQ ID NO: 23
V _{HJ}	SEQ ID NO: 15	SEQ ID NO: 10	SEQ ID NO: 11
V _{HK}	SEQ ID NO: 15	SEQ ID NO: 10	SEQ ID NO: 17
V _{HL}	SEQ ID NO: 15	SEQ ID NO: 10	SEQ ID NO: 23
V _{HM}	SEQ ID NO: 15	SEQ ID NO: 16	SEQ ID NO: 11
V _{HN}	SEQ ID NO: 15	SEQ ID NO: 16	SEQ ID NO: 17

V _{HO}	SEQ ID NO: 15	SEQ ID NO: 16	SEQ ID NO: 23
V _{HP}	SEQ ID NO: 15	SEQ ID NO: 22	SEQ ID NO: 11
V _{HQ}	SEQ ID NO: 15	SEQ ID NO: 22	SEQ ID NO: 17
V _{HR}	SEQ ID NO: 15	SEQ ID NO: 22	SEQ ID NO: 23
V _{HS}	SEQ ID NO: 21	SEQ ID NO: 10	SEQ ID NO: 11
V _{HT}	SEQ ID NO: 21	SEQ ID NO: 10	SEQ ID NO: 17
V _{HU}	SEQ ID NO: 21	SEQ ID NO: 10	SEQ ID NO: 23
V _{HV}	SEQ ID NO: 21	SEQ ID NO: 16	SEQ ID NO: 11
V _{HW}	SEQ ID NO: 21	SEQ ID NO: 16	SEQ ID NO: 17
V _{HX}	SEQ ID NO: 21	SEQ ID NO: 16	SEQ ID NO: 23
V _{HY}	SEQ ID NO: 21	SEQ ID NO: 22	SEQ ID NO: 11
V _{HZ}	SEQ ID NO: 21	SEQ ID NO: 22	SEQ ID NO: 17
V _{HAB}	SEQ ID NO: 21	SEQ ID NO: 22	SEQ ID NO: 23

[00144] In some embodiments, an antibody or antibody binding fragment thereof, comprises: (i) a light chain having any one of the foregoing recited combinations of LCDR1, LCDR2, and LCDR3 sequences; and (ii) a heavy chain having any one of the foregoing recited combinations of HCDR1, HCDR2, and HCDR3 sequences. The following combinations are provided with reference to Table 5 and 6 above. Thus, for example, an antibody or antibody binding fragment thereof comprising V_{LA} and V_{HA} is understood to comprise a light chain having a LCDR1 of SEQ ID NO: 12, a LCDR2 of SEQ ID NO: 13, a LCDR3 of SEQ ID NO: 14, a HCDR1 of SEQ ID NO: 9, a HCDR2 of SEQ ID NO: 10, and a HCDR3 of SEQ ID NO: 11.

[00145] Accordingly, in some embodiments, an antibody or antibody binding fragment thereof comprises V_{LA} and V_{HA}. In some embodiments, an antibody or antibody binding fragment thereof comprises V_{LB} and V_{HA}. In some embodiments, an antibody or antibody binding fragment thereof comprises V_{LC} and V_{HA}. In some embodiments, an antibody or antibody binding fragment thereof comprises V_{LD} and V_{HA}. In some embodiments, an antibody or antibody binding fragment thereof comprises V_{LE} and V_{HA}. In some embodiments, an antibody or antibody binding fragment thereof comprises V_{LF} and V_{HA}. In some embodiments, an antibody or antibody binding fragment thereof comprises V_{LG} and V_{HA}. In some embodiments, an antibody or antibody binding fragment thereof comprises V_{LH} and V_{HA}. In some

an antibody or antibody binding fragment thereof comprises V_LV and V_HO . In some embodiments, an antibody or antibody binding fragment thereof comprises V_LW and V_HO . In some embodiments, an antibody or antibody binding fragment thereof comprises V_LX and V_HO . In some embodiments, an antibody or antibody binding fragment thereof comprises V_LY and V_HO . In some embodiments, an antibody or antibody binding fragment thereof comprises V_LZ and V_HO . In some embodiments, an antibody or antibody binding fragment thereof comprises V_LAB and V_HO .

[illegible]

antibody or antibody binding fragment thereof comprises V_{LW} and V_{HP} . In some embodiments, an antibody or antibody binding fragment thereof comprises V_{LX} and V_{HP} . In some embodiments, an antibody or antibody binding fragment thereof comprises V_{LY} and V_{HP} . In some embodiments, an antibody or antibody binding fragment thereof comprises V_{LZ} and V_{HP} . In some embodiments, an antibody or antibody binding fragment thereof comprises V_{LAB} and V_{HP} .

[illegible]

some embodiments, an antibody or antibody binding fragment thereof comprises V_{LX} and V_{HQ} . In some embodiments, an antibody or antibody binding fragment thereof comprises V_{LY} and V_{HQ} . In some embodiments, an antibody or antibody binding fragment thereof comprises V_{LZ} and V_{HQ} . In some embodiments, an antibody or antibody binding fragment thereof comprises V_{LAB} and V_{HQ} .

[illegible]

and V_HV . In some embodiments, an antibody or antibody binding fragment thereof comprises V_{LAB} and V_HV .

[illegible]

and V_{HX} . In some embodiments, an antibody or antibody binding fragment thereof comprises V_{LAB} and V_{HX} .

[illegible]

antibody binding fragment thereof comprises V_{LAB} and V_{HAB}. The different CDR motifs can be combined in any combination including those not depicted in the table above. For example, the following embodiments are provided as non-limiting examples of such combinations.

[00172] In some embodiments, an antibody, or antigen binding fragment thereof, comprises: (i) a light chain variable region comprising light chain LCDR1, LCDR2, and LCDR3 sequences, wherein the light chain LCDR1 sequence has the amino acid sequence of SEQ ID NO: 12; the light chain LCDR2 has the amino acid sequence of SEQ ID NO: 13; and the light chain LCDR3 sequence has the amino acid sequence of SEQ ID NO: 14 and (ii) a heavy chain variable region comprising heavy chain HCDR1, HCDR2, and HCDR3 sequences, wherein the heavy chain HCDR1 sequence has the amino acid sequence of SEQ ID NO: 9; the heavy chain HCDR2 sequence has the amino acid sequence of SEQ ID NO: 10; and the heavy chain HCDR3 sequence has the amino acid sequence of SEQ ID NO: 11; or variants of any of the foregoing.

[00173] In some embodiments, an antibody, or antigen binding fragment thereof, comprises: (i) a light chain variable region comprising light chain LCDR1, LCDR2, and LCDR3 sequences, wherein the light chain LCDR1 sequence has the amino acid sequence of SEQ ID NO: 18; the light chain LCDR2 has the amino acid sequence of SEQ ID NO: 19; and the light chain LCDR3 sequence has the amino acid sequence of SEQ ID NO: 20 and (ii) a heavy chain variable region comprising heavy chain HCDR1, HCDR2, and HCDR3 sequences, wherein the heavy chain HCDR1 sequence has the amino acid sequence of SEQ ID NO: 15; the heavy chain HCDR2 sequence has the amino acid sequence of SEQ ID NO: 16; and the heavy chain HCDR3 sequence has the amino acid sequence of SEQ ID NO: 17; or variants of any of the foregoing.

[00174] In some embodiments, an antibody, or antigen binding fragment thereof, comprises: (i) a light chain variable region comprising light chain LCDR1, LCDR2, and LCDR3 sequences, wherein the light chain LCDR1 sequence has the amino acid sequence of SEQ ID NO: 24; the light chain LCDR2 has the amino acid sequence of SEQ ID NO: 25; and the light chain LCDR3 sequence has the amino acid sequence of SEQ ID NO: 26 and (ii) a heavy chain variable region comprising heavy chain HCDR1, HCDR2, and HCDR3 sequences, wherein the heavy chain HCDR1 sequence has the amino acid sequence of SEQ ID NO: 21; the heavy chain HCDR2 sequence has the amino acid sequence of SEQ ID NO: 22; and the heavy chain HCDR3 sequence has the amino acid sequence of SEQ ID NO: 23; or variants of any of the foregoing.

[00175] Although the preceding paragraphs may make reference to CDRs under the Kabat system the equivalent CDR sequences can be used from the IMGT and CHOTHIA designations.

[00176] For clarity, the following tables are provided depicting non-limiting exemplary combinations of light chain (Table 7) and heavy chain (Table 8) CDRs using IMGT designations:

Table 7:

Combination	LCDR1	LCDR2	LCDR3
VLAA	SEQ ID NO: 45	SEQ ID NO: 30	SEQ ID NO: 14
VLBA	SEQ ID NO: 45	SEQ ID NO: 30	SEQ ID NO: 20
VLCA	SEQ ID NO: 45	SEQ ID NO: 30	SEQ ID NO: 26
VLDA	SEQ ID NO: 45	SEQ ID NO: 35	SEQ ID NO: 14
VLEA	SEQ ID NO: 45	SEQ ID NO: 35	SEQ ID NO: 20
VLFA	SEQ ID NO: 45	SEQ ID NO: 35	SEQ ID NO: 26
VLGA	SEQ ID NO: 45	SEQ ID NO: 40	SEQ ID NO: 14
VLHA	SEQ ID NO: 45	SEQ ID NO: 40	SEQ ID NO: 20
VLIA	SEQ ID NO: 45	SEQ ID NO: 40	SEQ ID NO: 26
VLJA	SEQ ID NO: 49	SEQ ID NO: 30	SEQ ID NO: 14
VLKA	SEQ ID NO: 49	SEQ ID NO: 30	SEQ ID NO: 20
VL LA	SEQ ID NO: 49	SEQ ID NO: 30	SEQ ID NO: 26
VLMA	SEQ ID NO: 49	SEQ ID NO: 35	SEQ ID NO: 14
VLNA	SEQ ID NO: 49	SEQ ID NO: 35	SEQ ID NO: 20
VLOA	SEQ ID NO: 49	SEQ ID NO: 35	SEQ ID NO: 26
VLPA	SEQ ID NO: 49	SEQ ID NO: 40	SEQ ID NO: 14
VLQA	SEQ ID NO: 49	SEQ ID NO: 40	SEQ ID NO: 20
VLRA	SEQ ID NO: 49	SEQ ID NO: 40	SEQ ID NO: 26
VL SA	SEQ ID NO: 53	SEQ ID NO: 30	SEQ ID NO: 14
VLTA	SEQ ID NO: 53	SEQ ID NO: 30	SEQ ID NO: 20
VLUA	SEQ ID NO: 53	SEQ ID NO: 30	SEQ ID NO: 26
VLVA	SEQ ID NO: 53	SEQ ID NO: 35	SEQ ID NO: 14
VLWA	SEQ ID NO: 53	SEQ ID NO: 35	SEQ ID NO: 20

V _L Xa	SEQ ID NO: 53	SEQ ID NO: 35	SEQ ID NO: 26
V _L Ya	SEQ ID NO: 53	SEQ ID NO: 40	SEQ ID NO: 14
V _L Za	SEQ ID NO: 53	SEQ ID NO: 40	SEQ ID NO: 20
V _L ABa	SEQ ID NO: 53	SEQ ID NO: 40	SEQ ID NO: 26

Table 8:

Combination	HCDR1	HCDR2	HCDR3
V _H Aa	SEQ ID NO: 42	SEQ ID NO: 43	SEQ ID NO: 44
V _H Ba	SEQ ID NO: 42	SEQ ID NO: 43	SEQ ID NO: 48
V _H Ca	SEQ ID NO: 42	SEQ ID NO: 43	SEQ ID NO: 52
V _H Da	SEQ ID NO: 42	SEQ ID NO: 47	SEQ ID NO: 44
V _H Ea	SEQ ID NO: 42	SEQ ID NO: 47	SEQ ID NO: 48
V _H Fa	SEQ ID NO: 42	SEQ ID NO: 47	SEQ ID NO: 52
V _H Ga	SEQ ID NO: 42	SEQ ID NO: 51	SEQ ID NO: 44
V _H Ha	SEQ ID NO: 42	SEQ ID NO: 51	SEQ ID NO: 48
V _H Ia	SEQ ID NO: 42	SEQ ID NO: 51	SEQ ID NO: 52
V _H Ja	SEQ ID NO: 46	SEQ ID NO: 43	SEQ ID NO: 44
V _H Ka	SEQ ID NO: 46	SEQ ID NO: 43	SEQ ID NO: 48
V _H La	SEQ ID NO: 46	SEQ ID NO: 43	SEQ ID NO: 52
V _H Ma	SEQ ID NO: 46	SEQ ID NO: 47	SEQ ID NO: 44
V _H Na	SEQ ID NO: 46	SEQ ID NO: 47	SEQ ID NO: 48
V _H Oa	SEQ ID NO: 46	SEQ ID NO: 47	SEQ ID NO: 52
V _H Pa	SEQ ID NO: 46	SEQ ID NO: 51	SEQ ID NO: 44
V _H Qa	SEQ ID NO: 46	SEQ ID NO: 51	SEQ ID NO: 48
V _H Ra	SEQ ID NO: 46	SEQ ID NO: 51	SEQ ID NO: 52
V _H Sa	SEQ ID NO: 50	SEQ ID NO: 43	SEQ ID NO: 44
V _H Ta	SEQ ID NO: 50	SEQ ID NO: 43	SEQ ID NO: 48
V _H Ua	SEQ ID NO: 50	SEQ ID NO: 43	SEQ ID NO: 52
V _H Va	SEQ ID NO: 50	SEQ ID NO: 47	SEQ ID NO: 44
V _H Wa	SEQ ID NO: 50	SEQ ID NO: 47	SEQ ID NO: 48

V _H Xa	SEQ ID NO: 50	SEQ ID NO: 47	SEQ ID NO: 52
V _H Ya	SEQ ID NO: 50	SEQ ID NO: 51	SEQ ID NO: 44
V _H Za	SEQ ID NO: 50	SEQ ID NO: 51	SEQ ID NO: 48
V _H ABa	SEQ ID NO: 50	SEQ ID NO: 51	SEQ ID NO: 52

[00177] In some embodiments, an antibody or antibody binding fragment thereof, comprises: (i) a light chain having any one of the foregoing recited combinations of LCDR1, LCDR2, and LCDR3 sequences; and (ii) a heavy chain having any one of the foregoing recited combinations of HCDR1, HCDR2, and HCDR3 sequences. The following combinations are provided with reference to Table 7 and Table 8 above. Thus, for example, an antibody or antibody binding fragment thereof comprising V_{LA}a and V_{HA}a is understood to comprise a light chain having a LCDR1 of SEQ ID NO: 45, a LCDR2 of SEQ ID NO: 30, a LCDR3 of SEQ ID NO: 14, a HCDR1 of SEQ ID NO: 42, a HCDR2 of SEQ ID NO: 43, and a HCDR3 of SEQ ID NO: 44.

[00178] Accordingly, in some embodiments, an antibody or antibody binding fragment thereof comprises V_{LA}a and V_{HA}a. In some embodiments, an antibody or antibody binding fragment thereof comprises V_{LB}a and V_{HA}a. In some embodiments, an antibody or antibody binding fragment thereof comprises V_{LC}a and V_{HA}a. In some embodiments, an antibody or antibody binding fragment thereof comprises V_{LD}a and V_{HA}a. In some embodiments, an antibody or antibody binding fragment thereof comprises V_{LE}a and V_{HA}a. In some embodiments, an antibody or antibody binding fragment thereof comprises V_{LF}a and V_{HA}a. In some embodiments, an antibody or antibody binding fragment thereof comprises V_{LG}a and V_{HA}a. In some embodiments, an antibody or antibody binding fragment thereof comprises V_{LH}a and V_{HA}a. In some embodiments, an antibody or antibody binding fragment thereof comprises V_{LI}a and V_{HA}a. In some embodiments, an antibody or antibody binding fragment thereof comprises V_{LJ}a and V_{HA}a. In some embodiments, an antibody or antibody binding fragment thereof comprises V_{LK}a and V_{HA}a. In some embodiments, an antibody or antibody binding fragment thereof comprises V_{LL}a and V_{HA}a. In some embodiments, an antibody or antibody binding fragment thereof comprises V_{LM}a and V_{HA}a. In some embodiments, an antibody or antibody binding fragment thereof comprises V_{LN}a and V_{HA}a. In some embodiments, an antibody or antibody binding fragment thereof comprises V_{LO}a and V_{HA}a. In some embodiments, an antibody or antibody binding fragment thereof comprises V_{LP}a and V_{HA}a. In some

[illegible]

comprises V_LVa and V_HGa. In some embodiments, an antibody or antibody binding fragment thereof comprises V_LWa and V_HGa. In some embodiments, an antibody or antibody binding fragment thereof comprises V_LXa and V_HGa. In some embodiments, an antibody or antibody binding fragment thereof comprises V_LYa and V_HGa. In some embodiments, an antibody or antibody binding fragment thereof comprises V_LZa and V_HGa. In some embodiments, an antibody or antibody binding fragment thereof comprises V_LABa and V_HGa.

[illegible]

thereof comprises V_LWa and V_HHa. In some embodiments, an antibody or antibody binding fragment thereof comprises V_LXa and V_HHa. In some embodiments, an antibody or antibody binding fragment thereof comprises V_LYa and V_HHa. In some embodiments, an antibody or antibody binding fragment thereof comprises V_LZa and V_HHa. In some embodiments, an antibody or antibody binding fragment thereof comprises V_LABa and V_HHa.

[illegible]

comprises V_LXa and V_HIa. In some embodiments, an antibody or antibody binding fragment thereof comprises V_LYa and V_HIa. In some embodiments, an antibody or antibody binding fragment thereof comprises V_LZa and V_HIa. In some embodiments, an antibody or antibody binding fragment thereof comprises V_LABa and V_HIa.

[illegible]

binding fragment thereof comprises V_LZa and V_HLa. In some embodiments, an antibody or antibody binding fragment thereof comprises V_LABa and V_HLa.

[illegible]

antibody binding fragment thereof comprises V_LZa and V_HNa. In some embodiments, an antibody or antibody binding fragment thereof comprises V_LABa and V_HNa.

[illegible]

binding fragment thereof comprises V_LZa and V_HPa. In some embodiments, an antibody or antibody binding fragment thereof comprises V_LABa and V_HPa.

[illegible]

binding fragment thereof comprises V_LZa and V_HTa. In some embodiments, an antibody or antibody binding fragment thereof comprises V_LABa and V_HTa.

[illegible]

antibody binding fragment thereof comprises V_LZa and V_HUa. In some embodiments, an antibody or antibody binding fragment thereof comprises V_LABa and V_HUa.

[illegible]

antibody binding fragment thereof comprises V_LZa and V_HVa. In some embodiments, an antibody or antibody binding fragment thereof comprises V_LABa and V_HVa.

[illegible]

antibody binding fragment thereof comprises V_LZa and V_HYa. In some embodiments, an antibody or antibody binding fragment thereof comprises V_LABa and V_HYa.

[illegible]

binding fragment thereof comprises V_LZa and V_HZa . In some embodiments, an antibody or antibody binding fragment thereof comprises V_LABa and V_HZa .

[illegible]

some embodiments, an antibody or antibody binding fragment thereof comprises V_LABa and V_HABa.

[00204] The equivalent CDRs may also be used from the CHOTHIA designation. For clarity, the following tables are provided depicting non-limiting exemplary combinations of light chain (Table 9) and heavy chain (Table 10) CDRs using IMGT designations:

Table 9

Combination	LCDR1	LCDR2	LCDR3
V _L Ab	SEQ ID NO: 29	SEQ ID NO: 30	SEQ ID NO: 31
V _L Bb	SEQ ID NO: 29	SEQ ID NO: 30	SEQ ID NO: 36
V _L Cb	SEQ ID NO: 29	SEQ ID NO: 30	SEQ ID NO: 41
V _L Db	SEQ ID NO: 29	SEQ ID NO: 35	SEQ ID NO: 31
V _L Eb	SEQ ID NO: 29	SEQ ID NO: 35	SEQ ID NO: 36
V _L Fb	SEQ ID NO: 29	SEQ ID NO: 35	SEQ ID NO: 41
V _L Gb	SEQ ID NO: 29	SEQ ID NO: 40	SEQ ID NO: 31
V _L Hb	SEQ ID NO: 29	SEQ ID NO: 40	SEQ ID NO: 36
V _L Ib	SEQ ID NO: 29	SEQ ID NO: 40	SEQ ID NO: 41
V _L Jb	SEQ ID NO: 34	SEQ ID NO: 30	SEQ ID NO: 31
V _L Kb	SEQ ID NO: 34	SEQ ID NO: 30	SEQ ID NO: 36
V _L Lb	SEQ ID NO: 34	SEQ ID NO: 30	SEQ ID NO: 41
V _L Mb	SEQ ID NO: 34	SEQ ID NO: 35	SEQ ID NO: 31
V _L Nb	SEQ ID NO: 34	SEQ ID NO: 35	SEQ ID NO: 36
V _L Ob	SEQ ID NO: 34	SEQ ID NO: 35	SEQ ID NO: 41
V _L Pb	SEQ ID NO: 34	SEQ ID NO: 40	SEQ ID NO: 31
V _L Qb	SEQ ID NO: 34	SEQ ID NO: 40	SEQ ID NO: 36
V _L Rb	SEQ ID NO: 34	SEQ ID NO: 40	SEQ ID NO: 41
V _L Sb	SEQ ID NO: 39	SEQ ID NO: 30	SEQ ID NO: 31
V _L Tb	SEQ ID NO: 39	SEQ ID NO: 30	SEQ ID NO: 36
V _L Ub	SEQ ID NO: 39	SEQ ID NO: 30	SEQ ID NO: 41
V _L Vb	SEQ ID NO: 39	SEQ ID NO: 35	SEQ ID NO: 31
V _L Wb	SEQ ID NO: 39	SEQ ID NO: 35	SEQ ID NO: 36

V _L Xb	SEQ ID NO: 39	SEQ ID NO: 35	SEQ ID NO: 41
V _L Yb	SEQ ID NO: 39	SEQ ID NO: 40	SEQ ID NO: 31
V _L Zb	SEQ ID NO: 39	SEQ ID NO: 40	SEQ ID NO: 36
V _L ABb	SEQ ID NO: 39	SEQ ID NO: 40	SEQ ID NO: 41

Table 10

Combination	HCDR1	HCDR2	HCDR3
V _H Ab	SEQ ID NO: 27	SEQ ID NO: 28	SEQ ID NO: 11
V _H Bb	SEQ ID NO: 27	SEQ ID NO: 28	SEQ ID NO: 17
V _H Cb	SEQ ID NO: 27	SEQ ID NO: 28	SEQ ID NO: 23
V _H Db	SEQ ID NO: 27	SEQ ID NO: 33	SEQ ID NO: 11
V _H Eb	SEQ ID NO: 27	SEQ ID NO: 33	SEQ ID NO: 17
V _H Fb	SEQ ID NO: 27	SEQ ID NO: 33	SEQ ID NO: 23
V _H Gb	SEQ ID NO: 27	SEQ ID NO: 38	SEQ ID NO: 11
V _H Hb	SEQ ID NO: 27	SEQ ID NO: 38	SEQ ID NO: 17
V _H Ib	SEQ ID NO: 27	SEQ ID NO: 38	SEQ ID NO: 23
V _H Jb	SEQ ID NO: 32	SEQ ID NO: 28	SEQ ID NO: 11
V _H Kb	SEQ ID NO: 32	SEQ ID NO: 28	SEQ ID NO: 17
V _H Lb	SEQ ID NO: 32	SEQ ID NO: 28	SEQ ID NO: 23
V _H Mb	SEQ ID NO: 32	SEQ ID NO: 33	SEQ ID NO: 11
V _H Nb	SEQ ID NO: 32	SEQ ID NO: 33	SEQ ID NO: 17
V _H Ob	SEQ ID NO: 32	SEQ ID NO: 33	SEQ ID NO: 23
V _H Pb	SEQ ID NO: 32	SEQ ID NO: 38	SEQ ID NO: 11
V _H Qb	SEQ ID NO: 32	SEQ ID NO: 38	SEQ ID NO: 17
V _H Rb	SEQ ID NO: 32	SEQ ID NO: 38	SEQ ID NO: 23
V _H Sb	SEQ ID NO: 37	SEQ ID NO: 28	SEQ ID NO: 11
V _H Tb	SEQ ID NO: 37	SEQ ID NO: 28	SEQ ID NO: 17
V _H Ub	SEQ ID NO: 37	SEQ ID NO: 28	SEQ ID NO: 23
V _H Vb	SEQ ID NO: 37	SEQ ID NO: 33	SEQ ID NO: 11
V _H Wb	SEQ ID NO: 37	SEQ ID NO: 33	SEQ ID NO: 17

V _H Xb	SEQ ID NO: 37	SEQ ID NO: 33	SEQ ID NO: 23
V _H Yb	SEQ ID NO: 37	SEQ ID NO: 38	SEQ ID NO: 11
V _H Zb	SEQ ID NO: 37	SEQ ID NO: 38	SEQ ID NO: 17
V _H ABb	SEQ ID NO: 37	SEQ ID NO: 38	SEQ ID NO: 23

[00205] In some embodiments, an antibody or antibody binding fragment thereof, comprises: (i) a light chain having any one of the foregoing recited combinations of LCDR1, LCDR2, and LCDR3 sequences; and (ii) a heavy chain having any one of the foregoing recited combinations of HCDR1, HCDR2, and HCDR3 sequences. The following combinations are provided with reference to Table 9 and Table 10 above. Thus, for example, an antibody or antibody binding fragment thereof comprising V_LAb and V_HAb is understood to comprise a light chain having a LCDR1 of SEQ ID NO: 29, a LCDR2 of SEQ ID NO: 30, a LCDR3 of SEQ ID NO: 31, a HCDR1 of SEQ ID NO: 27, a HCDR2 of SEQ ID NO: 28, and a HCDR3 of SEQ ID NO: 11.

[00206] Accordingly, in some embodiments, an antibody or antibody binding fragment thereof comprises V_LAb and V_HAb. In some embodiments, an antibody or antibody binding fragment thereof comprises V_LBb and V_HAb. In some embodiments, an antibody or antibody binding fragment thereof comprises V_LCb and V_HAb. In some embodiments, an antibody or antibody binding fragment thereof comprises V_LDb and V_HAb. In some embodiments, an antibody or antibody binding fragment thereof comprises V_LEb and V_HAb. In some embodiments, an antibody or antibody binding fragment thereof comprises V_LFb and V_HAb. In some embodiments, an antibody or antibody binding fragment thereof comprises V_LGb and V_HAb. In some embodiments, an antibody or antibody binding fragment thereof comprises V_LHb and V_HAb. In some embodiments, an antibody or antibody binding fragment thereof comprises V_LIb and V_HAb. In some embodiments, an antibody or antibody binding fragment thereof comprises V_LJb and V_HAb. In some embodiments, an antibody or antibody binding fragment thereof comprises V_LKb and V_HAb. In some embodiments, an antibody or antibody binding fragment thereof comprises V_LLb and V_HAb. In some embodiments, an antibody or antibody binding fragment thereof comprises V_LMb and V_HAb. In some embodiments, an antibody or antibody binding fragment thereof comprises V_LNb and V_HAb. In some embodiments, an antibody or antibody binding fragment thereof comprises V_LOb and V_HAb. In some embodiments, an antibody or antibody binding fragment thereof comprises V_LPb and V_HAb. In some

[illegible]

comprises V_{LUb} and V_{HGb}. In some embodiments, an antibody or antibody binding fragment thereof comprises V_{LVb} and V_{HGb}. In some embodiments, an antibody or antibody binding fragment thereof comprises V_{LWb} and V_{HGb}. In some embodiments, an antibody or antibody binding fragment thereof comprises V_{LXb} and V_{HGb}. In some embodiments, an antibody or antibody binding fragment thereof comprises V_{LYb} and V_{HGb}. In some embodiments, an antibody or antibody binding fragment thereof comprises V_{LZb} and V_{HGb}. In some embodiments, an antibody or antibody binding fragment thereof comprises V_{LABb} and V_{HGb}.

[illegible]

thereof comprises V_LVb and V_HHb. In some embodiments, an antibody or antibody binding fragment thereof comprises V_LWb and V_HHb. In some embodiments, an antibody or antibody binding fragment thereof comprises V_LXb and V_HHb. In some embodiments, an antibody or antibody binding fragment thereof comprises V_LYb and V_HHb. In some embodiments, an antibody or antibody binding fragment thereof comprises V_LZb and V_HHb. In some embodiments, an antibody or antibody binding fragment thereof comprises V_LABb and V_HHb.

[illegible]

comprises V_LWb and V_HIb. In some embodiments, an antibody or antibody binding fragment thereof comprises V_LXb and V_HIb. In some embodiments, an antibody or antibody binding fragment thereof comprises V_LYb and V_HIb. In some embodiments, an antibody or antibody binding fragment thereof comprises V_LZb and V_HIb. In some embodiments, an antibody or antibody binding fragment thereof comprises V_LABb and V_HIb.

[illegible]

antibody binding fragment thereof comprises V_LZb and V_HLb. In some embodiments, an antibody or antibody binding fragment thereof comprises V_LABb and V_HLb.

[illegible]

some embodiments, an antibody or antibody binding fragment thereof comprises V_LABb and V_HMb.

[illegible]

antibody or antibody binding fragment thereof comprises V_LZb and V_HNb. In some embodiments, an antibody or antibody binding fragment thereof comprises V_LABb and V_HNb.

[illegible]

antibody or antibody binding fragment thereof comprises V_LZb and V_HOb. In some embodiments, an antibody or antibody binding fragment thereof comprises V_LABb and V_HOb.

[illegible]

antibody binding fragment thereof comprises V_LZb and V_HPb. In some embodiments, an antibody or antibody binding fragment thereof comprises V_LABb and V_HPb.

[illegible]

antibody or antibody binding fragment thereof comprises V_LZb and V_HQb. In some embodiments, an antibody or antibody binding fragment thereof comprises V_LABb and V_HQb.

[illegible]

antibody or antibody binding fragment thereof comprises V_LZb and V_HRb. In some embodiments, an antibody or antibody binding fragment thereof comprises V_LABb and V_HRb.

[illegible]

antibody binding fragment thereof comprises V_LZb and V_HSb. In some embodiments, an antibody or antibody binding fragment thereof comprises V_LABb and V_HSb.

[illegible]

antibody binding fragment thereof comprises V_LZb and V_HTb. In some embodiments, an antibody or antibody binding fragment thereof comprises V_LABb and V_HTb.

[illegible]

antibody or antibody binding fragment thereof comprises V_LZb and V_HUb. In some embodiments, an antibody or antibody binding fragment thereof comprises V_LABb and V_HUb.

[illegible]

antibody or antibody binding fragment thereof comprises V_LZb and V_HVb. In some embodiments, an antibody or antibody binding fragment thereof comprises V_LABb and V_HVb.

[illegible]

some embodiments, an antibody or antibody binding fragment thereof comprises V_LABb and V_HWb.

[illegible]

antibody or antibody binding fragment thereof comprises V_LZb and V_HXb. In some embodiments, an antibody or antibody binding fragment thereof comprises V_LABb and V_HXb.

[illegible]

antibody binding fragment thereof comprises V_LZb and V_HZb. In some embodiments, an antibody or antibody binding fragment thereof comprises V_LABb and V_HZb.

[illegible]

In some embodiments, an antibody or antibody binding fragment thereof comprises V_LABb and V_HABb.

[00233] In some embodiments, the light chain variable region L_{CDR}1 is replaced with any of the other light chain L_{CDR}1 sequences. In some embodiments, the light chain variable region L_{CDR}2 is replaced with any of the other light chain L_{CDR}2 sequences. In some embodiments, the light chain variable region L_{CDR}3 is replaced with any of the other light chain L_{CDR}3 sequences. In some embodiments, the heavy chain variable region H_{CDR}1 is replaced with any of the other heavy chain H_{CDR}1 sequences. In some embodiments, the heavy chain variable region H_{CDR}2 is replaced with any of the other heavy chain H_{CDR}2 sequences. In some embodiments, the heavy chain variable region H_{CDR}3 is replaced with any of the other heavy chain H_{CDR}3 sequences.

[00234] In some embodiments, any L_{CDR}1, L_{CDR}2, and L_{CDR}3 pairing from any of the Kabat, IMGT, or CHOTHIA designations may be paired with any H_{CDR}1, H_{CDR}2, and H_{CDR}3 pairing from any of the Kabat, IMGT, or CHOTHIA designations. For example, using the designations as recited in Tables 6 - 10, an antibody or antibody fragment may comprise V_LA and any one of V_HA, V_HB, V_HC, V_HD, V_HE, V_HF, V_HG, V_HH, V_HI, V_HJ, V_HK, V_HL, V_HM, V_HN, V_HO, V_HP, V_HQ, V_HR, V_HS, V_HT, V_HU, V_HV, V_HW, V_HX, V_HY, V_HZ, V_HAB, V_HAa, V_HBa, V_HCa, V_HDa, V_HEa, V_HFa, V_HGa, V_HHa, V_HIa, V_HJa, V_HKa, V_HLa, V_HMa, V_HNa, V_HOa, V_HPa, V_HQa, V_HRa, V_HSa, V_HTa, V_HUa, V_HVa, V_HWa, V_HXa, V_HYa, V_HZa, V_HABa, V_HAb, V_HBb, V_HCb, V_HDb, V_HEb, V_HFb, V_HGb, V_HHb, V_HIb, V_HJb, V_HKb, V_HLb, V_HMb, V_HNb, V_HOb, V_HPb, V_HQb, V_HRb, V_HSb, V_HTb, V_HUb, V_HVb, V_HWb, V_HXb, V_HYb, V_HZb, or V_HABb. It is to be understood that the above example is for illustrative purposes only and is not meant to be limiting in any way. Thus, it is to be understood that the above embodiment recited for V_LA is also true for V_LB, V_LC, V_LD, V_LE, V_LF, V_LG, V_LH, V_LI, V_LJ, V_LK, V_LL, V_LM, V_LN, V_LO, V_LP, V_LQ, V_LR, V_LS, V_LT, V_LU, V_LV, V_LW, V_LX, V_LY, V_LZ, V_LAB, V_LAa, V_LBa, V_LCa, V_LDa, V_LEa, V_LFa, V_LGa, V_LHa, V_LIa, V_LJa, V_LKa, V_LLa, V_LMa, V_LNa, V_LOa, V_LPa, V_LQa, V_LRa, V_LSa, V_LTa, V_LUa, V_LVa, V_LWa, V_LXa, V_LYa, V_LZa, V_LABa, V_LAb, V_LBb, V_LCb, V_LDb, V_LEb, V_LFb, V_LGb, V_LHb, V_LIb, V_LJb, V_LKb, V_LLb, V_LMb, V_LNb, V_LOb, V_LPb, V_LQb, V_LRb, V_LSb, V_LTb, V_LUb, V_LVb, V_LWb, V_LXb, V_LYb, V_LZb, and V_LABb, and all such combinations are within the scope of the present disclosure.

[00235] In some embodiments, an antibody or antigen-binding fragment thereof is provided, wherein the HCDR1, HCDR2, and HCDR3 are selected from SEQ ID NO: 9, SEQ ID NO: 10, and SEQ ID NO: 11, respectively, from SEQ ID NO: 27, SEQ ID NO: 28, and SEQ ID NO: 11, respectively, or from SEQ ID NO: 42, SEQ ID NO: 43, and SEQ ID NO: 44, respectively, and the LCDR1, LCDR2, and LCDR3 are selected from SEQ ID NO: 12, SEQ ID NO: 13, and SEQ ID NO: 14, respectively, from SEQ ID NO: 29, SEQ ID NO: 30, and SEQ ID NO: 31, respectively, or from SEQ ID NO: 45, SEQ ID NO: 30, and SEQ ID NO: 14 respectively.

[00236] In some embodiments, an antibody or antigen-binding fragment thereof is provided, wherein the HCDR1, HCDR2, and HCDR3 are selected from SEQ ID NO: 15, SEQ ID NO: 16, and SEQ ID NO: 17, respectively, from SEQ ID NO: 32, SEQ ID NO: 33, and SEQ ID NO: 17, respectively, or from SEQ ID NO: 46, SEQ ID NO: 47, and SEQ ID NO: 48, respectively, and the LCDR1, LCDR2, and LCDR3 are selected from SEQ ID NO: 18, SEQ ID NO: 19, and SEQ ID NO: 20, respectively, from SEQ ID NO: 34, SEQ ID NO: 35, and SEQ ID NO: 36, respectively, or from SEQ ID NO: 49, SEQ ID NO: 35, and SEQ ID NO: 20 respectively.

[00237] In some embodiments, an antibody or antigen-binding fragment thereof is provided, wherein the HCDR1, HCDR2, and HCDR3 are selected from SEQ ID NO: 21, SEQ ID NO: 22, and SEQ ID NO: 23, respectively, from SEQ ID NO: 37, SEQ ID NO: 38, and SEQ ID NO: 23, respectively, or from SEQ ID NO: 50, SEQ ID NO: 51, and SEQ ID NO: 52, respectively, and the LCDR1, LCDR2, and LCDR3 are selected from SEQ ID NO: 24, SEQ ID NO: 25, and SEQ ID NO: 26, respectively, from SEQ ID NO: 39, SEQ ID NO: 40, and SEQ ID NO: 41, respectively, or from SEQ ID NO: 53, SEQ ID NO: 40, and SEQ ID NO: 26 respectively.

[00238] In some embodiments, the antibody comprises a heavy chain variable region peptide having one of the following sequences, or a variant thereof:

Table 11:

SEQ ID NO:	AB ID NO.	Sequence
1	MAB1	QVQLVQSGAEVKKPGASVKVSCKVSGDTLTLSMHWVRQ APGKGLEWMGTFDPEEGETIYAQKFQGRVTMTEDTSTD TAYMELSSLRSEDTAVYYCVTEGLAGRPFDSWGQGT LTVTVSS
3	MAB2	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAP GKGLEWVSYISRSGSTKYYADSVKGRFTISRDN AKNSLYLQMNSLRAEDTAVYYCARDYALDYWGQGT LTVTVSS

SEQ ID NO:	AB ID NO.	Sequence
5	MAB3	EVQLVESGGGVVPRPGGSLRLSCAASGFTFDDYGMSWVRQA PGKGLEWVSGINWEGGSTGYADSVKGRFTISRDNKNSLYL QMNSLRAEDTALYYCARDEQLGGNYYYYYYMDVWGKGT TVTVSS

[00239] In some embodiments, the antibody comprises a light chain variable region peptide having one of the following sequences, or a variant thereof:

Table 12:

SEQ ID NO:	AB ID NO.	Sequence
2	MAB1	DIQMTQSPSTLSASVGDRVTITCRASQSISSWLAWYQQKPGK APKLLIYKASSLESGVPSRFSGSGSGTEFTLTISLQPDFFATY YCQQYNSYSWTFGQGTKVEIK
4	MAB2	DIQMTQSPSSLSASVGDRVTITCQASQDISNYLNWYQQKPG KAPKLLIYDASNLETGVPSRFSGSGSGTDFTFITISLQPEDAT YYCQQYEDLPLTFGGGTKVEIK
6	MAB3	DIQMTQSPSSLSASVGDRVTITCRASQGIRNDLGWYQQKPG KAPKRLIYTASNLSGVPSRFSGSGSGTEFTLTISLQPEDFAT YYCLQYNSYPLTFGGGTKVEIK

[00240] In some embodiments, an antibody, or antigen binding fragment thereof, comprises a sequence selected from one or more of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, or any variants thereof.

[00241] In some embodiments, an antibody, or antigen binding fragment thereof, comprises a V_H peptide of SEQ ID NO: 1, 3, or 5, or any variant thereof. In some embodiments, an antibody, or antigen binding fragment thereof, comprises a V_H peptide having at least 85% identity to SEQ ID NO: 1, 3, or 5. In some embodiments, an antibody, or antigen binding fragment thereof, comprises a V_H peptide having at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 1, 3, or 5. In some embodiments, an antibody, or antigen binding fragment thereof, comprises a V_H peptide of SEQ ID NO: 1, 3, or 5. In some embodiments, an antibody, or antigen binding fragment thereof, comprises a V_H peptide of SEQ ID NO: 1. In some embodiments, an antibody, or antigen binding fragment thereof, comprises a V_H peptide having at least 85% identity to SEQ ID NO: 1. In some embodiments, an antibody, or antigen binding fragment thereof, comprises a V_H peptide having at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity to

SEQ ID NO: 1. In some embodiments, an antibody, or antigen binding fragment thereof, comprises a V_H peptide of SEQ ID NO: 3. In some embodiments, an antibody, or antigen binding fragment thereof, comprises a V_H peptide having at least 85% identity to SEQ ID NO: 3. In some embodiments, an antibody, or antigen binding fragment thereof, comprises a V_H peptide having at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 3. In some embodiments, an antibody, or antigen binding fragment thereof, comprises a V_H peptide of SEQ ID NO: 5. In some embodiments, an antibody, or antigen binding fragment thereof, comprises a V_H peptide having at least 85% identity to SEQ ID NO: 5. In some embodiments, an antibody, or antigen binding fragment thereof, comprises a V_H peptide having at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 5. In some embodiments, an antibody, or antigen binding fragment thereof, comprises a V_L peptide of SEQ ID NO: 2, 4, or 6, or any variant thereof. In some embodiments, an antibody, or antigen binding fragment thereof, comprises a V_L peptide having at least 85% identity to SEQ ID NO: 2, 4, or 6. In some embodiments, an antibody, or antigen binding fragment thereof, comprises a V_L peptide having at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 2, 4, or 6. In some embodiments, an antibody, or antigen binding fragment thereof, comprises a V_L peptide of SEQ ID NO: 2, 4, or 6. In some embodiments, an antibody, or antigen binding fragment thereof, comprises a V_L peptide of SEQ ID NO: 2. In some embodiments, an antibody, or antigen binding fragment thereof, comprises a V_L peptide having at least 85% identity to SEQ ID NO: 2. In some embodiments, an antibody, or antigen binding fragment thereof, comprises a V_L peptide having at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 2. In some embodiments, an antibody, or antigen binding fragment thereof, comprises a V_L peptide of SEQ ID NO: 4. In some embodiments, an antibody, or antigen binding fragment thereof, comprises a V_L peptide having at least 85% identity to SEQ ID NO: 4. In some embodiments, an antibody, or antigen binding fragment thereof, comprises a V_L peptide having at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 4. In some embodiments, an antibody, or antigen binding fragment thereof, comprises a V_L peptide of SEQ ID NO: 6. In some embodiments, an antibody, or antigen binding fragment thereof, comprises a V_L peptide having at least 85% identity to SEQ ID NO: 6. In some

embodiments, an antibody, or antigen binding fragment thereof, comprises a V_L peptide having at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 6. In some embodiments, an antibody, or antigen binding fragment thereof, comprises a V_H peptide and a V_L peptide, wherein the V_H peptide comprises a sequence of SEQ ID NO: 1, 3, or 5 or a variant thereof; and the V_L peptide comprises a sequence of SEQ ID NO: 2, 4, or 6 or a variant thereof. In some embodiments, an antibody, or antigen binding fragment thereof, comprises a V_H peptide and a V_L peptide, wherein the V_H peptide has at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 1, 3, or 5; and the V_L peptide has at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 2, 4, or 6. In some of these embodiments, the V_H peptide comprises a sequence of SEQ ID NO: 1, 3, or 5; and the V_L peptide comprises a sequence of SEQ ID NO: 2, 4, or 6.

[00242] In some embodiments, the heavy chain of the antibody or antigen binding fragment thereof comprises a heavy chain variable region having at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identity to SEQ ID NO: 1, wherein the antibody or antigen binding fragment thereof maintains a HCDR1 sequence of SEQ ID NO: 9, SEQ ID NO: 27, or SEQ ID NO: 42, maintains a HCDR2 sequence of SEQ ID NO: 10, SEQ ID NO: 28, or SEQ ID NO: 43, maintains a HCDR3 sequence of SEQ ID NO: 11 or SEQ ID NO: 44, maintains a LCDR1 sequence of SEQ ID NO: 12, SEQ ID NO: 29, or SEQ ID NO: 45, maintains a LCDR2 sequence of SEQ ID NO: 13, or SEQ ID NO: 30, and maintains a LCDR3 sequence SEQ ID NO: 14, or SEQ ID NO: 31.

[00243] In some embodiments, the heavy chain of the antibody or antigen binding fragment thereof comprises a heavy chain variable region having at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identity to SEQ ID NO: 3, wherein the antibody or antigen binding fragment thereof maintains a HCDR1 sequence of SEQ ID NO: 15, SEQ ID NO: 32, or SEQ ID NO: 46, maintains a HCDR2 sequence of SEQ ID NO: 16, SEQ ID NO: 33, or SEQ ID NO: 47, maintains a HCDR3 sequence of SEQ ID NO: 17 or SEQ ID NO: 48, maintains a LCDR1 sequence of SEQ ID NO: 18, SEQ ID NO: 34, or SEQ ID NO: 49, maintains a LCDR2 sequence of SEQ ID NO: 19, or SEQ ID NO: 35, and maintains a LCDR3 sequence SEQ ID NO: 20, or SEQ ID NO: 36.

[00244] In some embodiments, the heavy chain of the antibody or antigen binding fragment thereof comprises a heavy chain variable region having at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identity to SEQ ID NO: 5, wherein the antibody or antigen binding fragment thereof maintains a HCDR1 sequence of SEQ ID NO: 21, SEQ ID NO: 37, or SEQ ID NO: 50, maintains a HCDR2 sequence of SEQ ID NO: 22, SEQ ID NO: 38, or SEQ ID NO: 51, maintains a HCDR3 sequence of SEQ ID NO: 23 or SEQ ID NO: 52, maintains a LCDR1 sequence of SEQ ID NO: 24, SEQ ID NO: 39, or SEQ ID NO: 53, maintains a LCDR2 sequence of SEQ ID NO: 25, or SEQ ID NO: 40, and maintains a LCDR3 sequence SEQ ID NO: 26, or SEQ ID NO: 41.

[00245] In some embodiments, the light chain of the antibody or antigen binding fragment thereof comprises a light chain variable region having at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identity to SEQ ID NO: 2, wherein the antibody or antigen binding fragment thereof maintains a HCDR1 sequence of SEQ ID NO: 9, SEQ ID NO: 27, or SEQ ID NO: 42, maintains a HCDR2 sequence of SEQ ID NO: 10, SEQ ID NO: 28, or SEQ ID NO: 43, maintains a HCDR3 sequence of SEQ ID NO: 11 or SEQ ID NO: 44, maintains a LCDR1 sequence of SEQ ID NO: 12, SEQ ID NO: 29, or SEQ ID NO: 45, maintains a LCDR2 sequence of SEQ ID NO: 13, or SEQ ID NO: 30, and maintains a LCDR3 sequence SEQ ID NO: 14, or SEQ ID NO: 31.

[00246] In some embodiments, the light chain of the antibody or antigen binding fragment thereof comprises a light chain variable region having at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identity to SEQ ID NO: 4, wherein the antibody or antigen binding fragment thereof maintains a HCDR1 sequence of SEQ ID NO: 15, SEQ ID NO: 32, or SEQ ID NO: 46, maintains a HCDR2 sequence of SEQ ID NO: 16, SEQ ID NO: 33, or SEQ ID NO: 47, maintains a HCDR3 sequence of SEQ ID NO: 17 or SEQ ID NO: 48, maintains a LCDR1 sequence of SEQ ID NO: 18, SEQ ID NO: 34, or SEQ ID NO: 49, maintains a LCDR2 sequence of SEQ ID NO: 19, or SEQ ID NO: 35, and maintains a LCDR3 sequence SEQ ID NO: 20, or SEQ ID NO: 36.

[00247] In some embodiments, the light chain of the antibody or antigen binding fragment thereof comprises a light chain variable region having at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identity to SEQ ID NO: 6, wherein the antibody or antigen binding fragment thereof maintains a HCDR1 sequence of SEQ ID NO:

21, SEQ ID NO: 37, or SEQ ID NO: 50, maintains a HCDR2 sequence of SEQ ID NO: 22, SEQ ID NO: 38, or SEQ ID NO: 51, maintains a HCDR3 sequence of SEQ ID NO: 23 or SEQ ID NO: 52, maintains a LCDR1 sequence of SEQ ID NO: 24, SEQ ID NO: 39, or SEQ ID NO: 53, maintains a LCDR2 sequence of SEQ ID NO: 25, or SEQ ID NO: 40, and maintains a LCDR3 sequence SEQ ID NO: 26, or SEQ ID NO: 41.

[00248] The VH and the VL sequences can be in any format, including, but not limited to an scFv format where the VH and VL regions are linked with a peptide linker. Examples of peptide linkers that can be used to link various peptides provided for herein include, but are not limited to: (GGGGS)_n (SEQ ID NO: 54); (GGGGA)_n (SEQ ID NO: 55), or any combination thereof, wherein each n is independently 1-5. In some embodiments, each n is, independently, 1. In some embodiments, each n is, independently, 2. In some embodiments, each n is, independently, 3. In some embodiments, each n is, independently, 4. In some embodiments, each n is, independently, 5. In some embodiments, the variable regions are not linked with a peptide linker. In some embodiments, the antibody comprises SEQ ID NO: 1 and SEQ ID NO: 2. In some embodiments, the antibody comprises SEQ ID NO: 3 and SEQ ID NO: 4. In some embodiments, the antibody comprises SEQ ID NO: 5 and SEQ ID NO: 6.

[00249] As provided for herein, the different peptides (V_H or V_L) described herein can be linked with a peptide linker or not linked with a peptide linker and instead form a contiguous sequence. In some embodiments, the heavy chain variable region and the light chain variable region are not linked by a linker. In some embodiments, the heavy chain variable region and the light chain variable region are linked via a peptide linker. In some embodiments, the peptide linker comprises a sequence of (GGGGS)_n (SEQ ID NO: 54); (GGGGA)_n (SEQ ID NO: 55), or any combination thereof, wherein each n is independently 1-5. In some embodiments, each n is, independently, 1. In some embodiments, each n is, independently, 2. In some embodiments, each n is, independently, 3. In some embodiments, each n is, independently, 4. In some embodiments, each n is, independently, 5. The linked peptide format can be represented by a formula of V_H-Z-V_L or V_L-Z-V_H, wherein Z is the peptide linker. In some embodiments, Z is (GGGGS)_n (SEQ ID NO: 54); (GGGGA)_n (SEQ ID NO: 55), or any combination thereof, wherein each n is independently 1-5. In some embodiments, each n is, independently, 1. In some embodiments, each n is, independently, 2. In some embodiments, each n is, independently,

3. In some embodiments, each n is, independently, 4. In some embodiments, each n is, independently, 5.

[00250] In some embodiments, the V_H and V_L polypeptides are linked to a Fc region, such as “IgG4 S228P L235E LS” or “IgG4 S228P L235E YTE”. In some embodiments, the Fc region is as provided for herein. In some embodiments, the Fc region is “IgG4 S228P L235E LS”. In some embodiments, the Fc region is “IgG4 S228 L235E YTE”.

[00251] In some embodiments, an antibody, or antigen binding fragment thereof, comprises a V_H peptide and a V_L peptide, wherein the V_H peptide comprises a sequence that is at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to a sequence of SEQ ID NO: 1, 3, or 5, and the V_L peptide comprises a sequence that is at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to a sequence of SEQ ID NO: 2, 4, or 6. In some embodiments, the V_H peptide comprises a sequence that is at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to a sequence of SEQ ID NO: 1. In some embodiments, the V_H peptide comprises a sequence of SEQ ID NO: 1. In some embodiments, the V_H peptide comprises a sequence that is at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to a sequence of SEQ ID NO: 3. In some embodiments, the V_H peptide comprises a sequence of SEQ ID NO: 3. In some embodiments, the V_H peptide comprises a sequence that is at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to a sequence of SEQ ID NO: 5. In some embodiments, the V_H peptide comprises a sequence of SEQ ID NO: 5. In some embodiments, the V_L peptide comprises a sequence that is at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to a sequence of SEQ ID NO: 2. In some embodiments, the V_L peptide comprises a sequence of SEQ ID NO: 2. In some embodiments, the V_L peptide comprises a sequence that is at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to a sequence of SEQ ID NO: 4. In some embodiments, the V_L peptide comprises a sequence of SEQ ID NO: 4. In some embodiments, the V_L peptide comprises a sequence that is at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to a sequence of SEQ ID NO: 6. In some embodiments, the V_L peptide comprises a sequence of SEQ ID NO: 6.

[00252] In some embodiments, an antibody, or antigen binding fragment thereof, comprises a V_H peptide and a V_L peptide, wherein the V_H peptide comprises a sequence that is at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to a sequence of SEQ ID NO: 1, 3, or 5, and the V_L peptide comprises a sequence that is at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to a sequence of SEQ ID NO: 2, 4, or 6 provided that the V_H peptide and a V_L peptide comprises a light chain LCDR having a sequence of SEQ ID NO: 12, 13, 14, 18, 19, 20, 24, 25, 26, 29, 30, 31, 34, 35, 36, 39, 40, 41, 45, 49, or 53; and/or a heavy chain HCDR having a sequence of SEQ ID NO: 9, 10, 11, 15, 16, 17, 21, 22, 23, 27, 28, 32, 33, 37, 38, 42, 43, 44, 46, 47, 48, 50, 51, or 52. In some embodiments, the CDRs in the V_H or V_L chain are as set forth in the combinations provided for herein.

[00253] In some embodiments, an antibody, or antigen binding fragment thereof, comprises a V_H peptide and a V_L peptide, wherein the V_H peptide comprises a sequence that is at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to a sequence of SEQ ID NO: 1, 3, or 5, and the V_L peptide comprises a sequence that is at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to a sequence of SEQ ID NO: 2, 4, or 6 provided that the V_L peptide comprises a LCDR1 having a sequence selected from SEQ ID NO: 12, 18, 24, 29, 34, 39, 45, 49, or 53; a LCDR2 having a sequence selected from SEQ ID NO: 13, 19, 25, 30, 35, or 40; and a LCDR3 having a sequence selected from SEQ ID NO: 14, 20, 26, 31, 36, or 41; and the V_H peptide comprises a HCDR1 having a sequence selected from SEQ ID NO: 9, 15, 21, 27, 32, 37, 42, 46, or 50; a HCDR2 having a sequence selected from SEQ ID NO: 10, 16, 22, 28, 33, 38, 43, 47, or 51; and a HCDR3 having a sequence selected from SEQ ID NO: 11, 17, 23, 44, 48, or 52.

[00254] In some embodiments, an antibody, or antigen binding fragment thereof, comprises a V_H peptide and a V_L peptide, wherein the V_H peptide comprises a sequence that is at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to a sequence of SEQ ID NO: 1, 3, or 5, and the V_L peptide comprises a sequence that is at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to a sequence of SEQ ID NO: 2, 4, or 6, provided that the V_L peptide comprises a LCDR1 having a sequence selected from SEQ ID NO: 12, 18, 24, 29, 34, 39, 45, 49, or 53, wherein the LCDR1 comprises at most 1 conservative amino acid substitution, a LCDR2 having a sequence selected

from SEQ ID NO: 13, 19, 25, 30, 35, or 40, wherein the LCDR2 comprises at most 1 conservative amino acid substitution, and a LCDR3 having a sequence selected from SEQ ID NO: 14, 20, 26, 31, 36, or 41, wherein the LCDR3 comprises at most 1 conservative amino acid substitution and the V_H peptide comprises a HCDR1 having a sequence selected from SEQ ID NO: 9, 15, 21, 27, 32, 37, 42, 46, or 50, wherein the HCDR1 comprises at most 1 conservative amino acid substitution, a HCDR2 having a sequence selected from SEQ ID NO: 10, 16, 22, 28, 33, 38, 43, 47, or 51, wherein the HCDR2 comprises at most 1 conservative amino acid substitution, and a HCDR3 having a sequence selected from SEQ ID NO: 11, 17, 23, 44, 48, or 52, wherein the HCDR3 comprises at most 1 conservative amino acid substitution.

[00255] In some embodiments, the antibody or antigen-binding fragment thereof comprises a light chain variable region and a heavy chain variable region, wherein the light chain variable region of the light chain has at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identity to SEQ ID NO: 1, the heavy chain variable region of the heavy chain has at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identity to SEQ ID NO: 2, and wherein the antibody or antigen binding fragment thereof maintains a HCDR1 sequence of SEQ ID NO: 9, SEQ ID NO: 27, or SEQ ID NO: 42, maintains a HCDR2 sequence of SEQ ID NO: 10, SEQ ID NO: 28, or SEQ ID NO: 43, maintains a HCDR3 sequence of SEQ ID NO: 11 or SEQ ID NO: 44, maintains a LCDR1 sequence of SEQ ID NO: 12, SEQ ID NO: 29, or SEQ ID NO: 45, maintains a LCDR2 sequence of SEQ ID NO: 13, or SEQ ID NO: 30, and maintains a LCDR3 sequence SEQ ID NO: 14, or SEQ ID NO: 31.

[00256] In some embodiments, the antibody or antigen-binding fragment thereof comprises a light chain variable region and a heavy chain variable region, wherein the light chain variable region of the light chain has at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identity to SEQ ID NO: 3, the heavy chain variable region of the heavy chain has at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identity to SEQ ID NO: 4, and wherein the antibody or antigen binding fragment thereof maintains a HCDR1 sequence of SEQ ID NO: 15, SEQ ID NO: 32, or SEQ ID NO: 46, maintains a HCDR2 sequence of SEQ ID NO: 16, SEQ ID NO: 33, or SEQ ID NO: 47, maintains a HCDR3 sequence of SEQ ID NO: 17 or SEQ ID NO: 48, maintains a LCDR1 sequence of SEQ ID NO: 18, SEQ ID NO: 34, or SEQ ID NO: 49, maintains a LCDR2

sequence of SEQ ID NO: 19, or SEQ ID NO: 35, and maintains a LCDR3 sequence SEQ ID NO: 20, or SEQ ID NO: 36.

[00257] In some embodiments, the antibody or antigen-binding fragment thereof comprises a light chain variable region and a heavy chain variable region, wherein the light chain variable region of the light chain has at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identity to SEQ ID NO: 5, the heavy chain variable region of the heavy chain has at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identity to SEQ ID NO: 6, and wherein the antibody or antigen binding fragment thereof maintains a HCDR1 sequence of SEQ ID NO: 21, SEQ ID NO: 37, or SEQ ID NO: 50, maintains a HCDR2 sequence of SEQ ID NO: 22, SEQ ID NO: 38, or SEQ ID NO: 51, maintains a HCDR3 sequence of SEQ ID NO: 23 or SEQ ID NO: 52, maintains a LCDR1 sequence of SEQ ID NO: 24, SEQ ID NO: 39, or SEQ ID NO: 53, maintains a LCDR2 sequence of SEQ ID NO: 25, or SEQ ID NO: 40, and maintains a LCDR3 sequence SEQ ID NO: 26, or SEQ ID NO: 41.

[00258] In some embodiments, an antibody, or antigen binding fragment thereof, comprises a V_H peptide and a V_L peptide, wherein the V_H peptide comprises a sequence of SEQ ID NO: 1 and the V_L peptide comprises a sequence of SEQ ID NO: 2.

[00259] In some embodiments, an antibody, or antigen binding fragment thereof, comprises a V_H peptide and a V_L peptide, wherein the V_H peptide comprises a sequence of SEQ ID NO: 1 and the V_L peptide comprises a sequence of SEQ ID NO: 4.

[00260] In some embodiments, an antibody, or antigen binding fragment thereof, comprises a V_H peptide and a V_L peptide, wherein the V_H peptide comprises a sequence of SEQ ID NO: 1 and the V_L peptide comprises a sequence of SEQ ID NO: 6.

[00261] In some embodiments, an antibody, or antigen binding fragment thereof, comprises a V_H peptide and a V_L peptide, wherein the V_H peptide comprises a sequence of SEQ ID NO: 3 and the V_L peptide comprises a sequence of SEQ ID NO: 2.

[00262] In some embodiments, an antibody, or antigen binding fragment thereof, comprises a V_H peptide and a V_L peptide, wherein the V_H peptide comprises a sequence of SEQ ID NO: 3 and the V_L peptide comprises a sequence of SEQ ID NO: 4.

[00263] In some embodiments, an antibody, or antigen binding fragment thereof, comprises a V_H peptide and a V_L peptide, wherein the V_H peptide comprises a sequence of SEQ ID NO: 3 and the V_L peptide comprises a sequence of SEQ ID NO: 6.

[00264] In some embodiments, an antibody, or antigen binding fragment thereof, comprises a V_H peptide and a V_L peptide, wherein the V_H peptide comprises a sequence of SEQ ID NO: 5 and the V_L peptide comprises a sequence of SEQ ID NO: 2.

[00265] In some embodiments, an antibody, or antigen binding fragment thereof, comprises a V_H peptide and a V_L peptide, wherein the V_H peptide comprises a sequence of SEQ ID NO: 5 and the V_L peptide comprises a sequence of SEQ ID NO: 4.

[00266] In some embodiments, an antibody, or antigen binding fragment thereof, comprises a V_H peptide and a V_L peptide, wherein the V_H peptide comprises a sequence of SEQ ID NO: 5 and the V_L peptide comprises a sequence of SEQ ID NO: 6.

[00267] In some embodiments, the antibody comprises a heavy chain as set forth below, which includes the variable region and the constant domain:

Table 13:

SEQ ID NO:	AB ID NO.	Sequence
66	MAB1 with constant domain PE and LS mutations	QVQLVQSGAEVKKPGASVKVSCKVSGDTLTELSMHWVRQ APGKGLEWMGTFDPEEGETIYAQKFQGRVTMTEDTSTD TAYMELSSLRSED TAVYYCVTEGLAGRPFD SWGQGLTVTVSSA STKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVT VSWNS GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLG TKTYTCNV DHKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSV FLFPPKP KDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDG VEVHNA KTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCK VSNKG LPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQ VSLTCLVK GFYPSDIAVEWESNGQPENNYKTTPVLDSDGSF FLYSRLTV DKSRWQEGNVFSCSVLHEALHSHYTQKSLSLSLG
67	MAB1 with with constant domain PE and YTE mutations	QVQLVQSGAEVKKPGASVKVSCKVSGDTLTELSMHWVRQ APGKGLEWMGTFDPEEGETIYAQKFQGRVTMTEDTSTD TAYMELSSLRSED TAVYYCVTEGLAGRPFD SWGQGLTVTVSSA STKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVT VSWNS GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLG TKTYTCNV DHKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSV FLFPPKP KDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDG VEVHNA KTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCK VSNKG LPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQ VSLTCLVK GFYPSDIAVEWESNGQPENNYKTTPVLDSDGSF FLYSRLTV DKSRWQEGNVFSCSVLHEALHSHYTQKSLSLSLG

SEQ ID NO:	AB ID NO.	Sequence
68	MAB2 with constant domain PE and LS mutations	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAP GKGLEWVSYISRSGSTKYYADSVKGRFTISRDNANKNSLYLQ MNSLRAEDTAVYYCARDETDYALDYWGQGTLLTVSSASTK GPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGAL TSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGKTYTCNVDPHK PSNTKVDKR VESKYGPPCPPCPAPEFEGGPSVFLFPPKPKDTL MISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKP REEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSI EKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSR WQEGNVFSCSVLHEALHSHYTQKSLSLSLG
69	MAB2 with with constant domain PE and YTE mutations	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAP GKGLEWVSYISRSGSTKYYADSVKGRFTISRDNANKNSLYLQ MNSLRAEDTAVYYCARDETDYALDYWGQGTLLTVSSASTK GPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGAL TSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGKTYTCNVDPHK PSNTKVDKR VESKYGPPCPPCPAPEFEGGPSVFLFPPKPKDTL YITREPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKP REEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSI EKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSR WQEGNVFSCSVMEALHNHYTQKSLSLSLG
70	MAB3 with constant domain PE and LS mutations	EVQLVESGGGVVRPGGSLRLSCAASGFTFDDYGMWVRQA PGKGLEWVSGINWEGGSTGYADSVKGRFTISRDNANKNSLYL QMNSLRAEDTALYYCARDEQLGGNYYYYYYMDVWGKGT TVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGK TYTCNVDPHKPSNTKVDKR VESKYGPPCPPCPAPEFEGGPSVF LFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGV EVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCK VSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVS LTCLVKGFYPSPDIAVEWESNGQPENNYKTTPPVLDSDGSFFL YSRLTVDKSRWQEGNVFSCSVLHEALHSHYTQKSLSLSLG
71	MAB3 with with constant domain PE and YTE mutations	EVQLVESGGGVVRPGGSLRLSCAASGFTFDDYGMWVRQA PGKGLEWVSGINWEGGSTGYADSVKGRFTISRDNANKNSLYL QMNSLRAEDTALYYCARDEQLGGNYYYYYYMDVWGKGT TVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGK TYTCNVDPHKPSNTKVDKR VESKYGPPCPPCPAPEFEGGPSVF LFPPKPKDTLYITREPEVTCVVVDVSQEDPEVQFNWYVDGV EVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCK VSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVS LTCLVKGFYPSPDIAVEWESNGQPENNYKTTPPVLDSDGSFFL YSRLTVDKSRWQEGNVFSCSVMEALHNHYTQKSLSLSLG

[00268] In some embodiments, the antibody comprises a light chain as set forth below, which includes the variable region and a constant domain, such as the human kappa constant domain:

Table 14:

SEQ ID NO:	AB ID NO.	Sequence
72	MAB1 plus kappa constant domain	DIQMTQSPSTLSASVGDRVTITCRASQSISSWLAWYQQKPGKAPKL LIYKASSLESQVPSRFSGSGSGTEFTLTISSLQPDDEFATYYCQQYNSY SWTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYP REAKVQWKVDNALQSGNSQESVTEQDSKDSSTYLSSTLTLSKADY EKHKVYACEVTHQGLSSPVTKSFNRGEC
73	MAB2 plus kappa constant domain	DIQMTQSPSSLSASVGDRVTITCQASQDISNYLNWYQQKPG KAPKLLIYDASNLETGVPSRFSGSGSGTDFTFITISSLQPEDIAT YYCQQYEDLPLTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKS GTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQD SKDSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSF NRGEC
74	MAB3 plus kappa constant domain	DIQMTQSPSSLSASVGDRVTITCRASQGIRNDLGWYQQKPG KAPKRLIYTASNLSQVPSRFSGSGSGTEFTLTISSLQPEDFAT YYCLQYNSYPLTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKS GTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQD SKDSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSF NRGEC

[00269] In some embodiments, the antibody or antigen binding fragment thereof of any of the embodiments as provided for herein may comprise any constant domain known, such as but not limited to an IgG constant domain. In some embodiments, the constant domain is as provided for herein. In some non-limiting embodiments, the constant domain is selected from the group including, but not limited to, SEQ ID NO: 7, 8, 57, 58, 65, or a variant thereof as provided for herein. In some embodiments, the constant domain has at least 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99% sequence identity to a sequence selected from the group including, but not limited to, SEQ ID NO: 7, 8, 57, 58, 65, or a variant thereof as provided for herein.

[00270] In some embodiments, the antibody, or antigen-binding fragment thereof, comprises a heavy chain that has at least 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO:66 or SEQ ID NO: 67, wherein the antibody or antigen binding fragment thereof maintains the sequences of the heavy chain and light chain CDRs of MAB1. In some embodiments, the antibody, or antigen-binding fragment thereof, comprises a heavy chain that has at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to SEQ ID NO:66 or SEQ ID NO: 67, wherein the antibody or antigen binding fragment thereof maintains a HCDR1 sequence of SEQ ID NO: 9, SEQ ID NO: 27, or SEQ ID NO: 42, maintains a HCDR2 sequence of SEQ ID NO: 10, SEQ ID NO: 28, or SEQ ID NO: 43, maintains a HCDR3 sequence of SEQ ID NO: 11 or SEQ ID NO: 44, maintains a LCDR1 sequence of SEQ ID NO: 12, SEQ ID NO: 29, or SEQ ID NO: 45, maintains a LCDR2

sequence of SEQ ID NO: 13, or SEQ ID NO: 30, and maintains a LCDR3 sequence SEQ ID NO: 14, or SEQ ID NO: 31.

[00271] In some embodiments, the antibody, or antigen-binding fragment thereof, comprises a heavy chain that has at least 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO:68 or SEQ ID NO: 69, wherein the antibody or antigen binding fragment thereof maintains the sequences of the heavy chain and light chain CDRs of MAB2. In some embodiments, the antibody, or antigen-binding fragment thereof, comprises a heavy chain that has at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to SEQ ID NO: 68 or SEQ ID NO: 69, wherein the antibody or antigen binding fragment thereof maintains a HCDR1 sequence of SEQ ID NO: 15, SEQ ID NO: 32, or SEQ ID NO: 46, maintains a HCDR2 sequence of SEQ ID NO: 16, SEQ ID NO: 33, or SEQ ID NO: 47, maintains a HCDR3 sequence of SEQ ID NO: 17 or SEQ ID NO: 48, maintains a LCDR1 sequence of SEQ ID NO: 18, SEQ ID NO: 34, or SEQ ID NO: 49, maintains a LCDR2 sequence of SEQ ID NO: 19, or SEQ ID NO: 35, and maintains a LCDR3 sequence SEQ ID NO: 20, or SEQ ID NO: 36.

[00272] In some embodiments, the antibody, or antigen-binding fragment thereof, comprises a heavy chain that has at least 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO:70 or SEQ ID NO: 71, wherein the antibody or antigen binding fragment thereof maintains the sequences of the heavy chain and light chain CDRs of MAB3. In some embodiments, the antibody, or antigen-binding fragment thereof, comprises a heavy chain that has at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to SEQ ID NO: 70 or SEQ ID NO: 71, wherein the antibody or antigen binding fragment thereof maintains a HCDR1 sequence of SEQ ID NO: 21, SEQ ID NO: 37, or SEQ ID NO: 50, maintains a HCDR2 sequence of SEQ ID NO: 22, SEQ ID NO: 38, or SEQ ID NO: 51, maintains a HCDR3 sequence of SEQ ID NO: 23 or SEQ ID NO: 52, maintains a LCDR1 sequence of SEQ ID NO: 24, SEQ ID NO: 39, or SEQ ID NO: 53, maintains a LCDR2 sequence of SEQ ID NO: 25, or SEQ ID NO: 40, and maintains a LCDR3 sequence SEQ ID NO: 26, or SEQ ID NO: 41.

[00273] In some embodiments, the antibody, or antigen-binding fragment thereof, comprises a light chain that has at least 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO:72, wherein the antibody or antigen binding fragment thereof maintains the sequences of the

heavy chain and light chain CDRs of MAB1. In some embodiments, the antibody, or antigen-binding fragment thereof, comprises a light chain that has at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to SEQ ID NO: 72, wherein the antibody or antigen binding fragment thereof maintains a HCDR1 sequence of SEQ ID NO: 9, SEQ ID NO: 27, or SEQ ID NO: 42, maintains a HCDR2 sequence of SEQ ID NO: 10, SEQ ID NO: 28, or SEQ ID NO: 43, maintains a HCDR3 sequence of SEQ ID NO: 11 or SEQ ID NO: 44, maintains a LCDR1 sequence of SEQ ID NO: 12, SEQ ID NO: 29, or SEQ ID NO: 45, maintains a LCDR2 sequence of SEQ ID NO: 13, or SEQ ID NO: 30, and maintains a LCDR3 sequence SEQ ID NO: 14, or SEQ ID NO: 31.

[00274] In some embodiments, the antibody, or antigen-binding fragment thereof, comprises a light chain that has at least 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO:73, wherein the antibody or antigen binding fragment thereof maintains the sequences of the heavy chain and light chain CDRs of MAB2. In some embodiments, the antibody, or antigen-binding fragment thereof, comprises a light chain that has at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to SEQ ID NO: 73, wherein the antibody or antigen binding fragment thereof maintains a HCDR1 sequence of SEQ ID NO: 15, SEQ ID NO: 32, or SEQ ID NO: 46, maintains a HCDR2 sequence of SEQ ID NO: 16, SEQ ID NO: 33, or SEQ ID NO: 47, maintains a HCDR3 sequence of SEQ ID NO: 17 or SEQ ID NO: 48, maintains a LCDR1 sequence of SEQ ID NO: 18, SEQ ID NO: 34, or SEQ ID NO: 49, maintains a LCDR2 sequence of SEQ ID NO: 19, or SEQ ID NO: 35, and maintains a LCDR3 sequence SEQ ID NO: 20, or SEQ ID NO: 36.

[00275] In some embodiments, the antibody, or antigen-binding fragment thereof, comprises a light chain that has at least 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO:74, wherein the antibody or antigen binding fragment thereof maintains the sequences of the heavy chain and light chain CDRs of MAB3. In some embodiments, the antibody, or antigen-binding fragment thereof, comprises a light chain that has at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to SEQ ID NO: 74, wherein the antibody or antigen binding fragment thereof maintains a HCDR1 sequence of SEQ ID NO: 21, SEQ ID NO: 37, or SEQ ID NO: 50, maintains a HCDR2 sequence of SEQ ID NO: 22, SEQ ID NO: 38, or SEQ ID NO: 51, maintains a HCDR3 sequence of SEQ ID NO: 23 or SEQ ID NO: 52, maintains a LCDR1 sequence of SEQ ID NO: 24, SEQ ID NO: 39, or

SEQ ID NO: 53, maintains a LCDR2 sequence of SEQ ID NO: 25, or SEQ ID NO: 40, and maintains a LCDR3 sequence SEQ ID NO: 26, or SEQ ID NO: 41.

[00276] In some embodiments, the antibody or antigen-binding fragment thereof, comprises a light chain that has at least 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO:72, and a heavy chain that has at least 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO:66 or SEQ ID NO: 67 (HC of MAB1), wherein the antibody or antigen binding fragment thereof maintains the sequences of the heavy chain and light chain CDRs of MAB1. In some embodiments, the antibody or antigen-binding fragment thereof, comprises a light chain that has at least 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO:72, and a heavy chain that has at least 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO:66 or SEQ ID NO: 67, wherein the antibody or antigen binding fragment thereof maintains a HCDR1 sequence of SEQ ID NO: 9, SEQ ID NO: 27, or SEQ ID NO: 42, maintains a HCDR2 sequence of SEQ ID NO: 10, SEQ ID NO: 28, or SEQ ID NO: 43, maintains a HCDR3 sequence of SEQ ID NO: 11 or SEQ ID NO: 44, maintains a LCDR1 sequence of SEQ ID NO: 12, SEQ ID NO: 29, or SEQ ID NO: 45, maintains a LCDR2 sequence of SEQ ID NO: 13, or SEQ ID NO: 30, and maintains a LCDR3 sequence SEQ ID NO: 14, or SEQ ID NO: 31.

[00277] In some embodiments, the antibody or antigen-binding fragment thereof, comprises a light chain that has at least 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO:73, and a heavy chain that has at least 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO:68 or SEQ ID NO: 69, wherein the antibody or antigen binding fragment thereof maintains the sequences of the heavy chain and light chain CDRs of MAB2. In some embodiments, the antibody or antigen-binding fragment thereof, comprises a light chain that has at least 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO:73, and a heavy chain that has at least 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO:68 or SEQ ID NO: 69, wherein the antibody or antigen binding fragment thereof maintains a HCDR1 sequence of SEQ ID NO: 15, SEQ ID NO: 32, or SEQ ID NO: 46, maintains a HCDR2 sequence of SEQ ID NO: 16, SEQ ID NO: 33, or SEQ ID NO: 47, maintains a HCDR3 sequence of SEQ ID NO: 17 or SEQ ID NO: 48, maintains a LCDR1 sequence of SEQ ID NO: 18, SEQ ID NO: 34, or SEQ ID NO: 49, maintains a LCDR2 sequence

of SEQ ID NO: 19, or SEQ ID NO: 35, and maintains a LCDR3 sequence SEQ ID NO: 20, or SEQ ID NO: 36.

[00278] In some embodiments, the antibody or antigen-binding fragment thereof, comprises a light chain that has at least 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO:74 (LC of MAB3), and a heavy chain that has at least 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO:70 or SEQ ID NO: 71, wherein the antibody or antigen binding fragment thereof maintains the sequences of the heavy chain and light chain CDRs of MAB3. In some embodiments, the antibody or antigen-binding fragment thereof, comprises a light chain that has at least 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO:74, and a heavy chain that has at least 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO:70 or SEQ ID NO: 71, wherein the antibody or antigen binding fragment thereof maintains a HCDR1 sequence of SEQ ID NO: 21, SEQ ID NO: 37, or SEQ ID NO: 50, maintains a HCDR2 sequence of SEQ ID NO: 22, SEQ ID NO: 38, or SEQ ID NO: 51, maintains a HCDR3 sequence of SEQ ID NO: 23 or SEQ ID NO: 52, maintains a LCDR1 sequence of SEQ ID NO: 24, SEQ ID NO: 39, or SEQ ID NO: 53, maintains a LCDR2 sequence of SEQ ID NO: 25, or SEQ ID NO: 40, and maintains a LCDR3 sequence SEQ ID NO: 26, or SEQ ID NO: 41.

[00279] In some embodiments, the antibody, or antigen-binding fragment thereof, comprises a light chain having a sequence of SEQ ID NO:72 and a heavy chain that comprises a sequence of SEQ ID NO: 66 or SEQ ID NO: 67.

[00280] In some embodiments, the antibody, or antigen-binding fragment thereof, comprises a light chain having a sequence of SEQ ID NO:73 and a heavy chain that comprises a sequence of SEQ ID NO: 68 or SEQ ID NO: 69.

[00281] In some embodiments, the antibody, or antigen-binding fragment thereof, comprises a light chain having a sequence of SEQ ID NO:74 and a heavy chain that comprises a sequence of SEQ ID NO: 70 or SEQ ID NO: 71.

[00282] As provided for herein, the antibodies, or antigen binding fragments thereof can be variants of the sequences. Accordingly, in some embodiments, a variant of an antibody or antigen binding fragment thereof provided for herein is provided. In some embodiments, the variant comprises mutations selected from substitutions, deletions, insertions, or a combination thereof. In some embodiments, the variant comprises between 1 and 20 mutations. In some

embodiments, the variant comprises between 1 and 10 mutations. In some embodiments, the variant comprises between 1 and 5 mutations. In some embodiments, the variant comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 mutations. In some embodiments, the variant comprises at least 1 mutation. Accordingly, in some embodiments, the variant comprises up to or more than 20 mutations. In some embodiments, the variant comprises 1-10 mutations, wherein the mutations are selected from substitutions, deletions, insertions, or a combination thereof. In some embodiments, the variant comprises 1-10 mutations, wherein the mutations are conservative substitutions. Examples of conservative substitutions are as provided for herein (Table 1). Further, one of skill in the art will recognize and understand the substitutions that are encompassed by the term “conservative substitutions”. Such substitutions are within the scope of the present disclosure.

[00283] The antibody or antigen binding fragment may comprise an antibody fragment as defined and provided for herein. In some embodiments, the antibody binding fragment is as provided for herein. In some embodiments, the antibody fragment is a scFv antibody, a Fab fragment, a Fab' fragment, or a F(ab')₂ fragment. In some embodiments, the antibody fragment is a scFv antibody. In some embodiments, the antibody fragment is a Fab fragment. In some embodiments, the antibody fragment is a Fab' fragment. In some embodiments, the antibody fragment is a F(ab')₂ fragment.

[00284] The sequences of the antibodies can be modified to yield human IgG antibodies. The conversion of the sequences provided herein can be modified to yield other types of antibodies. The CDRs can also be linked to other antibodies, proteins, or molecules to create antibody fragments that bind C1s. This can be in the form of an antibody drug conjugate (“ADC”), or a multi-specific molecule. The sequences can also be made into chimeric antibodies as described herein.

[00285] In some embodiments, the antibody comprises an amino acid sequence comprising a sequence provided for herein or a fragment thereof. In some embodiments, the antibody is a monoclonal antibody. In some embodiments, the antibody is a polyclonal antibody. In some embodiments, the antibody is a humanized antibody. In some embodiments, the antibody comprises one or more amino acid sequences as provided herein, an antigen binding fragments, thereof, or a human IgG variant thereof. “A human IgG variant thereof” refers to an antibody

that has been modified to be a human IgG when the starting antibody is not a human IgG antibody.

[00286] As described herein the production of antibodies with a known sequence is routine and can be done by any method. Accordingly, in some embodiments, a nucleic acid molecule encoding an antibody or fragment thereof is provided. In some embodiments, the nucleic acid encodes a sequence provided for herein. The antibodies can also be modified to be chimeric antibodies or human antibodies. The antibodies can also be used in injectable pharmaceutical compositions. As also described herein, the antibodies can be isolated antibodies or engineered antibodies.

[00287] In some embodiments, an isolated nucleic acid molecule is provided. In some embodiments, the nucleic acid molecule encodes for an antibody, or antigen binding fragment thereof as provided for herein. In some embodiments, the nucleic acid molecule encodes for an antibody, or antigen binding fragment thereof comprising a heavy chain variable region, a light chain variable region, a heavy chain, a light chain or any combination thereof as provided for herein. In some embodiments, the nucleic acid molecule encoding the variable heavy chain is as set forth below:

Table 15:

SEQ ID NO:	AB ID NO.	Sequence
59	MAB1	CAAGTTCAACTGGTTCAAAGCGGGGCCGAGGTAAAGAAG CCAGGCGCTTCTGTGAAAGTCAGTTGCAAGGTGAGTGGG GATACATTGACCGAGCTGAGTATGCACTGGGTCCGGCAA GCTCCTGGCAAGGGTTTGGAATGGATGGGTACTTTTGACC CGGAGGAGGGAGAGACCATCTACGCGCAAAAATTCCAAG GTAGGGTGACCATGACGGAGGATACCAGCACGGATACTG CTTACATGGAGCTCAGCTCCCTCAGAAGTGAAGATACTGC CGTCTACTACTGTGTGACCGAGGGTTTGGCCGGGCGCCCG TTTGATTTCATGGGGGCAGGGGACGCTGGTAACGGTCTCG AGT
61	MAB2	CAGGTGCAGCTTGTTGAAAGTGGTGGGGGTTTGGTTAAAC CTGGCGGTTCCCTTCGACTTAGCTGCGCGGCGTCAGGGTT CACATTCTCAGATTATTACATGTCTTGATTTCGGCAAGCC CCTGGTAAGGGACTGGAGTGGGTAAGCTACATATCTCGG TCAGGAAGTACAAAGTACTATGCAGATTCAAGTGAAGGGC AGGTTTACGATTAGCCGAGACAACGCAAGAAGTCTCTTT ATCTGCAGATGAATTCAGTGAAGACAGAGATACCGCTG TCTATTATTGTGCCAGAGACGAGACCGATTACGCTCTTGA CTACTGGGGCCAAGGTACGCTGGTTACGGTCTCGAGT

SEQ ID NO:	AB ID NO.	Sequence
63	MAB3	GAAGTCCAGCTTGTTGAGTCTGGCGGAGGGGTGGTTAGG CCAGGAGGTTCCCTTAGGCTTTCCTGTGCGGCATCAGGAT TTACCTTCGATGACTACGGAATGTCATGGGTACGACAAGC TCCCGGCAAAGGCCTCGAATGGGTTTCTGGCATCAACTGG GAGGGCGGTTCCACTGGCTACGCGGACTCAGTTAAGGGT AGGTTACACATAAGCAGGGACAATGCGAAGAAGTCACTG TATCTCCAAATGAACAGTCTCCGCGCCGAGGATACAGCCC TTTACTATTGTGCACGAGATGAGCAATTGGGGGGGAATTA TTATTATTACTATTACATGGACGTGTGGGGTAAAGGAACG ACCGTCACAGTCTCGAGT

[00288] In some embodiments, the nucleic acid molecule encoding the variable light chain is as set forth below:

Table 16:

SEQ ID NO:	AB ID NO.	Sequence
60	MAB1	GACATACAAATGACTCAATCACCCCTCTACACTTTCGCCT CTGTGCGGACAGGGTAACGATAACTTGCCGGGCAAGTC AATCAATCAGCTCCTGGCTTGCTTGGTATCAACAAAAACC AGGCAAGGCACCTAAGCTCCTCATTTACAAGGCGTCATCA CTTGAATCAGGGGTGCCTTCACGATTCAGCGGATCAGGAT CTGGTACTGAATTCCTCTGACCATTTCAAGTCTTCAGCC TGATGACTTTGCGACCTATTATTGCCAGCAGTACAATAGC TACTCATGGACGTTTCGGGCAGGGTACTAAAGTCGAGATT AAA
62	MAB2	GACATTCAGATGACGCAAAGCCCCTCTAGCTTGTCCGCTA GTGTGGGTGACAGGGTCACCATTACCTGCCAGGCTTCACA AGACATCAGTAATTACCTCAACTGGTATCAGCAGAAACCT GGGAAGGCCCTAAGCTGTTGATTTACGATGCTAGTAAGT TGGAGACCGGGGTACCCAGCAGATTTAGCGGGAGCGGAA GTGGTACGGATTTTACGTTTACCATTAGCAGCTTGCAGCC CGAGGACATCGCTACATATTACTGTGTCAGCAGTATGAGGA CCTCCCTCTTACCTTCGGCGGTGGAACGAAAGTTGAGATT AAG
64	MAB3	GACATACAGATGACTCAGTCCCCAAGTAGTCTGAGCGCCT CTGTGCGGACCGCGTTACCATTACTTGCCGGGCGAGTCA AGGGATACGCAACGATTTGGGTTGGTATCAGCAAAAGCC CGGAAAGGCCCCAAAGCGGCTGATATACACCGCCTCAAA CCTCCAGTCTGGAGTTCCATCAAGGTTTAGTGGATCTGGA TCTGGCACTGAGTTTACTCTCACTATAAGCTCCCTTCAGC CTGAAGACTTCGCAACTTATTATTGCTTGAGTATAAATAG TTATCCACTCACTTTTGGCGGTGGCACCAAAGTGGAGATT AAG

[00289] In some embodiments, the nucleic acid molecule comprises a sequence of SEQ ID NO: 59, SEQ ID NO: 61, or SEQ ID NO: 63. In some embodiments, the nucleic acid molecule comprises a sequence of SEQ ID NO: 59. In some embodiments, the nucleic acid molecule comprises a sequence of SEQ ID NO: 61. In some embodiments, the nucleic acid molecule comprises a sequence of SEQ ID NO: 63. In some embodiments, a nucleic acid molecule is provided that comprises a sequence of SEQ ID NO: 60, SEQ ID NO: 62, or SEQ ID NO: 64. In some embodiments, the nucleic acid molecule comprises a sequence of SEQ ID NO: 60. In some embodiments, the nucleic acid molecule comprises a sequence of SEQ ID NO: 62. In some embodiments, the nucleic acid molecule comprises a sequence of SEQ ID NO: 64. It is to be understood that the sequences of SEQ ID NO: 59, 60, 61, 62, 63, and 64 (as well as other nucleotide sequences provided for herein) are exemplary sequences and are not meant to be limiting in any way. Due to the degenerate nature of codons, other nucleic acid molecules can be used. In some embodiments, the nucleic acid molecule is codon optimized for expression in a bacterial system. In some embodiments, the nucleic acid molecule is codon optimized for expression in a eukaryotic system or cell. In some embodiments, the nucleic acid molecule is a DNA or RNA molecule that encodes a polypeptide as provided for herein. In some embodiments, the RNA molecule is a mRNA molecule. Accordingly, in some embodiments, the nucleic acid molecule comprises a sequence that is substantially similar to SEQ ID NO: 59, SEQ ID NO: 61, or SEQ ID NO: 63. In some embodiments, the nucleic acid molecule comprises a sequence that has at least 60% % identity to SEQ ID NO: 59, SEQ ID NO: 61, or SEQ ID NO: 63. In some embodiments, the nucleic acid molecule comprises a sequence that has at least 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% identity to SEQ ID NO: 59, SEQ ID NO: 61, or SEQ ID NO: 63, or any percent identity falling within any of the recited percent identities. In some embodiments, the nucleic acid molecule comprises a sequence that is substantially similar to SEQ ID NO: 60, SEQ ID NO: 62, or SEQ ID NO: 64. In some embodiments, the nucleic acid molecule comprises a sequence that has at least 60% % identity to SEQ ID NO: 60, SEQ ID NO: 62, or SEQ ID NO: 64. In some embodiments, the nucleic acid molecule comprises a sequence that has at least 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% identity to SEQ ID NO: 60, SEQ ID NO: 62, or SEQ ID NO: 64, or any percent identity falling within any of the recited percent identities.

[00290] In some embodiments, an expression vector is provided. In some embodiments, the expression vector comprises a nucleic acid molecule encoding an antibody or antigen-binding fragment thereof as provided for herein. In some embodiments, the expression vector comprises a nucleic acid molecule as provided for herein. The vector may be any vector known in the art. In some embodiments the vector is as provided for herein. In some embodiments, the vector is a plasmid. In some embodiments the vector is a virus.

[00291] In some embodiments, “derivatives” of the antibodies, fragments, regions or derivatives thereof, which term includes those proteins encoded by truncated or modified genes to yield molecular species functionally resembling the immunoglobulin fragments are provided. The modifications include, but are not limited to, addition of genetic sequences coding for cytotoxic proteins such as plant and bacterial toxins. The modification can also include a reporter protein, such as a fluorescent or chemiluminescent tag. The fragments and derivatives can be produced in any manner.

[00292] The identification of these antibodies, or antigen binding fragments thereof, provide the information necessary to generate additional monoclonal antibodies with similar binding characteristics and therapeutic or diagnostic utility that parallel the embodiments of this application.

[00293] The antibodies can be generated according the examples provided herein. Once the sequences are known, the antibodies can also be generated according to known methods. The antibodies can also be converted to different types, such as being converted to Human IgGs and the like. By converting the antibodies to a human antibody, a human subject should not identify the antibodies as foreign. The conversion of a non-human IgG antibody to a human IgG antibody is well known and can routinely be done once the native sequence is known. As discussed herein, the antibodies can be modified according to known methods. Such methods are described in, for example, Riechmann L, Clark M, Waldmann H, Winter G (1988). Reshaping human antibodies for therapy”. *Nature* 332 (6162): 332–323; Tsurushita N, Park M, Pakabunto K, Ong K, Avdalovic A, Fu H, Jia A, Vásquez M, Kumar S. (2004), which is incorporated by reference in its entirety.

[00294] In some embodiments, a host cell is provided. In some embodiments, the host cell comprises an antibody or antigen-binding fragment thereof as provided for herein. In some embodiments, the host cell comprises a nucleic acid molecule encoding for antibody or antigen-

binding fragment thereof as provided for herein. In some embodiments, the host cell comprises nucleic acid molecules selected from the group including, but not limited to, SEQ ID NO. 59, 60, 61, 62, 63, 64, any variats thereof as provided for herein, or any combination thereof. In some embodiments, the host cell comprises a vector, said vector comprising comprises a nucleic acid molecule encoding for antibody or antigen-binding fragment thereof as provided for herein. In some embodiments, the vector comprises nucleic acid molecules selected from the group including, but not limited to, SEQ ID NO. 59, 60, 61, 62, 63, 64, any variats thereof as provided for herein, or any combination thereof.

[00295] In some embodiments, the host cell produces an antibody or antigen-binding fragment thereof as provided for herein. In some embodiments, an antibody or antigen-binding fragment thereof as provided for herein is provided, wherein the antibody or antigen-binding fragment thereof as provided for herein is produced by the host cell.

[00296] In some embodiments, a method of producing a polypeptide is provided. In some embodiments, the polypeptide comprises a heavy chain variable region as provided for herein, a light chain variable region as provided for herein, or a combination thereof. In some embodiments, the method comprises growing a host cell under conditions so that the host cell expresses the polypeptide comprising the heavy chain variable region, light chain variable region, or combination thereof, and purifying the polypeptide comprising the heavy chain variable region, the light chain variable region, or a combination thereof, thereby producing the polypeptide. In some embodiments, the host cell is a host cell as provided for herein.

[00297] In some embodiments, a method of producing an antibody or antigen binding fragment thereof is provided. In some embodiments, the antibody binds human C1s. In some embodiments, the antigen binding fragment binds human C1s. In some embodiments, the method comprises growing a host cell under conditions so that the host cell expresses a polypeptide or polypeptides comprising the immunoglobulin heavy chain variable region and/or the immunoglobulin light chain variable region, thereby producing the antibody or the antigen binding fragment of the antibody, and purifying the antibody or the antigen binding fragment of the antibody. In some embodiments, the polypeptide or polypeptides comprise the immunoglobulin heavy chain variable region. In some embodiments, the polypeptide or polypeptides comprise the immunoglobulin light chain variable region. In some embodiments, the polypeptide or polypeptides comprise the immunoglobulin heavy chain variable region and

the immunoglobulin light chain variable region. In some embodiments, the host cell is a host cell as provided for herein. In some embodiments, the antibody or antigen binding fragment thereof is as provided for herein.

[00298] The polypeptide or antibody-producing cell contributing the nucleotide sequences encoding the antigen-binding region of the chimeric antibody can also be produced by transformation of a non-human, such as a primate, or a human cell. For example, a B lymphocyte which produces the antibody can be infected and transformed with a virus such as Epstein-Barr virus to yield an immortal antibody producing cell (Kozbor et al., *Immunol. Today* 4:72-79 (1983)). Alternatively, the B lymphocyte can be transformed by providing a transforming gene or transforming gene product, as is well-known in the art. See, *e.g.*, Ausubel *infra*, Harlow *infra*, and Colligan *infra*, the contents of which references are incorporated entirely herein by reference. The cell fusions are accomplished by standard procedures well known to those skilled in the field of immunology, such as producing cells can also be a hybridoma which is generated by fusing a B-cell with an immortal myeloma cell. Fusion partner cell lines and methods for fusing and selecting hybridomas and screening for mAbs are well known in the art. See, *e.g.*, Ausubel *infra*, Harlow *infra*, and Colligan *infra*, the contents of which references are incorporated entirely herein by reference.

[00299] The nucleic acid sequence encoding an antibody described herein can be genomic DNA or cDNA, or RNA (*e.g.* mRNA) which encodes at least one of the variable regions described herein. A convenient alternative to the use of chromosomal gene fragments as the source of DNA encoding the V region antigen-binding segment is the use of cDNA for the construction of chimeric immunoglobulin genes, *e.g.*, as reported by Liu et al. (*Proc. Natl. Acad. Sci., USA* 84:3439 (1987) and *J. Immunology* 139:3521 (1987)), which references are hereby entirely incorporated herein by reference. The use of cDNA requires that gene expression elements appropriate for the host cell be combined with the gene in order to achieve synthesis of the desired protein. The use of cDNA sequences is advantageous over genomic sequences (which contain introns), in that cDNA sequences can be expressed in bacteria or other hosts which lack appropriate RNA splicing systems.

[00300] For example, a cDNA encoding a V region antigen-binding segment able to detect, bind, to or neutralize C1s can be provided using known methods based on the use of the amino acid sequences provided herein. Because the genetic code is degenerate, more than one codon

can be used to encode a particular amino acid (Watson, et al., *infra*). Using the genetic code, one or more different oligonucleotides can be identified, each of which would be capable of encoding the amino acid. The probability that a particular oligonucleotide will, in fact, constitute the actual XXX-encoding sequence can be estimated by considering abnormal base pairing relationships and the frequency with which a particular codon is actually used (to encode a particular amino acid) in eukaryotic or prokaryotic cells expressing an antibody or fragment. Such “codon usage rules” are disclosed by Lathe, et al., *J. Molec. Biol.* 183:1 12 (1985). Using the “codon usage rules” of Lathe, a single oligonucleotide, or a set of oligonucleotides, that contains a theoretical “most probable” nucleotide sequence capable of encoding an antibody variable or constant region sequences is identified.

[00301] The variable regions described herein can be combined with any type of constant region including a human constant region or murine constant region. Human genes which encode the constant (C) regions of the antibodies, fragments and regions can be derived from a human fetal liver library, by known methods. Human C region genes can be derived from any human cell including those which express and produce human immunoglobulins. The human C_H region can be derived from any of the known classes or isotypes of human H chains, including gamma, μ , α , δ or ϵ , and subtypes thereof, such as G1, G2, G3 and G4. Since the H chain isotype is responsible for the various effector functions of an antibody, as well as antibody recycling by interaction with FcRn, the choice of C_H region will be guided by the desired effector functions, such as complement fixation, or activity in antibody-dependent cellular cytotoxicity (ADCC). Preferably, the C_H region is derived from gamma 1 (IgG1), gamma 3 (IgG3), gamma 4 (IgG4), or μ (IgM). The human C_L region can be derived from either human L chain isotype, kappa or lambda.

[00302] Methods of purifying polypeptides or proteins (including antibodies or antigen binding fragments thereof) are known in the art, and any such method is within the scope of the present application. Further, the host cell is not limited by the examples recited above. Any suitable cell may be used to generate the polypeptides or proteins of the present disclosure.

[00303]

Pharmaceutical Compositions

[00304] In some embodiments, a pharmaceutical composition is provided. In some embodiments, the pharmaceutical composition comprises an antibody or antigen-binding fragment thereof as provided for herein.

[00305] In some embodiments, to prepare pharmaceutical or sterile compositions of the anti-C1s antibodies or other proteins provided herein, the antibody or antigen binding fragment thereof or other proteins provided herein are admixed with a pharmaceutically acceptable carrier or excipient. See, *e.g.*, *Remington's Pharmaceutical Sciences* and *U.S. Pharmacopeia: National Formulary*, Mack Publishing Company, Easton, PA (1984).

[00306] Formulations of therapeutic or the antibodies provided herein may be prepared by mixing with acceptable carriers, excipients, or stabilizers in the form of, *e.g.*, lyophilized powders, slurries, aqueous solutions or suspensions (see, *e.g.*, Hardman, *et al.* (2001) *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, McGraw-Hill, New York, NY; Gennaro (2000) *Remington: The Science and Practice of Pharmacy*, Lippincott, Williams, and Wilkins, New York, NY; Avis, *et al.* (eds.) (1993) *Pharmaceutical Dosage Forms: Parenteral Medications*, Marcel Dekker, NY; Lieberman, *et al.* (eds.) (1990) *Pharmaceutical Dosage Forms: Tablets*, Marcel Dekker, NY; Lieberman, *et al.* (eds.) (1990) *Pharmaceutical Dosage Forms: Disperse Systems*, Marcel Dekker, NY; Weiner and Kotkoskie (2000) *Excipient Toxicity and Safety*, Marcel Dekker, Inc., New York, NY). In some embodiments, the antibodies are diluted to an appropriate concentration in a sodium acetate solution pH 5-6, and NaCl or sucrose is added for tonicity. Additional agents, such as polysorbate 20 or polysorbate 80, may be added to enhance stability.

[00307] Toxicity and therapeutic efficacy of the antibody compositions, administered alone or in combination with another agent, can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, *e.g.*, for determining the LD₅₀ (the dose lethal to 50% of the population) and the ED₅₀ (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index (LD₅₀/ ED₅₀). In particular aspects, antibodies exhibiting high therapeutic indices are desirable. The data obtained from these cell culture assays and animal studies can be used in formulating a range of dosage for use in human. The dosage of such compounds lies preferably within a range of circulating concentrations that include the ED₅₀ with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration.

[00308] In some embodiments, a composition is administered to a subject in accordance with the Physicians' Desk Reference 2003 (Thomson Healthcare; 57th edition (November 1, 2002)).

[00309] The mode of administration can vary. Suitable routes of administration include oral, rectal, transmucosal, intestinal, parenteral; intramuscular, subcutaneous, intradermal, intramedullary, intrathecal, direct intraventricular, intravenous, intraperitoneal, intranasal, intraocular, inhalation, insufflation, topical, cutaneous, transdermal, or intra-arterial. In some embodiments, the composition is an injectable pharmaceutical composition. In some embodiments, the composition is formulated for intravenous or subcutaneous injection. In some embodiments, the composition is formulated for intravenous injection. In some embodiments, the composition is formulated for subcutaneous injection.

[00310] In some embodiments, the antibody or antigen binding fragment thereof can be administered by an invasive route such as by injection. In some embodiments, the antibodies or antigen binding fragment thereof, or pharmaceutical composition thereof, is administered intravenously, subcutaneously, intramuscularly, intraarterially, intra-articularly (*e.g.* in arthritis joints), intratumorally, or by inhalation, aerosol delivery. Administration by non-invasive routes (*e.g.*, orally; for example, in a pill, capsule or tablet) is also within the scope of the present embodiments.

[00311] In some embodiments, the anti-C1s antibody, or antigen binding fragment thereof, is administered in combination with at least one additional therapeutic agent, such as, but not limited to any therapeutic used to treat the disorders provided for herein. In some embodiments, the antibody is administered in combination with another treatment for the disorders provided for herein.

[00312] Compositions can be administered with medical devices known in the art. For example, a pharmaceutical composition of the invention can be administered by injection with a hypodermic needle, including, *e.g.*, a prefilled syringe or autoinjector.

[00313] The pharmaceutical compositions may also be administered with a needleless hypodermic injection device; such as the devices disclosed in U.S. Patent Nos. 6,620,135; 6,096,002; 5,399,163; 5,383,851; 5,312,335; 5,064,413; 4,941,880; 4,790,824 or 4,596,556.

[00314] The pharmaceutical compositions may also be administered by infusion. Examples of well-known implants and modules for administering pharmaceutical compositions include: U.S. Patent No. 4,487,603, which discloses an implantable micro-infusion pump for dispensing

medication at a controlled rate; U.S. Patent No. 4,447,233, which discloses a medication infusion pump for delivering medication at a precise infusion rate; U.S. Patent No. 4,447,224, which discloses a variable flow implantable infusion apparatus for continuous drug delivery; U.S. Patent No. 4,439,196, which discloses an osmotic drug delivery system having multi-chamber compartments. Many other such implants, delivery systems, and modules are well known to those skilled in the art.

[00315] Alternately, one may administer the antibody in a local rather than systemic manner, for example, via injection of the antibody directly into an arthritic joint or pathogen-induced lesion characterized by immunopathology, often in a depot or sustained release formulation. Furthermore, one may administer the antibody in a targeted drug delivery system, for example, in a liposome coated with a tissue-specific antibody, targeting, for example, arthritic joint or pathogen-induced lesion characterized by immunopathology. The liposomes will be targeted to and taken up selectively by the afflicted tissue.

[00316] The administration regimen depends on several factors, including the serum or tissue turnover rate of the therapeutic antibody, the level of symptoms, the immunogenicity of the therapeutic antibody, and the accessibility of the target cells in the biological matrix. Preferably, the administration regimen delivers sufficient therapeutic antibody to effect improvement in the target disease state, while simultaneously minimizing undesired side effects. Accordingly, the amount of biologic delivered depends in part on the particular therapeutic antibody and the severity of the condition being treated. Guidance in selecting appropriate doses of therapeutic antibodies is available (see, *e.g.*, Wawrzynczak (1996) *Antibody Therapy*, Bios Scientific Pub. Ltd, Oxfordshire, UK; Kresina (ed.) (1991) *Monoclonal Antibodies, Cytokines and Arthritis*, Marcel Dekker, New York, NY; Bach (ed.) (1993) *Monoclonal Antibodies and Peptide Therapy in Autoimmune Diseases*, Marcel Dekker, New York, NY; Baert, *et al.* (2003) *New Engl. J. Med.* 348:601-608; Milgrom *et al.* (1999) *New Engl. J. Med.* 341:1966-1973; Slamon *et al.* (2001) *New Engl. J. Med.* 344:783-792; Beniaminovitz *et al.* (2000) *New Engl. J. Med.* 342:613-619; Ghosh *et al.* (2003) *New Engl. J. Med.* 348:24-32; Lipsky *et al.* (2000) *New Engl. J. Med.* 343:1594-1602).

[00317] Determination of the appropriate dose can be made by the clinician, *e.g.*, using parameters or factors known or suspected in the art to affect treatment. Generally, the dose begins with an amount somewhat less than the optimum dose and it is increased by small

increments thereafter until the desired or optimum effect is achieved relative to any negative side effects. Important diagnostic measures include those of symptoms of, *e.g.*, the inflammation or level of inflammatory cytokines produced. In general, it is desirable that a biologic that will be used is derived from the same species as the animal targeted for treatment, thereby minimizing any immune response to the reagent. In the case of human subjects, for example, chimeric, humanized and fully human antibodies are may be desirable.

[00318] Antibodies or antigen binding fragments thereof can be provided by continuous infusion, or by doses administered, *e.g.*, daily, 1-7 times per week, weekly, bi-weekly, monthly, bimonthly, or quarterly. In some embodiments, a total weekly dose is generally at least 0.05 µg/kg body weight, more generally at least 0.2 µg/kg, 0.5 µg/kg, 1 µg/kg, 10 µg/kg, 100 µg/kg, 0.25 mg/kg, 1.0 mg/kg, 2.0 mg/kg, 5.0 mg/ml, 10 mg/kg, 25 mg/kg, 50 mg/kg or more (see, *e.g.*, Yang, *et al.* (2003) *New Engl. J. Med.* 349:427-434; Herold, *et al.* (2002) *New Engl. J. Med.* 346:1692-1698; Liu, *et al.* (1999) *J. Neurol. Neurosurg. Psych.* 67:451-456; Portielji, *et al.* (20003) *Cancer Immunol. Immunother.* 52:133-144). Doses may also be provided to achieve a pre-determined target concentration of the antibody in the subject's serum, such as 0.1, 0.3, 1, 3, 10, 30, 100, 300 µg/ml or more. In other embodiments, a fully human antibody is administered subcutaneously or intravenously, on a weekly, biweekly, "every 4 weeks," monthly, bimonthly, or quarterly basis at 10, 20, 50, 80, 100, 200, 500, 1000 or 2500 mg/subject.

[00319] As used herein, "inhibit" or "treat" or "treatment" includes a postponement of development of the symptoms associated with a disorder and/or a reduction in the severity of the symptoms of such disorder. The terms further include ameliorating existing uncontrolled or unwanted symptoms, preventing additional symptoms, and ameliorating or preventing the underlying causes of such symptoms. Thus, the terms denote that a beneficial result has been conferred on a vertebrate subject with a disorder, disease or symptom, or with the potential to develop such a disorder, disease or symptom.

[00320] As used herein, the terms "therapeutically effective amount", "therapeutically effective dose" and "effective amount" refer to an amount of the antibody, or antigen binding fragment thereof, that, when administered alone or in combination with an additional therapeutic agent to a cell, tissue, or subject, is effective to cause a measurable improvement in one or more symptoms of a disease or condition or the progression of such disease or condition. A therapeutically effective dose further refers to that amount of the binding compound sufficient to result in at

least partial amelioration of symptoms, *e.g.*, treatment, healing, prevention or amelioration of the relevant medical condition, or an increase in rate of treatment, healing, prevention or amelioration of such conditions. When applied to an individual active ingredient administered alone, a therapeutically effective dose refers to that ingredient alone. When applied to a combination, a therapeutically effective dose refers to combined amounts of the active ingredients that result in the therapeutic effect, whether administered in combination, serially or simultaneously. An effective amount of a therapeutic will result in an improvement of a diagnostic measure or parameter by at least 10%; usually by at least 20%; preferably at least about 30%; more preferably at least 40%, and most preferably by at least 50%. An effective amount can also result in an improvement in a subjective measure in cases where subjective measures are used to assess disease severity. In some embodiments, an amount is a therapeutically effective amount if it is an amount that can be used to treat or ameliorate tumors or gastric tumors.

[00321] The term “subject” as used throughout includes any organism, such as an animal, including a mammal (*e.g.*, rat, mouse, dog, cat, rabbit) and, for example, a human. In one embodiment, the subject is a human. A subject can also be referred to as a patient. In some embodiments, the subject is a subject in need thereof. A subject that is “in need thereof” refers to a subject that has been identified as requiring treatment for the condition that is to be treated and is treated with the specific intent of treating such condition. The conditions can be, for example, any of the conditions described herein.

[00322] In some embodiments, the methods comprise administering a therapeutically or prophylactically effective amount of one or more antibodies or antigen binding fragments of the antibodies described herein to a susceptible subject or to one exhibiting a condition in which C1s is known to have caused the pathology observed. Any active form of the antibody can be administered, including, but not limited to scFv, Fab and F(ab')₂ fragments and other forms of antibodies provided for herein.

[00323] The present disclosure provides a method to treat an individual having a complement-mediated disease or disorder, the method comprising administering to the individual an anti-C1s antibody of any of the embodiments disclosed herein or a pharmaceutical composition thereof. In some embodiments, the individual is a mammal. In some embodiments, the individual is a human. In some embodiments, the administering is intravenous. In some embodiments, the

administering is intrathecal. In some embodiments, the administering results in an outcome selected from the group consisting of: (a) a reduction in complement activation; (b) an improvement in cognitive function; (c) a reduction in neuron loss; (d) a reduction in phospho-Tau levels in neurons; (e) a reduction in glial cell activation; (f) a reduction in lymphocyte infiltration; (g) a reduction in macrophage infiltration; (h) a reduction in antibody deposition, (i) a reduction in glial cell loss; (j) a reduction in oligodendrocyte loss; (k) a reduction in dendritic cell infiltration; (l) a reduction in neutrophil infiltration; (m) a reduction in red blood cell lysis; (n) a reduction in red blood cell phagocytosis; (o) a reduction in platelet phagocytosis; (p) a reduction in platelet lysis; (q) an improvement in transplant graft survival; (r) a reduction in macrophage mediated phagocytosis; (s) an improvement in vision; (t) an improvement in motor control; (u) an improvement in thrombus formation; (v) an improvement in clotting; (w) an improvement in kidney function; (x) a reduction in antibody mediated complement activation; (y) a reduction in autoantibody mediated complement activation; (z) an improvement in anemia; (aa) reduction of demyelination; (ab) reduction of eosinophilia; (ac) a reduction in autoantibody mediated blister formation; (ad) a reduction in autoantibody induced pruritis; (ae) a reduction in autoantibody induced erythematosis; (af) a reduction in autoantibody mediated skin erosion; (ag) a reduction in red blood cell destruction due to transfusion reactions; (ah) a reduction in red blood cell lysis due to alloantibodies; (ai) a reduction in hemolysis due to transfusion reactions; (aj) a reduction in allo-antibody mediated platelet lysis; and (ak) a reduction in platelet lysis due to transfusion reactions. In some embodiments, the reduction in glial cell activation comprises reduction in astrocyte activation or reduction in microglia activation.

[00324] In some embodiments, a method of treating a subject with a C1s mediated disorder is provided. In some embodiments, the method comprises administering to the subject an antibody or antigen-binding fragment thereof as provided for herein or a pharmaceutical composition comprising an antibody or antigen-binding fragment thereof as provided for herein, thereby treating the C1s mediated disorder. The an antibody or antigen-binding fragment thereof of any of the embodiments provided for herein or the pharmaceutical compositions of any of the embodiments provided for herein inhibit complement C1s activity in an individual having a complement-mediated disease or disorder. In some embodiments, the individual is a mammal. In some embodiments, the individual is a human. In some embodiments, the administering is intravenous. In some embodiments, the administering is intrathecal. In some embodiments, the

administering results in an outcome selected from the group consisting of: (a) a reduction in complement activation; (b) an improvement in cognitive function; (c) a reduction in neuron loss; (d) a reduction in phospho-Tau levels in neurons; (e) a reduction in glial cell activation; (f) a reduction in lymphocyte infiltration; (g) a reduction in macrophage infiltration; (h) a reduction in antibody deposition; (i) a reduction in glial cell loss; (j) a reduction in oligodendrocyte loss; (k) a reduction in dendritic cell infiltration; (l) a reduction in neutrophil infiltration; (m) a reduction in red blood cell lysis; (n) a reduction in red blood cell phagocytosis; (o) a reduction in platelet phagocytosis; (p) a reduction in platelet lysis; (q) an improvement in transplant graft survival; (r) a reduction in macrophage mediated phagocytosis; (s) an improvement in vision; (t) an improvement in motor control; (u) an improvement in thrombus formation; (v) an improvement in clotting; (w) an improvement in kidney function; (x) a reduction in antibody mediated complement activation; (y) a reduction in autoantibody mediated complement activation; (z) an improvement in anemia; (aa) reduction of demyelination; (ab) reduction of eosinophilia; (ac) a reduction in autoantibody mediated blister formation; (ad) a reduction in autoantibody induced pruritis; (ae) a reduction in autoantibody induced erythematosis; (af) a reduction in autoantibody mediated skin erosion; (ag) a reduction in red blood cell destruction due to transfusion reactions; (ah) a reduction in red blood cell lysis due to alloantibodies; (ai) a reduction in hemolysis due to transfusion reactions; (aj) a reduction in allo-antibody mediated platelet lysis; and (ak) a reduction in platelet lysis due to transfusion reactions. In some embodiments, the reduction in glial cell activation comprises reduction in astrocyte activation or reduction in microglia activation. . In some embodiments, the C1s mediated disorder is selected from the group including, but not limited to, hemolysis, Cold Agglutinin Disease, Immune Thrombocytopenia (ITP), Myasthenia Gravis, Glomerulopathies, Atypical Hemolytic uremic syndrome, antiphospholipid antibody syndrome, or transplant rejection. In some embodiments, the C1s mediated disorder is hemolysis. In some embodiments, the C1s mediated disorder is Cold Agglutinin Disease. In some embodiments, the C1s mediated disorder is Immune Thrombocytopenia (ITP). In some embodiments, the C1s mediated disorder is Myasthenia Gravis. In some embodiments, the C1s mediated disorder is Glomerulopathies. In some embodiments, the C1s mediated disorder is Atypical Hemolytic uremic syndrome. In some embodiments, the C1s mediated disorder is antiphospholipid antibody syndrome. In some embodiments, the C1s mediated disorder is transplant rejection.

[00325] In some embodiments, the antibody or antigen-binding fragment thereof of any of the embodiments as provided for herein, or a pharmaceutical composition comprising the antibody or antigen-binding fragment thereof of any of the embodiments as provided for herein is for the use in the treatment of a complement-mediated disease or disorder. . In some embodiments, the complement-mediated disorder is selected from the group including, but not limited to, hemolysis, Cold Agglutinin Disease, Immune Thrombocytopenia (ITP), Myastenia Gravis, Glomerulopathies, Atypical Hemolytic uremic syndrome, antiphospholipid antibody syndrome, or transplant rejection. In some embodiments, the C1s mediated disorder is hemolysis. In some embodiments, the C1s mediated disorder is Cold Agglutinin Disease. In some embodiments, the C1s mediated disorder is Immune Thrombocytopenia (ITP). In some embodiments, the C1s mediated disorder is Myastenia Gravis. In some embodiments, the C1s mediated disorder is Glomerulopathies. In some embodiments, the C1s mediated disorder is Atypical Hemolytic uremic syndrome. In some embodiments, the C1s mediated disorder is antiphospholipid antibody syndrome. In some embodiments, the C1s mediated disorder is transplant rejection. In some embodiments, the C1s mediated disorder is selected from the group including, but not limited to, hemolysis and Cold Agglutinin Disease. In some embodiments, the C1s mediated disorder is hemolysis. In some embodiments, the C1s mediated disorder is Cold Agglutinin Disease.

[00326] The present disclosure provides use of an anti-C1s antibody of any of the embodiments in the manufacture of a medicament for the treatment of an individual having a complement-mediated disease or disorder. Accordingly, in some embodiments, an antibody or binding fragment thereof or a pharmaceutical composition is provided for use as a medicament. In some embodiments, an antibody or binding fragment thereof is provided for use as a medicament. In some embodiments, a pharmaceutical composition is provided for use as a medicament. In some embodiments, the antibody or binding fragment thereof is an antibody or antigen binding fragment as provided for herein. In some embodiments, the pharmaceutical composition comprises an antibody or antigen binding fragment as provided for herein. In some embodiments, the pharmaceutical composition is as provided for herein. In some embodiments, the medicament is for use in treatment of a C1s mediated disease or disorder. In some embodiments, the complement-mediated disorder is, but not limited to, hemolysis, Cold Agglutinin Disease, Immune Thrombocytopenia (ITP), Myastenia Gravis, Glomerulopathies, Atypical Hemolytic uremic syndrome, antiphospholipid antibody syndrome, or transplant

rejection. In some embodiments, the C1s mediated disorder is hemolysis. In some embodiments, the C1s mediated disorder is Cold Agglutinin Disease. In some embodiments, the C1s mediated disorder is Immune Thrombocytopenia (ITP). In some embodiments, the C1s mediated disorder is Myasthenia Gravis. In some embodiments, the C1s mediated disorder is Glomerulopathies. In some embodiments, the C1s mediated disorder is Atypical Hemolytic uremic syndrome. In some embodiments, the C1s mediated disorder is antiphospholipid antibody syndrome. In some embodiments, the C1s mediated disorder is transplant rejection.

[00327] In some embodiments, a use of an antibody or antigen binding fragment as provided for herein or a pharmaceutical composition as provided for herein is provided. In some embodiments, the use is for the treatment of a C1a mediated disorder. In some embodiments, a use of an antibody or antigen binding fragment as provided for herein is provided, the use for the treatment of a C1a mediated disorder. In some embodiments, a use of a pharmaceutical composition comprising an antibody or antigen binding fragment as provided for herein is provided, the use for the treatment of a C1a mediated disorder. In some embodiments, the pharmaceutical composition is as provided for herein. The antibody of any of the embodiments or pharmaceutical compositions thereof inhibit complement C1s activity in an individual having a complement-mediated disease or disorder. In some embodiments, the complement-mediated disorder is, but not limited to, hemolysis, Cold Agglutinin Disease, Immune Thrombocytopenia (ITP), Myasthenia Gravis, Glomerulopathies, Atypical Hemolytic uremic syndrome, antiphospholipid antibody syndrome, or transplant rejection. In some embodiments, the C1s mediated disorder is hemolysis. In some embodiments, the C1s mediated disorder is Cold Agglutinin Disease. In some embodiments, the C1s mediated disorder is Immune Thrombocytopenia (ITP). In some embodiments, the C1s mediated disorder is Myasthenia Gravis. In some embodiments, the C1s mediated disorder is Glomerulopathies. In some embodiments, the C1s mediated disorder is Atypical Hemolytic uremic syndrome. In some embodiments, the C1s mediated disorder is antiphospholipid antibody syndrome. In some embodiments, the C1s mediated disorder is transplant rejection.

[00328] The present disclosure provides use of an anti-C1s antibody of any of the embodiments or a pharmaceutical composition thereof in the manufacture of a medicament for inhibiting complement C1s activity. In some embodiments, the present disclosure provides use of an anti-C1s antibody of any of the embodiments or a pharmaceutical composition thereof in the

manufacture of a medicament for inhibiting complement C1s activity in an individual having a complement-mediated disease or disorder. In some embodiments, the complement-mediated disorder is, but not limited to, hemolysis, Cold Agglutinin Disease, Immune Thrombocytopenia (ITP), Myasthenia Gravis, Glomerulopathies, Atypical Hemolytic uremic syndrome, antiphospholipid antibody syndrome, or transplant rejection.

[00329] The present disclosure provides an anti-C1s antibody of any of the embodiments or a pharmaceutical composition thereof for use in medical therapy.

[00330] The present disclosure provides an anti-C1s antibody of any of the embodiments or a pharmaceutical composition thereof for treating an individual having a complement-mediated disease or disorder. In some embodiments, the complement-mediated disorder is, but not limited to, hemolysis, Cold Agglutinin Disease, Immune Thrombocytopenia (ITP), Myasthenia Gravis, Glomerulopathies, Atypical Hemolytic uremic syndrome, antiphospholipid antibody syndrome, or transplant rejection. In some embodiments, the C1s mediated disorder is hemolysis. In some embodiments, the C1s mediated disorder is Cold Agglutinin Disease. In some embodiments, the C1s mediated disorder is Immune Thrombocytopenia (ITP). In some embodiments, the C1s mediated disorder is Myasthenia Gravis. In some embodiments, the C1s mediated disorder is Glomerulopathies. In some embodiments, the C1s mediated disorder is Atypical Hemolytic uremic syndrome. In some embodiments, the C1s mediated disorder is antiphospholipid antibody syndrome. In some embodiments, the C1s mediated disorder is transplant rejection.

[00331] The present disclosure provides an anti-C1s antibody of any of the embodiments or a pharmaceutical composition thereof for inhibiting complement C1s protein activity. The present disclosure provides an anti-C1s antibody of any of the embodiments or a pharmaceutical composition thereof for inhibiting complement C1s protein activity in an individual having a complement-mediated disease or disorder. In some embodiments, the complement-mediated disorder is, but not limited to, hemolysis, Cold Agglutinin Disease, Immune Thrombocytopenia (ITP), Myasthenia Gravis, Glomerulopathies, Atypical Hemolytic uremic syndrome, antiphospholipid antibody syndrome, or transplant rejection. In some embodiments, the C1s mediated disorder is hemolysis. In some embodiments, the C1s mediated disorder is Cold Agglutinin Disease. In some embodiments, the C1s mediated disorder is Immune Thrombocytopenia (ITP). In some embodiments, the C1s mediated disorder is Myasthenia Gravis. In some embodiments, the C1s mediated disorder is Glomerulopathies. In some embodiments, the

C1s mediated disorder is Atypical Hemolytic uremic syndrome. In some embodiments, the C1s mediated disorder is antiphospholipid antibody syndrome. In some embodiments, the C1s mediated disorder is transplant rejection.

[00332] The present disclosure provides a method to diagnose a complement-mediated disease or disorder in an individual, the method comprising: (a) determining the amount of a complement C1s protein in a biological sample obtained from the individual, wherein the step of determining comprises: (i) contacting the biological sample with an anti-C1s antibody of any of the embodiments; and (ii) quantitating binding of the antibody to complement C1s protein present in the sample; and (b) comparing the amount of the complement C1s protein to a normal control value that indicates the amount of complement C1s protein in a normal control individual, wherein a significant difference between the amount of C1s protein in the biological sample and the normal control value indicates that the individual has a complement-mediated disease or disorder. In some embodiments, the biological sample is selected from the group consisting of blood, serum, plasma, urine, saliva, cerebrospinal fluid, interstitial fluid, ocular fluid, synovial fluid, solid tissue sample, tissue culture sample, and cellular sample.

[00333] The present disclosure provides a method to monitor progression of a complement-mediated disease or disorder in an individual, the method comprising: (a) determining a first amount of complement a C1s protein in a biological sample obtained from the individual at a first time point; (b) determining a second amount of complement a C1s protein in a biological sample obtained from the individual at a second time point; and (c) comparing the second amount of complement C1s protein with the first amount of complement C1s protein. The steps of determining comprise: (i) contacting the biological sample with an anti-C1s antibody of any of the embodiments; and (ii) quantitating binding of the antibody to complement C1s protein present in the sample. In some embodiments, the first time point is a time point before initiation of a treatment regimen, and the second time point is a time point after initiation of a treatment regimen. In some embodiments, the biological sample is selected from the group consisting of blood, serum, plasma, urine, saliva, cerebrospinal fluid, interstitial fluid, ocular fluid, synovial fluid, solid tissue sample, tissue culture sample, and cellular sample.

[00334] The present disclosure provides an in vitro method to detect complement C1s protein in a biological sample obtained from an individual, the method comprising: (a) contacting the biological sample with an anti-C1s antibody of any of the embodiments; and (b) detecting

binding of the antibody to complement C1s protein present in the sample. In some embodiments, the biological sample is selected from the group consisting of blood, serum, plasma, urine, saliva, cerebrospinal fluid, interstitial fluid, ocular fluid, synovial fluid, solid tissue sample, tissue culture sample, and cellular sample. In some embodiments, the method is quantitative.

[00335] The present disclosure provides a method to detect complement C1s protein in a living individual in vivo, the method comprising: (a) administering to the individual an anti-C1s antibody of any of the embodiments; and (b) detecting binding of the antibody to complement C1s protein in the individual using an imaging method. In some embodiments, the binding is detected in the individual at a site altered by a complement-mediated disease or disorder. In some embodiments, the binding is detected in the brain of the individual. In some of the embodiments, the antibody comprises a contrast agent suitable for use in the imaging method. In some embodiments, the imaging method is selected from the group consisting of magnetic resonance imaging, positron emission tomography, and IVIS instrumentation. In some embodiments, the method is quantitative.

[00336] In some embodiments, the biological sample is selected from the group consisting of blood, serum, plasma, urine, saliva, cerebrospinal fluid, interstitial fluid, ocular fluid, synovial fluid, solid tissue sample, tissue culture sample, and a cellular sample.

[00337] In some embodiments, the methods of the present disclosure provide that the individual is suspected of having a complement-mediated disease or disorder, has been diagnosed as having a complement-mediated disease or disorder, or has a genetic predisposition to developing a complement-mediated disease or disorder.

[00338] The present disclosure provides a composition comprising: (a) an anti-C1s antibody of any of the embodiments; and (b) a solution comprising one or more agents that maintain an organ or a tissue intended for transplantation into a recipient individual. In some embodiments, the solution is an organ preservation solution or a tissue preservation solution. In some embodiments, the solution is an organ perfusion solution or a tissue perfusion solution. In some embodiments, the solution comprises: i) a salt; ii) an agent that reduces edema; iii) an oxygen free radical scavenger; and iii) an energy supply system component. In some embodiments, the composition comprises potassium lactobionate, KH_2PO_4 , MgSO_4 , raffinose, adenosine, glutathione, allopurinol, and/or hydroxyethyl starch.

[00339] The present disclosure provides an organ or tissue preservation solution comprising an anti-C1s antibody of any of the embodiments or a pharmaceutical composition thereof.

[00340] The present disclosure provides an organ or tissue perfusion solution comprising an anti-C1s antibody of any of the embodiments or a pharmaceutical composition thereof.

[00341] The present disclosure provides a method for maintaining an organ or tissue for transplant, the method comprising contacting the organ or the tissue with a composition comprising: (a) an anti-C1s antibody of any of the embodiments; and (b) an organ or tissue preservation solution of any of the embodiments or an organ or tissue perfusion solution of any of the embodiments.

[00342] The present disclosure provides an isolated organ or tissue maintained in a composition comprising: (a) an anti-C1s antibody of any of the embodiments; and (b) an organ or tissue preservation solution of any of the embodiments or an organ or tissue perfusion solution of any of the embodiments. In some embodiments, the organ is selected from the group consisting of an eye, a heart, an intestine, a kidney, a liver, a lung, a pancreas, a stomach, and a thymus. In some embodiments, the tissue is selected from the group consisting of bone, bone marrow, cornea, heart valve, islet of Langerhans, tendon, skin, and vein.

[00343] The present disclosure provides an in vitro method for inhibiting complement C1s activity in an organ or a tissue, the method comprising contacting the organ or the tissue with an anti-C1s antibody of any of the embodiments or a pharmaceutical composition thereof.

[00344] Treatment of individuals may comprise the administration of a therapeutically effective amount of the antibodies described herein. The antibodies can be provided in a kit, such as those provided herein. The antibodies can be used or administered alone or in admixture with another therapeutic, analgesic, or diagnostic agent, such as provided for herein. In providing a patient with an antibody, or fragment thereof, capable of binding to C1s, or an antibody capable of protecting against C1s in a recipient patient, the dosage of administered agent will vary depending upon such factors as the patient's age, weight, height, sex, general medical condition, previous medical history, etc.

[00345] An antibody, capable treating a condition associated with C1s activity or use to treat a C1s related pathology, is intended to be provided to subjects in an amount sufficient to affect a reduction, resolution, or amelioration in the C1s related symptom or pathology. Examples of such pathologies are provided for herein.

[00346] Accordingly, in some embodiments, methods of treating a subject with a C1s mediated disorder are provided. In some embodiments, the method comprises administering a pharmaceutical composition comprising an antibody, or antigen binding fragment thereof, as provided herein. In some embodiments, the disorder is as provided for herein.

[00347] As provided for herein, the antibodies, or antigen binding fragments thereof, can be administered with other therapeutics. These can be administered simultaneously or sequentially.

[00348] Kits are also provided which are useful for carrying out embodiments described herein. The present kits can comprise a first container containing or packaged in association with the above-described antibodies. The kit may also comprise another container containing or packaged in association solutions necessary or convenient for carrying out the embodiments. The containers can be made of glass, plastic or foil and can be a vial, bottle, pouch, tube, bag, etc. The kit may also contain written information, such as procedures for carrying out the embodiments or analytical information, such as the amount of reagent contained in the first container means. The container may be in another container apparatus, *e.g.* a box or a bag, along with the written information.

[00349] In some embodiments, antibodies that bind to a C1s protein are provided. In some embodiments, the antibodies are antibodies or antigen binding fragments as provided for herein. In some embodiments, the antibodies or antigen binding fragments comprise an amino acid sequence as provided for herein, or a variant thereof as provided for herein. In some embodiments, the antibody is isolated. In some embodiments, the antibody binds specifically to the active form of C1s.

[00350] In some embodiments, the antibody inhibits or neutralizes the function of an active form of C1s protein. As used herein, the term “neutralize” means that the activity or function of the protein is inhibited. The inhibition can be complete or partial. In some embodiments, the activity or function of the protein is inhibited at least 10, 20, 30, 40, 50, 60, 70, 80, 90, 95, or 99%. The percent inhibition can be based upon the function or activity of the protein in the absence of the antibody. In some embodiments, the antibody inhibits the function facilitated by C1s.

Enumerated Embodiments

[00351] In some embodiments, the following embodiments are provided.

1. An antibody, or an antigen binding fragment thereof, wherein the antibody or antibody fragment comprises:

(a) a heavy chain variable region comprising heavy chain HCDR1, HCDR2, and HCDR3 sequences, wherein the heavy chain HCDR1 sequence has the amino acid sequence of SEQ ID NO: 9; the heavy chain HCDR2 has the amino acid sequence of SEQ ID NO: 10 and the heavy chain HCDR3 sequence has the amino acid sequence of SEQ ID NO: 11 or variants of any of the foregoing; and (ii) a light chain variable region comprising light chain LCDR1, LCDR2, and LCDR3 sequences, wherein the light chain LCDR1 sequence has the amino acid sequence SEQ ID NO: 12; the light chain LCDR2 sequence has the amino acid sequence of SEQ ID NO: 13; and the light chain LCDR3 sequence has the amino acid sequence of SEQ ID NO: 14; or variants of any of the foregoing;

(b) a heavy chain variable region comprising heavy chain HCDR1, HCDR2, and HCDR3 sequences, wherein the heavy chain HCDR1 sequence has the amino acid sequence of SEQ ID NO: 15; the heavy chain HCDR2 has the amino acid sequence of SEQ ID NO: 16 and the heavy chain HCDR3 sequence has the amino acid sequence of SEQ ID NO: 17 or variants of any of the foregoing; and (ii) a light chain variable region comprising light chain LCDR1, LCDR2, and LCDR3 sequences, wherein the light chain LCDR1 sequence has the amino acid sequence SEQ ID NO: 18; the light chain LCDR2 sequence has the amino acid sequence of SEQ ID NO: 19; and the light chain LCDR3 sequence has the amino acid sequence of SEQ ID NO: 20; or variants of any of the foregoing; or

(c) a heavy chain variable region comprising heavy chain HCDR1, HCDR2, and HCDR3 sequences, wherein the heavy chain HCDR1 sequence has the amino acid sequence of SEQ ID NO: 21; the heavy chain HCDR2 has the amino acid sequence of SEQ ID NO: 22 and the heavy chain HCDR3 sequence has the amino acid sequence of SEQ ID NO: 23 or variants of any of the foregoing; and (ii) a light chain variable region comprising light chain LCDR1, LCDR2, and LCDR3 sequences, wherein the light chain LCDR1 sequence has the amino acid sequence SEQ ID NO: 24; the light chain LCDR2 sequence has the amino acid sequence of SEQ ID NO: 25; and the light chain LCDR3 sequence has the amino acid sequence of SEQ ID NO: 26; or variants of any of the foregoing.

2. An antibody, or an antigen binding fragment thereof, wherein the antibody or antibody fragment comprises:

(a) a heavy chain variable region comprising heavy chain HCDR1, HCDR2, and HCDR3 sequences, wherein the heavy chain HCDR1 sequence has the amino acid sequence of SEQ ID NO: 27; the heavy chain HCDR2 has the amino acid sequence of SEQ ID NO: 28 and the heavy chain HCDR3 sequence has the amino acid sequence of SEQ ID NO: 11 or variants of any of the foregoing; and (ii) a light chain variable region comprising light chain LCDR1, LCDR2, and LCDR3 sequences, wherein the light chain LCDR1 sequence has the amino acid sequence SEQ ID NO: 29; the light chain LCDR2 sequence has the amino acid sequence of SEQ ID NO: 30; and the light chain LCDR3 sequence has the amino acid sequence of SEQ ID NO: 31; or variants of any of the foregoing;

(b) a heavy chain variable region comprising heavy chain HCDR1, HCDR2, and HCDR3 sequences, wherein the heavy chain HCDR1 sequence has the amino acid sequence of SEQ ID NO: 32; the heavy chain HCDR2 has the amino acid sequence of SEQ ID NO: 33 and the heavy chain HCDR3 sequence has the amino acid sequence of SEQ ID NO: 17 or variants of any of the foregoing; and (ii) a light chain variable region comprising light chain LCDR1, LCDR2, and LCDR3 sequences, wherein the light chain LCDR1 sequence has the amino acid sequence SEQ ID NO: 34; the light chain LCDR2 sequence has the amino acid sequence of SEQ ID NO: 35; and the light chain LCDR3 sequence has the amino acid sequence of SEQ ID NO: 36; or variants of any of the foregoing; or

(c) a heavy chain variable region comprising heavy chain HCDR1, HCDR2, and HCDR3 sequences, wherein the heavy chain HCDR1 sequence has the amino acid sequence of SEQ ID NO: 37; the heavy chain HCDR2 has the amino acid sequence of SEQ ID NO: 38 and the heavy chain HCDR3 sequence has the amino acid sequence of SEQ ID NO: 23 or variants of any of the foregoing; and (ii) a light chain variable region comprising light chain LCDR1, LCDR2, and LCDR3 sequences, wherein the light chain LCDR1 sequence has the amino acid sequence SEQ ID NO: 39; the light chain LCDR2 sequence has the amino acid sequence of SEQ ID NO: 40; and the light chain LCDR3 sequence has the amino acid sequence of SEQ ID NO: 41; or variants of any of the foregoing.

3. An antibody, or an antigen binding fragment thereof, wherein the antibody or antibody fragment comprises:

(a) a heavy chain variable region comprising heavy chain HCDR1, HCDR2, and HCDR3 sequences, wherein the heavy chain HCDR1 sequence has the amino acid sequence of SEQ ID NO: 42; the heavy chain HCDR2 has the amino acid sequence of SEQ ID NO: 43 and the heavy chain HCDR3 sequence has the amino acid sequence of SEQ ID NO: 44 or variants of any of the foregoing; and (ii) a light chain variable region comprising light chain LCDR1, LCDR2, and LCDR3 sequences, wherein the light chain LCDR1 sequence has the amino acid sequence SEQ ID NO: 45; the light chain LCDR2 sequence has the amino acid sequence of SEQ ID NO: 30; and the light chain LCDR3 sequence has the amino acid sequence of SEQ ID NO: 14; or variants of any of the foregoing;

(b) a heavy chain variable region comprising heavy chain HCDR1, HCDR2, and HCDR3 sequences, wherein the heavy chain HCDR1 sequence has the amino acid sequence of SEQ ID NO: 46; the heavy chain HCDR2 has the amino acid sequence of SEQ ID NO: 47 and the heavy chain HCDR3 sequence has the amino acid sequence of SEQ ID NO: 48 or variants of any of the foregoing; and (ii) a light chain variable region comprising light chain LCDR1, LCDR2, and LCDR3 sequences, wherein the light chain LCDR1 sequence has the amino acid sequence SEQ ID NO: 49; the light chain LCDR2 sequence has the amino acid sequence of SEQ ID NO: 35; and the light chain LCDR3 sequence has the amino acid sequence of SEQ ID NO: 20; or variants of any of the foregoing; or

(c) a heavy chain variable region comprising heavy chain HCDR1, HCDR2, and HCDR3 sequences, wherein the heavy chain HCDR1 sequence has the amino acid sequence of SEQ ID NO: 50; the heavy chain HCDR2 has the amino acid sequence of SEQ ID NO: 51 and the heavy chain HCDR3 sequence has the amino acid sequence of SEQ ID NO: 52 or variants of any of the foregoing; and (ii) a light chain variable region comprising light chain LCDR1, LCDR2, and LCDR3 sequences, wherein the light chain LCDR1 sequence has the amino acid sequence SEQ ID NO: 53; the light chain LCDR2 sequence has the amino acid sequence of SEQ ID NO: 40; and the light chain LCDR3 sequence has the amino acid sequence of SEQ ID NO: 26; or variants of any of the foregoing.

4. An antibody, or antigen-binding fragment thereof, wherein:

a. the HCDR1, HCDR2 and HCDR3 are selected from SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, respectively, from SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID NO: 11, respectively, and from SEQ ID NO: 42, SEQ ID NO: 43, SEQ ID NO: 44, respectively, and the LCDR1, LCDR2 and LCDR3 are selected from from SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, respectively, from SEQ ID NO: 29, SEQ ID NO: 30, SEQ ID NO: 31, respectively, and from SEQ ID NO: 45, SEQ ID NO: 30, SEQ ID NO: 14, respectively; or

b. the HCDR1, HCDR2 and HCDR3 are selected from SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, respectively, from SEQ ID NO: 32, SEQ ID NO: 33, SEQ ID NO: 17, respectively, and from SEQ ID NO: 46, SEQ ID NO: 47, SEQ ID NO: 48, respectively, and the LCDR1, LCDR2 and LCDR3 are selected from from SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 20, respectively, from SEQ ID NO: 34, SEQ ID NO: 35, SEQ ID NO: 36, respectively, and from SEQ ID NO: 49, SEQ ID NO: 35, SEQ ID NO: 20, respectively; or

c. the HCDR1, HCDR2 and HCDR3 are selected from SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO: 23, respectively, SEQ ID NO: 37, SEQ ID NO: 38, SEQ ID NO: 23, respectively, and SEQ ID NO: 50, SEQ ID NO: 51, SEQ ID NO: 52, respectively, and the LCDR1, LCDR2 and LCDR3 are selected from SEQ ID NO: 24, SEQ ID NO: 25, SEQ ID NO: 26, respectively, SEQ ID NO: 39, SEQ ID NO: 40, SEQ ID NO: 41, respectively, and SEQ ID NO: 53, SEQ ID NO: 40, SEQ ID NO: 26, respectively.

5. The antibody or antigen-binding fragment thereof of any one of embodiments 1-4, wherein the heavy chain comprises:

a. a heavy chain variable region having at least 90% sequence identity to SEQ ID NO:1, wherein the antibody or antigen binding fragment thereof maintains the sequences of HCDR1, HCDR2, HCDR2, LCDR1, LCD2, and LCDR3 set forth in subpart a of any one of embodiments 1-4; or

b. a heavy chain variable region having at least 90% sequence identity to SEQ ID NO:3, wherein the antibody or antigen binding fragment thereof maintains the sequences of

HCDR1, HCDR2, HCDR2, LCDR1, LCD2, and LCDR3 set forth in subpart b of any one of embodiments 1-4; or

c. a heavy chain variable region having at least 90% sequence identity to SEQ ID NO:5, wherein the antibody or antigen binding fragment thereof maintains the sequences of HCDR1, HCDR2, HCDR2, LCDR1, LCD2, and LCDR3 set forth in subpart c of any one of embodiments 1-4.

6. The antibody or antigen-binding fragment thereof of any one of embodiments 1-4, wherein the light chain comprises:

a. a light chain variable region having at least 90% sequence identity to SEQ ID NO:2, wherein the antibody or antigen binding fragment thereof maintains the sequences of HCDR1, HCDR2, HCDR2, LCDR1, LCD2, and LCDR3 set forth in subpart a of any one of embodiments 1-4; or

b. a light chain variable region having at least 90% sequence identity to SEQ ID NO:4, wherein the antibody or antigen binding fragment thereof maintains the sequences of HCDR1, HCDR2, HCDR2, LCDR1, LCD2, and LCDR3 set forth in subpart b of any one of embodiments 1-4; or

c. a light chain variable region having at least 90% sequence identity to SEQ ID NO:6, wherein the antibody or antigen binding fragment thereof maintains the sequences of HCDR1, HCDR2, HCDR2, LCDR1, LCD2, and LCDR3 set forth in subpart c of any one of embodiments 1-4.

7. The antibody or antigen-binding fragment thereof of any one of embodiments 1-4, wherein the antibody or antigen binding fragment thereof comprises:

a. a light chain variable region of the light chain having at least 90% sequence identity to SEQ ID NO:2, and a heavy chain variable region of the heavy chain having at least

90% sequence identity to SEQ ID NO:1, wherein the antibody or antigen binding fragment thereof maintains the sequences of HCDR1, HCDR2, HCDR2, LCDR1, LCD2, and LCDR3 set forth in subpart a of any one of embodiments 1-4; or

b. a light chain variable region of the light chain having at least 90% sequence identity to SEQ ID NO:4, and a heavy chain variable region of the heavy chain having at least 90% sequence identity to SEQ ID NO:3, wherein the antibody or antigen binding fragment thereof maintains the sequences of HCDR1, HCDR2, HCDR2, LCDR1, LCD2, and LCDR3 set forth in subpart b of any one of embodiments 1-4; or

c. a light chain variable region of the light chain having at least 90% sequence identity to SEQ ID NO:6, and a heavy chain variable region of the heavy chain having at least 90% sequence identity to SEQ ID NO:5, wherein the antibody or antigen binding fragment thereof maintains the sequences of HCDR1, HCDR2, HCDR2, LCDR1, LCD2, and LCDR3 set forth in subpart c of any one of embodiments 1-4.

8. The antibody or antigen-binding fragment thereof of embodiment 7, wherein the light chain variable region comprises SEQ ID NO:2, and the heavy chain variable region comprises SEQ ID NO:1.

9. The antibody or antigen-binding fragment thereof of any one of embodiments 1-4, wherein:

a. the heavy chain has at least 90% sequence identity to SEQ ID NO:66 or SEQ ID NO: 67, wherein the antibody or antigen binding fragment thereof maintains the sequences of HCDR1, HCDR2, HCDR2, LCDR1, LCD2, and LCDR3 set forth in subpart a of any one of embodiments 1-4; or

b. the heavy chain has at least 90% sequence identity to SEQ ID NO:68 or SEQ ID NO: 69, wherein the antibody or antigen binding fragment thereof maintains the sequences of HCDR1, HCDR2, HCDR2, LCDR1, LCD2, and LCDR3 set forth in subpart b of any one of embodiments 1-4; or

c. the heavy chain has at least 90% sequence identity to SEQ ID NO:70 or SEQ ID NO: 71, wherein the antibody or antigen binding fragment thereof maintains the sequences of HCDR1, HCDR2, HCDR2, LCDR1, LCD2, and LCDR3 set forth in subpart c of any one of embodiments 1-4.

10. The antibody or antigen-binding fragment thereof of any one of embodiments 1-4, wherein the light chain comprises:

a. the light chain has at least 90% sequence identity to SEQ ID NO:72, wherein the antibody or antigen binding fragment thereof maintains the sequences of HCDR1, HCDR2, HCDR2, LCDR1, LCD2, and LCDR3 set forth in subpart a of any one of embodiments 1-4; or

b. the light chain has at least 90% sequence identity to SEQ ID NO:73, wherein the antibody or antigen binding fragment thereof maintains the sequences of HCDR1, HCDR2, HCDR2, LCDR1, LCD2, and LCDR3 set forth in subpart b of any one of embodiments 1-4; or

c. the light chain has at least 90% sequence identity to SEQ ID NO:74, wherein the antibody or antigen binding fragment thereof maintains the sequences of HCDR1, HCDR2, HCDR2, LCDR1, LCD2, and LCDR3 set forth in subpart c of any one of embodiments 1-4.

11. The antibody or antigen-binding fragment thereof of any one of embodiments 1-4, wherein:

a. the light chain has at least 90% sequence identity to SEQ ID NO:72, and the heavy chain has at least 90% sequence identity to SEQ ID NO:66 or SEQ ID NO: 67, wherein the antibody or antigen binding fragment thereof maintains the sequences of HCDR1, HCDR2, HCDR2, LCDR1, LCD2, and LCDR3 set forth in subpart a of any one of embodiments 1-4; or

b. the light chain has at least 90% sequence identity to SEQ ID NO:73, and the heavy chain has at least 90% sequence identity to SEQ ID NO:68 or SEQ ID NO: 69, wherein

the antibody or antigen binding fragment thereof maintains the sequences of HCDR1, HCDR2, HCDR2, LCDR1, LCD2, and LCDR3 set forth in subpart b of any one of embodiments 1-4; or

c. the light chain has at least 90% sequence identity to SEQ ID NO:74, and the heavy chain has at least 90% sequence identity to SEQ ID NO:70 or SEQ ID NO: 71, wherein the antibody or antigen binding fragment thereof maintains the sequences of HCDR1, HCDR2, HCDR2, LCDR1, LCD2, and LCDR3 set forth in subpart c of any one of embodiments 1-4.

12. The antibody or antigen-binding fragment thereof of embodiment 11, wherein:

the light chain comprises SEQ ID NO:72, and the heavy chain comprises SEQ ID NO: 66 or SEQ ID NO: 67;

the light chain comprises SEQ ID NO:73, and the heavy chain comprises SEQ ID NO: 68 or SEQ ID NO: 69; or

the light chain comprises SEQ ID NO:74, and the heavy chain comprises SEQ ID NO: 70 or SEQ ID NO: 71;

13. The antibody or antigen-binding fragment thereof of any one of the preceding embodiments, wherein the antibody binding fragment is a scFv antibody, a Fab fragment, a Fab' fragment, or an F(ab')₂ fragment.

14. The antibody or antigen binding fragment thereof of any one of the preceding embodiments, wherein the antibody is a monoclonal antibody.

15. The antibody or antigen binding fragment thereof of any one of the preceding embodiments, wherein the antibody is a humanized antibody.

16. The antibody or antigen binding fragment thereof of any one of the preceding embodiments, wherein the antibody or antigen binding fragment thereof comprises the sequence selected from one or more of the following sequences: SEQ ID NO: 1; SEQ ID NO: 2; SEQ ID NO: 3; SEQ ID NO: 4; SEQ ID NO: 5; SEQ ID NO: 6, or a variant thereof.

17. The antibody or antigen binding fragment thereof of any one of the preceding embodiments, wherein the antibody, or antigen binding fragment thereof, comprises a V_L peptide of SEQ ID NOs: 2, 4, or 6, or any variant thereof.
18. The antibody or antigen binding fragment thereof of any one of the preceding embodiments, wherein the antibody, or antigen binding fragment thereof, comprises a V_H peptide of SEQ ID NOs: 1, 3, or 5, or any variant thereof.
19. The antibody or antigen binding fragment thereof of any one of the preceding embodiments, wherein the antibody, or antigen binding fragment thereof, comprises a constant region as provided for herein.
20. The antibody or antigen binding fragment thereof of any one of the preceding embodiments, wherein the heavy chain variable region and the light chain variable region are not linked by a linker.
21. The antibody or antigen binding fragment thereof of any one of the preceding embodiments, wherein the heavy chain variable region and the light chain variable region are linked with a peptide linker.
22. The antibody or antigen binding fragment thereof of embodiment 21, wherein the peptide linker comprises a sequence of (GGGGS)_n (SEQ ID NO:54); (GGGGA)_n (SEQ ID NO: 55), or any combination thereof, wherein each n is independently 1-5.
23. A variant of the antibody or antigen binding fragment thereof of any one of the preceding embodiments, wherein the variant has 1-10 substitutions, deletions, or insertions.
24. A variant of the antibody or antigen binding fragment thereof of any one of the preceding embodiments, wherein the variant has 1-10 conservative substitutions.
25. A recombinant antibody or an antigen binding fragment thereof that binds to a C1s, wherein the antibody or antigen binding fragment thereof comprises an amino acid sequence, or a variant thereof, as provided for herein.

26. An isolated nucleic acid molecule encoding an antibody, or an antigen binding fragment thereof, a heavy chain variable region, a light chain variable region, heavy chain, or light chain, of any of the preceding embodiments.
27. The isolated nucleic acid sequence of embodiment 26 comprising SEQ ID NO:59, SEQ ID NO:61, or SEQ ID NO:63.
28. The isolated nucleic acid sequence of embodiment 27 comprising SEQ ID NO:59.
29. The isolated nucleic acid sequence of embodiment 26 comprising SEQ ID NO:60, SEQ ID NO:62, or SEQ ID NO:64.
30. The isolated nucleic acid sequence of embodiment 29 comprising SEQ ID NO:60.
31. An expression vector comprising the nucleic acid molecule of any one of embodiments 26-30.
32. A host cell comprising the nucleic acid molecule of any one of embodiments 26-30 or the vector of embodiment 31.
33. An antibody or antigen-binding fragment produced by the host cell of embodiment 32.
34. A pharmaceutical composition comprising an antibody, or antigen binding fragment thereof, of any one of embodiments 1-25.
35. The pharmaceutical composition of embodiment 34, wherein the composition is formulated for intravenous or subcutaneous injection.
36. The pharmaceutical composition of embodiment 34, wherein the composition is an injectable pharmaceutical composition.
37. A method of producing a polypeptide comprising a heavy chain variable region or light chain variable region, the method comprising:

(a) growing the host cell of embodiment 32 under conditions so that the host cell expresses the polypeptide comprising the heavy chain variable region or the light chain variable region; and

(b) purifying the polypeptide comprising the heavy chain variable region or the light chain variable region.

38. A method of producing an antibody that binds human C1s, or an antigen binding fragment of the antibody, the method comprising:

(a) growing the host cell of embodiment 32 under conditions so that the host cell expresses a polypeptide or polypeptides comprising the immunoglobulin heavy chain variable region and/or the immunoglobulin light chain variable region, thereby producing the antibody or the antigen-binding fragment of the antibody; and

(b) purifying the antibody or the antigen-binding fragment of the antibody.

39. A method of treating a subject with C1s mediated disorder, the method comprising administering to the subject an antibody, or antigen binding fragment thereof, of any one of embodiments 1-25 or 33 or a pharmaceutical composition of any one of embodiments 34-36.

40. The method of embodiment 39, wherein the disorder is hemolysis, Cold Agglutinin Disease, Immune Thrombocytopenia (ITP), Myasthenia Gravis, Glomerulopathies, Atypical Hemolytic uremic syndrome, antiphospholipid antibody syndrome, or transplant rejection.

41. An antibody or antigen binding fragment thereof of any one of embodiments 1-25 or 33, or a pharmaceutical composition comprising the antibody or antigen binding fragment thereof, for the use in the treatment of a C1s mediated disorder, such as those provided for herein, such as hemolysis, Cold Agglutinin Disease.

42. An antibody or binding fragment thereof of any one of embodiments 1-25 or 33 or a pharmaceutical composition comprising the antibody or antigen binding fragment thereof for use as a medicament.

43. The antibody or binding fragment thereof, or pharmaceutical composition of embodiment 42 for use in the treatment of a C1s mediated disorder, such as those provided for herein.

44. Use of the antibody or binding fragment thereof of any one of embodiments 1-25 or 33, or a pharmaceutical composition comprising the antibody or antigen binding fragment thereof, for the treatment of a C1s mediated disorder, such as those provided for herein.

[00352] The subject matter is now described with reference to the following examples. These examples are provided for the purpose of illustration only and the claims should in no way be construed as being limited to these examples, but rather should be construed to encompass any and all variations which become evident as a result of the teaching provided herein. Those of skill in the art will readily recognize a variety of non-critical parameters that could be changed or modified to yield essentially similar results.

[00353] Examples

[00354] Example 1: Production of monoclonal antibodies

[00355] Human immunoglobulin variable domain transgenic mice (Alloy Therapeutics) were immunized at LakePharma with human C1s (active form, Complement Technologies Cat. #A104, 10 ug per dose) via hock route using proprietary adjuvants once weekly for 4 weeks. Serum titers were monitored over time using an ELISA assay with 1 ug/ml C1s coated Maxisorb plates. Mice received a final boost with recombinant CCP2-SP, a fragment of C1s consisting of the second CCP domain and the serine protease domain, amino acids 358-688 of Uniprot P09871). Highest titer mice were sacrificed and lymphocytes from draining lymph nodes were harvested. One hundred million lymphocytes were transferred to Single Cell Technologies (SCT) for plasma cell enrichment and single cell screening. Thirty million lymphocytes were fused to generate hybridomas at LakePharma.

[00356] Hybridomas produced by electrofusion were plated in eight 384-well plates at an average density of 2.0 hybridomas per well. Supernatants were screened by ELISA for binding to C1s and proC1s (Complement Technologies Cat. #A103). Based on strong binding to C1s and lower signal to proC1s 192 lines were selected for propagation and secondary screening.

[00357] Example 2: Characterization of hybridoma hits

[00358] Supernatants with confirmed binding profile were tested at 50% dilution for inhibition of C1s enzymatic activity using N-Carbobenzyl-Lys-ThioBenzyl ester (ZKSBzl) (Bachem, Catalog # M1300) as substrate, as well as in the Classical Pathway (CP) Wieslab Kit (Eagle

Biosciences COMPL CP310) at 1:2 dilution. Hybridomas with inhibitory signal in either assay were subcloned, expanded, IgG purified from spent supernatants, and heavy and light chain variable domains determined. Purified IgG from hybridomas were tested at varying concentrations to determine potency in CP Wieslab assay. Recombinantly expressed anti-C1s antibodies TNT009 or TNT020, anti-C5 antibody eculizumab, as well as human plasma C1INH were used as reference standards.

[00359] Example 3: Single plasma cell screening

[00360] Lymphocytes harvested from immunized mice and transferred to SCT were enriched for plasma cells, which were distributed into the microfluidics device and cultured for 3 hrs. Secreted antibody was captured onto a slide and interrogated with fluorescently labeled C1s and proC1s. Barcoded primers were added to the wells and the cells were processed for Next-Gen sequencing of IgG variable domains. Forty-eight unique sequences representing various patterns of C1s and proC1s staining signals were expressed as IgG and purified antibodies were tested at 300 nM for inhibitory activity in the CP Wieslab kit resulting in 16 lineages that showed >80% inhibition. These were further tested in the CP Wieslab assay at varying concentrations to determine potency of CP inhibition (Figure 1).

[00361] Example 4: C3b deposition and RBC lysis assays

[00362] C3b deposition: To evaluate ability of antibodies to inhibit C3b deposition which leads to extravascular hemolysis select antibodies were tested by Flow Contract Site (Bothel, WA) for inhibition of C3b deposition on human red blood cells (RBCs) sensitized with rabbit anti-human RBC serum in the presence of 5% human serum. Four Fc variants of MAB1 were tested along side C1s inhibitory antibodies TNT009 and TNT020, as well as the C5 inhibitory antibody Ravulizumab. Lead antibodies of the invention inhibited C3b deposition in a dose dependent manner (Figure 2), with IC50 values ranging between 0.63 and 3.92 nM. As expected, Ravulizumab showed no inhibition, being downstream of C1s in the cascade. TNT009 and TNT020 also showed inhibitory activity with IC50 values of 5.0 and 6.5 nM, respectively.

[00363] RBC lysis: as a measure of ability of antibodies to inhibit intravascular lysis O-negative human red blood cells (RBCs) were washed 3 times in Gelatin Veronal Buffer (GVB) and sensitized with 1:60 dilution of rabbit anti-human RBC antibody (LSBio LS-C63000-2) for 30 min, centrifuged, and resuspended in GVB++ (GVB + 0.15 mM CaCl₂, 0.5 mM MgCl₂). Normal human serum (Quidel A113) preincubated with anti-complement antibodies at varying

concentrations was added to 10% final serum concentration, and incubated for 1 hr at 37°C. The hemolytic reaction was stopped by adding EDTA to a final concentration of 20 mM and absorbance of supernatants at 540 nm were read on a plate reader. Test sample lysis was calculated as a percentage of samples lysed with water (100% lysis). As shown in Figure 3 MAB1 variants inhibited RBC lysis more potently than TNT009, TNT020 and eculizumab.

[00364] Example 5: Assessment of selectivity against proC1s

[00365] Hybridoma and single-cell hits that demonstrated good inhibition of the Classical Pathway were evaluated for selectivity by SPR at Biosensor Tools (Salt Lake City, UT). For this purpose, a non-cleavable version of proC1s (proC1s_RQ) was used to avoid artifacts due to partial activation of proC1s during experimental manipulation. Test IgGs were captured on an anti-Fc surface, and C1s or proC1s_RQ binding was evaluated at various concentrations. Kinetic parameters and equilibrium dissociation constants were derived by global fitting of the data (Figure 4). Two hybridoma derived clones (MAB1 and MAB3) and one single cell derived clone (MAB2) showed favorable selectivity as well as potency of inhibition of the classical pathway.

[00366] Example 6: Sequence Modifications

[00367] Variable domain sequences of lead antibodies were examined for structural liabilities such as NG (deamidation risk) and DG (isomerization risk), and variants were expressed, purified and tested for activity in the CP Wieslab assay. In each case variants that removed the liability and maintained functional potency were identified.

[00368] To further modify the variable domain sequences by reducing risk of immunogenicity nearest human germline genes were identified and variants that had non-germline framework region residues converted to germline were expressed and tested. The most germlined, liability fixed constructs that maintained functional potency were designated as MAB1, MAB2, and MAB3.

[00369] The Fc region of lead antibodies was engineered in several ways. IgG4 and IgG2/4 chimeric scaffolds were tested to avoid effector function, and half-life extension mutations (Xencor LS or MedImmune YTE) were introduced to improve pharmacokinetic properties.

[00370] Example 7: Pharmacokinetics in cynomolgus monkeys

[00371] Lead antibodies and TNT009 were administered to cynomolgus monkeys at relatively low doses (0.05-0.1 mg/kg) where impact of target mediated clearance would be seen clearly. Consistent with published data, TNT009 at 0.1 mg/kg had fast clearance and a short half-life

(~0.2 days), while the more selective leads 4O11, 5L3 and sct-191 had half-lives of ~14 days. LS and YTE modified variants extended half-life even further to 18-23 days.

[00372] Example 8: Serine protease specificity

[00373] Lead antibodies were tested for inhibitory activity of a panel of related serine protease at Reaction Biology (Malvern, PA). The panel consisted of C1r, Protein C, Cathepsin G, Chymase, Factor VIIa, Factor Xa, Factor XIa, Granzyme B, Kallikrein 1, plasma kallikrein, Matrilysin 2, Plasmin, Thrombin, TPA and Urokinase. Enzyme and substrate concentrations were optimized in preliminary assays, followed by screening of lead antibodies. Inhibition by lead antibodies at 1 uM concentration was less than 50% in all cases. In addition, lead antibodies were tested in Complement Lectin Pathway and Alternative Pathway Wieslab kits as a surrogate for inhibition of MASP1, MASP2, MASP3 and Factor D.

[00374] All references cited herein are incorporated by reference to the same extent as if each individual publication, database entry (*e.g.* Genbank sequences or GeneID entries), patent application, or patent, was specifically and individually indicated to be incorporated by reference. This statement of incorporation by reference is intended by Applicants, pursuant to 37 C.F.R. §1.57(b)(1), to relate to each and every individual publication, database entry (*e.g.* Genbank sequences or GeneID entries), patent application, or patent, each of which is clearly identified in compliance with 37 C.F.R. §1.57(b)(2), even if such citation is not immediately adjacent to a dedicated statement of incorporation by reference. The inclusion of dedicated statements of incorporation by reference, if any, within the specification does not in any way weaken this general statement of incorporation by reference. Citation of the references herein is not intended as an admission that the reference is pertinent prior art, nor does it constitute any admission as to the contents or date of these publications or documents.

[00375] The present embodiments are not to be limited in scope by the specific embodiments described herein. Indeed, various modifications in addition to those described herein will become apparent to those skilled in the art from the foregoing description and the accompanying figures. Such modifications are intended to fall within the scope of the embodiments and any appended claims.

[00376] The present specification is considered to be sufficient to enable one skilled in the art to practice the embodiments. Various modifications in addition to those shown and described

herein will become apparent to those skilled in the art from the foregoing description and fall within the scope of the present disclosure and any appended claims.

What is claimed is:

1. An antibody, or an antigen binding fragment thereof, wherein the antibody or antibody fragment comprises:

(a) a heavy chain variable region comprising heavy chain HCDR1, HCDR2, and HCDR3 sequences, wherein the heavy chain HCDR1 sequence has the amino acid sequence of SEQ ID NO: 9; the heavy chain HCDR2 has the amino acid sequence of SEQ ID NO: 10 and the heavy chain HCDR3 sequence has the amino acid sequence of SEQ ID NO: 11 or variants of any of the foregoing; and (ii) a light chain variable region comprising light chain LCDR1, LCDR2, and LCDR3 sequences, wherein the light chain LCDR1 sequence has the amino acid sequence SEQ ID NO: 12; the light chain LCDR2 sequence has the amino acid sequence of SEQ ID NO: 13; and the light chain LCDR3 sequence has the amino acid sequence of SEQ ID NO: 14; or variants of any of the foregoing;

(b) a heavy chain variable region comprising heavy chain HCDR1, HCDR2, and HCDR3 sequences, wherein the heavy chain HCDR1 sequence has the amino acid sequence of SEQ ID NO: 15; the heavy chain HCDR2 has the amino acid sequence of SEQ ID NO: 16 and the heavy chain HCDR3 sequence has the amino acid sequence of SEQ ID NO: 17 or variants of any of the foregoing; and (ii) a light chain variable region comprising light chain LCDR1, LCDR2, and LCDR3 sequences, wherein the light chain LCDR1 sequence has the amino acid sequence SEQ ID NO: 18; the light chain LCDR2 sequence has the amino acid sequence of SEQ ID NO: 19; and the light chain LCDR3 sequence has the amino acid sequence of SEQ ID NO: 20; or variants of any of the foregoing; or

(c) a heavy chain variable region comprising heavy chain HCDR1, HCDR2, and HCDR3 sequences, wherein the heavy chain HCDR1 sequence has the amino acid sequence of SEQ ID NO: 21; the heavy chain HCDR2 has the amino acid sequence of SEQ ID NO: 22 and the heavy chain HCDR3 sequence has the amino acid sequence of SEQ ID NO: 23 or variants of any of the foregoing; and (ii) a light chain variable region comprising light chain LCDR1, LCDR2, and LCDR3 sequences, wherein the light chain LCDR1 sequence has the amino acid sequence SEQ ID NO: 24; the light chain LCDR2 sequence has the amino acid sequence of SEQ

ID NO: 25; and the light chain LCDR3 sequence has the amino acid sequence of SEQ ID NO: 26; or variants of any of the foregoing.

2. An antibody, or an antigen binding fragment thereof, wherein the antibody or antibody fragment comprises:

(a) a heavy chain variable region comprising heavy chain HCDR1, HCDR2, and HCDR3 sequences, wherein the heavy chain HCDR1 sequence has the amino acid sequence of SEQ ID NO: 27; the heavy chain HCDR2 has the amino acid sequence of SEQ ID NO: 28 and the heavy chain HCDR3 sequence has the amino acid sequence of SEQ ID NO: 11 or variants of any of the foregoing; and (ii) a light chain variable region comprising light chain LCDR1, LCDR2, and LCDR3 sequences, wherein the light chain LCDR1 sequence has the amino acid sequence SEQ ID NO: 29; the light chain LCDR2 sequence has the amino acid sequence of SEQ ID NO: 30; and the light chain LCDR3 sequence has the amino acid sequence of SEQ ID NO: 31; or variants of any of the foregoing;

(b) a heavy chain variable region comprising heavy chain HCDR1, HCDR2, and HCDR3 sequences, wherein the heavy chain HCDR1 sequence has the amino acid sequence of SEQ ID NO: 32; the heavy chain HCDR2 has the amino acid sequence of SEQ ID NO: 33 and the heavy chain HCDR3 sequence has the amino acid sequence of SEQ ID NO: 17 or variants of any of the foregoing; and (ii) a light chain variable region comprising light chain LCDR1, LCDR2, and LCDR3 sequences, wherein the light chain LCDR1 sequence has the amino acid sequence SEQ ID NO: 34; the light chain LCDR2 sequence has the amino acid sequence of SEQ ID NO: 35; and the light chain LCDR3 sequence has the amino acid sequence of SEQ ID NO: 36; or variants of any of the foregoing; or

(c) a heavy chain variable region comprising heavy chain HCDR1, HCDR2, and HCDR3 sequences, wherein the heavy chain HCDR1 sequence has the amino acid sequence of SEQ ID NO: 37; the heavy chain HCDR2 has the amino acid sequence of SEQ ID NO: 38 and the heavy chain HCDR3 sequence has the amino acid sequence of SEQ ID NO: 23 or variants of any of the foregoing; and (ii) a light chain variable region comprising light chain LCDR1, LCDR2, and LCDR3 sequences, wherein the light chain LCDR1 sequence has the amino acid sequence SEQ ID NO: 39; the light chain LCDR2 sequence has the amino acid sequence of SEQ

ID NO: 40; and the light chain LCDR3 sequence has the amino acid sequence of SEQ ID NO: 41; or variants of any of the foregoing.

3. An antibody, or an antigen binding fragment thereof, wherein the antibody or antibody fragment comprises:

(a) a heavy chain variable region comprising heavy chain HCDR1, HCDR2, and HCDR3 sequences, wherein the heavy chain HCDR1 sequence has the amino acid sequence of SEQ ID NO: 42; the heavy chain HCDR2 has the amino acid sequence of SEQ ID NO: 43 and the heavy chain HCDR3 sequence has the amino acid sequence of SEQ ID NO: 44 or variants of any of the foregoing; and (ii) a light chain variable region comprising light chain LCDR1, LCDR2, and LCDR3 sequences, wherein the light chain LCDR1 sequence has the amino acid sequence SEQ ID NO: 45; the light chain LCDR2 sequence has the amino acid sequence of SEQ ID NO: 30; and the light chain LCDR3 sequence has the amino acid sequence of SEQ ID NO: 14; or variants of any of the foregoing;

(b) a heavy chain variable region comprising heavy chain HCDR1, HCDR2, and HCDR3 sequences, wherein the heavy chain HCDR1 sequence has the amino acid sequence of SEQ ID NO: 46; the heavy chain HCDR2 has the amino acid sequence of SEQ ID NO: 47 and the heavy chain HCDR3 sequence has the amino acid sequence of SEQ ID NO: 48 or variants of any of the foregoing; and (ii) a light chain variable region comprising light chain LCDR1, LCDR2, and LCDR3 sequences, wherein the light chain LCDR1 sequence has the amino acid sequence SEQ ID NO: 49; the light chain LCDR2 sequence has the amino acid sequence of SEQ ID NO: 35; and the light chain LCDR3 sequence has the amino acid sequence of SEQ ID NO: 20; or variants of any of the foregoing; or

(c) a heavy chain variable region comprising heavy chain HCDR1, HCDR2, and HCDR3 sequences, wherein the heavy chain HCDR1 sequence has the amino acid sequence of SEQ ID NO: 50; the heavy chain HCDR2 has the amino acid sequence of SEQ ID NO: 51 and the heavy chain HCDR3 sequence has the amino acid sequence of SEQ ID NO: 52 or variants of any of the foregoing; and (ii) a light chain variable region comprising light chain LCDR1, LCDR2, and LCDR3 sequences, wherein the light chain LCDR1 sequence has the amino acid sequence SEQ ID NO: 53; the light chain LCDR2 sequence has the amino acid sequence of SEQ

ID NO: 40; and the light chain LCDR3 sequence has the amino acid sequence of SEQ ID NO: 26; or variants of any of the foregoing.

4. An antibody, or antigen-binding fragment thereof, wherein:

a. the HCDR1, HCDR2 and HCDR3 are selected from SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, respectively, from SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID NO: 11, respectively, and from SEQ ID NO: 42, SEQ ID NO: 43, SEQ ID NO: 44, respectively, and the LCDR1, LCDR2 and LCDR3 are selected from from SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, respectively, from SEQ ID NO: 29, SEQ ID NO: 30, SEQ ID NO: 31, respectively, and from SEQ ID NO: 45, SEQ ID NO: 30, SEQ ID NO: 14, respectively; or

b. the HCDR1, HCDR2 and HCDR3 are selected from SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, respectively, from SEQ ID NO: 32, SEQ ID NO: 33, SEQ ID NO: 17, respectively, and from SEQ ID NO: 46, SEQ ID NO: 47, SEQ ID NO: 48, respectively, and the LCDR1, LCDR2 and LCDR3 are selected from from SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 20, respectively, from SEQ ID NO: 34, SEQ ID NO: 35, SEQ ID NO: 36, respectively, and from SEQ ID NO: 49, SEQ ID NO: 35, SEQ ID NO: 20, respectively; or

c. the HCDR1, HCDR2 and HCDR3 are selected from SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO: 23, respectively, SEQ ID NO: 37, SEQ ID NO: 38, SEQ ID NO: 23, respectively, and SEQ ID NO: 50, SEQ ID NO: 51, SEQ ID NO: 52, respectively, and the LCDR1, LCDR2 and LCDR3 are selected from SEQ ID NO: 24, SEQ ID NO: 25, SEQ ID NO: 26, respectively, SEQ ID NO: 39, SEQ ID NO: 40, SEQ ID NO: 41, respectively, and SEQ ID NO: 53, SEQ ID NO: 40, SEQ ID NO: 26, respectively.

5. The antibody or antigen-binding fragment thereof of any one of claims 1-4, wherein the heavy chain comprises:

a. a heavy chain variable region having at least 90% sequence identity to SEQ ID NO:1, wherein the antibody or antigen binding fragment thereof maintains the sequences of HCDR1, HCDR2, HCDR2, LCDR1, LCD2, and LCDR3 set forth in subpart a of any one of claims 1-4; or

b. a heavy chain variable region having at least 90% sequence identity to SEQ ID NO:3, wherein the antibody or antigen binding fragment thereof maintains the sequences of HCDR1, HCDR2, HCDR2, LCDR1, LCD2, and LCDR3 set forth in subpart b of any one of claims 1-4; or

c. a heavy chain variable region having at least 90% sequence identity to SEQ ID NO:5, wherein the antibody or antigen binding fragment thereof maintains the sequences of HCDR1, HCDR2, HCDR2, LCDR1, LCD2, and LCDR3 set forth in subpart c of any one of claims 1-4.

6. The antibody or antigen-binding fragment thereof of any one of claims 1-4, wherein the light chain comprises:

a. a light chain variable region having at least 90% sequence identity to SEQ ID NO:2, wherein the antibody or antigen binding fragment thereof maintains the sequences of HCDR1, HCDR2, HCDR2, LCDR1, LCD2, and LCDR3 set forth in subpart a of any one of claims 1-4; or

b. a light chain variable region having at least 90% sequence identity to SEQ ID NO:4, wherein the antibody or antigen binding fragment thereof maintains the sequences of HCDR1, HCDR2, HCDR2, LCDR1, LCD2, and LCDR3 set forth in subpart b of any one of claims 1-4; or

c. a light chain variable region having at least 90% sequence identity to SEQ ID NO:6, wherein the antibody or antigen binding fragment thereof maintains the sequences of HCDR1, HCDR2, HCDR2, LCDR1, LCD2, and LCDR3 set forth in subpart c of any one of claims 1-4.

7. The antibody or antigen-binding fragment thereof of any one of claims 1-4, wherein the antibody or antigen binding fragment thereof comprises:

a. a light chain variable region of the light chain having at least 90% sequence identity to SEQ ID NO:2, and a heavy chain variable region of the heavy chain having at least 90% sequence identity to SEQ ID NO:1, wherein the antibody or antigen binding fragment

thereof maintains the sequences of HCDR1, HCDR2, HCDR2, LCDR1, LCD2, and LCDR3 set forth in subpart a of any one of claims 1-4; or

b. a light chain variable region of the light chain having at least 90% sequence identity to SEQ ID NO:4, and a heavy chain variable region of the heavy chain having at least 90% sequence identity to SEQ ID NO:3, wherein the antibody or antigen binding fragment thereof maintains the sequences of HCDR1, HCDR2, HCDR2, LCDR1, LCD2, and LCDR3 set forth in subpart b of any one of claims 1-4; or

c. a light chain variable region of the light chain having at least 90% sequence identity to SEQ ID NO:6, and a heavy chain variable region of the heavy chain having at least 90% sequence identity to SEQ ID NO:5, wherein the antibody or antigen binding fragment thereof maintains the sequences of HCDR1, HCDR2, HCDR2, LCDR1, LCD2, and LCDR3 set forth in subpart c of any one of claims 1-4.

8. The antibody or antigen-binding fragment thereof of claim 7, wherein the light chain variable region comprises SEQ ID NO:2, and the heavy chain variable region comprises SEQ ID NO:1.

9. The antibody or antigen-binding fragment thereof of any one of claims 1-4, wherein:

a. the heavy chain has at least 90% sequence identity to SEQ ID NO:66 or SEQ ID NO: 67, wherein the antibody or antigen binding fragment thereof maintains the sequences of HCDR1, HCDR2, HCDR2, LCDR1, LCD2, and LCDR3 set forth in subpart a of any one of claims 1-4; or

b. the heavy chain has at least 90% sequence identity to SEQ ID NO:68 or SEQ ID NO: 69, wherein the antibody or antigen binding fragment thereof maintains the sequences of HCDR1, HCDR2, HCDR2, LCDR1, LCD2, and LCDR3 set forth in subpart b of any one of claims 1-4; or

c. the heavy chain has at least 90% sequence identity to SEQ ID NO:70 or SEQ ID NO: 71, wherein the antibody or antigen binding fragment thereof maintains the sequences of

HCDR1, HCDR2, HCDR2, LCDR1, LCD2, and LCDR3 set forth in subpart c of any one of claims 1-4.

10. The antibody or antigen-binding fragment thereof of any one of claims 1-4, wherein the light chain comprises:

a. the light chain has at least 90% sequence identity to SEQ ID NO:72, wherein the antibody or antigen binding fragment thereof maintains the sequences of HCDR1, HCDR2, HCDR2, LCDR1, LCD2, and LCDR3 set forth in subpart a of any one of claims 1-4; or

b. the light chain has least 90% sequence identity to SEQ ID NO:73, wherein the antibody or antigen binding fragment thereof maintains the sequences of HCDR1, HCDR2, HCDR2, LCDR1, LCD2, and LCDR3 set forth in subpart b of any one of claims 1-4; or

c. the light chain has at least 90% sequence identity to SEQ ID NO:74, wherein the antibody or antigen binding fragment thereof maintains the sequences of HCDR1, HCDR2, HCDR2, LCDR1, LCD2, and LCDR3 set forth in subpart c of any one of claims 1-4.

11. The antibody or antigen-binding fragment thereof of any one of claims 1-4, wherein:

a. the light chain has at least 90% sequence identity to SEQ ID NO:72, and the heavy chain has at least 90% sequence identity to SEQ ID NO:66 or SEQ ID NO: 67, wherein the antibody or antigen binding fragment thereof maintains the sequences of HCDR1, HCDR2, HCDR2, LCDR1, LCD2, and LCDR3 set forth in subpart a of any one of claims 1-4; or

b. the light chain has at least 90% sequence identity to SEQ ID NO:73, and the heavy chain has at least 90% sequence identity to SEQ ID NO:68 or SEQ ID NO: 69, wherein the antibody or antigen binding fragment thereof maintains the sequences of HCDR1, HCDR2, HCDR2, LCDR1, LCD2, and LCDR3 set forth in subpart b of any one of claims 1-4; or

c. the light chain has at least 90% sequence identity to SEQ ID NO:74, and the heavy chain has at least 90% sequence identity to SEQ ID NO:70 or SEQ ID NO: 71, wherein the antibody or antigen binding fragment thereof maintains the sequences of HCDR1, HCDR2, HCDR2, LCDR1, LCD2, and LCDR3 set forth in subpart c of any one of claims 1-4.

12. The antibody or antigen-binding fragment thereof of claim 11, wherein:

the light chain comprises SEQ ID NO:72, and the heavy chain comprises SEQ ID NO: 66 or SEQ ID NO: 67;

the light chain comprises SEQ ID NO:73, and the heavy chain comprises SEQ ID NO: 68 or SEQ ID NO: 69; or

the light chain comprises SEQ ID NO:74, and the heavy chain comprises SEQ ID NO: 70 or SEQ ID NO: 71;

13. The antibody or antigen-binding fragment thereof of any one of the preceding claims, wherein the antibody binding fragment is a scFv antibody, a Fab fragment, a Fab' fragment, or an F(ab')₂ fragment.

14. The antibody or antigen binding fragment thereof of any one of the preceding claims, wherein the antibody is a monoclonal antibody.

15. The antibody or antigen binding fragment thereof of any one of the preceding claims, wherein the antibody is a humanized antibody.

16. The antibody or antigen binding fragment thereof of any one of the preceding claims, wherein the antibody or antigen binding fragment thereof comprises the sequence selected from one or more of the following sequences: SEQ ID NO: 1; SEQ ID NO: 2; SEQ ID NO: 3; SEQ ID NO: 4; SEQ ID NO: 5, SEQ ID NO: 6, or a variant thereof.

17. The antibody or antigen binding fragment thereof of any one of the preceding claims, wherein the antibody, or antigen binding fragment thereof, comprises a V_L peptide of SEQ ID NOs: 2, 4, or 6, or any variant thereof.

18. The antibody or antigen binding fragment thereof of any one of the preceding claims, wherein the antibody, or antigen binding fragment thereof, comprises a V_H peptide of SEQ ID NOs: 1, 3, or 5, or any variant thereof.

19. The antibody or antigen binding fragment thereof of any one of the preceding claims, wherein the antibody, or antigen binding fragment thereof, comprises a constant region as provided for herein.
20. The antibody or antigen binding fragment thereof of any one of the preceding claims, wherein the heavy chain variable region and the light chain variable region are not linked by a linker.
21. The antibody or antigen binding fragment thereof of any one of the preceding claims, wherein the heavy chain variable region and the light chain variable region are linked with a peptide linker.
22. The antibody or antigen binding fragment thereof of claim 21, wherein the peptide linker comprises a sequence of (GGGGS)_n (SEQ ID NO:54); (GGGGA)_n (SEQ ID NO: 55), or any combination thereof, wherein each n is independently 1-5.
23. A variant of the antibody or antigen binding fragment thereof of any one of the preceding claims, wherein the variant has 1-10 substitutions, deletions, or insertions.
24. A variant of the antibody or antigen binding fragment thereof of any one of the preceding claims, wherein the variant has 1-10 conservative substitutions.
25. A recombinant antibody or an antigen binding fragment thereof that binds to a C1s, wherein the antibody or antigen binding fragment thereof comprises an amino acid sequence, or a variant thereof, as provided for herein.
26. An isolated nucleic acid molecule encoding an antibody, or an antigen binding fragment thereof, a heavy chain variable region, a light chain variable region, heavy chain, or light chain, of any of the preceding claims.
27. The isolated nucleic acid sequence of claim 26 comprising SEQ ID NO:59, SEQ ID NO:61, or SEQ ID NO:63.

28. The isolated nucleic acid sequence of claim 27 comprising SEQ ID NO:59.
29. The isolated nucleic acid sequence of claim 26 comprising SEQ ID NO:60, SEQ ID NO:62, or SEQ ID NO:64.
30. The isolated nucleic acid sequence of claim 29 comprising SEQ ID NO:60.
31. An expression vector comprising the nucleic acid molecule of any one of claims 26-30.
32. A host cell comprising the nucleic acid molecule of any one of claims 26-30 or the vector of claim 31.
33. An antibody or antigen-binding fragment produced by the host cell of claim 32.
34. A pharmaceutical composition comprising an antibody, or antigen binding fragment thereof, of any one of claims 1-25.
35. The pharmaceutical composition of claim 34, wherein the composition is formulated for intravenous or subcutaneous injection.
36. The pharmaceutical composition of claim 34, wherein the composition is an injectable pharmaceutical composition.
37. A method of producing a polypeptide comprising a heavy chain variable region or light chain variable region, the method comprising:
- (a) growing the host cell of claim 32 under conditions so that the host cell expresses the polypeptide comprising the heavy chain variable region or the light chain variable region; and
 - (b) purifying the polypeptide comprising the heavy chain variable region or the light chain variable region.
38. A method of producing an antibody that binds human C1s, or an antigen binding fragment of the antibody, the method comprising:
- (a) growing the host cell of claim 32 under conditions so that the host cell expresses a polypeptide or polypeptides comprising the immunoglobulin heavy chain variable region and/or

the immunoglobulin light chain variable region, thereby producing the antibody or the antigen-binding fragment of the antibody; and

(b) purifying the antibody or the antigen-binding fragment of the antibody.

39. A method of treating a subject with C1s mediated disorder, the method comprising administering to the subject an antibody, or antigen binding fragment thereof, of any one of claims 1-25 or 33 or a pharmaceutical composition of any one of claims 34-36.

40. The method of claim 39, wherein the disorder is hemolysis, Cold Agglutinin Disease, Immune Thrombocytopenia (ITP), Myasthenia Gravis, Glomerulopathies, Atypical Hemolytic uremic syndrome, antiphospholipid antibody syndrome, or transplant rejection.

41. An antibody or antigen binding fragment thereof of any one of claims 1-25 or 33, or a pharmaceutical composition comprising the antibody or antigen binding fragment thereof, for the use in the treatment of a C1s mediated disorder, such as those provided for herein, such as hemolysis, Cold Agglutinin Disease.

42. An antibody or binding fragment thereof of any one of claims 1-25 or 33 or a pharmaceutical composition comprising the antibody or antigen binding fragment thereof for use as a medicament.

43. The antibody or binding fragment thereof, or pharmaceutical composition of claim 42 for use in the treatment of a C1s mediated disorder, such as those provided for herein.

44. Use of the antibody or binding fragment thereof of any one of claims 1-25 or 33, or a pharmaceutical composition comprising the antibody or antigen binding fragment thereof, for the treatment of a C1s mediated disorder, such as those provided for herein.

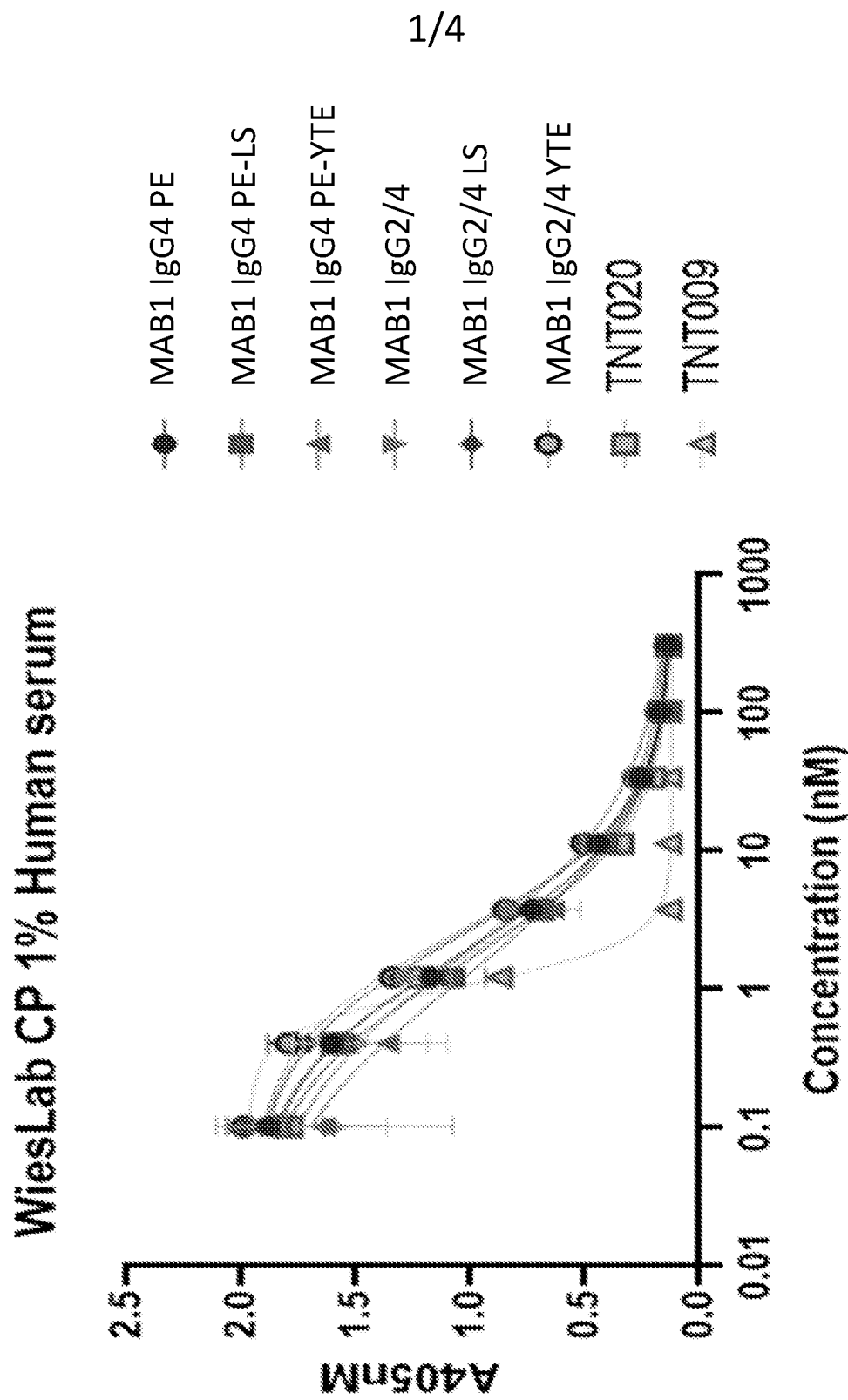


Figure 1

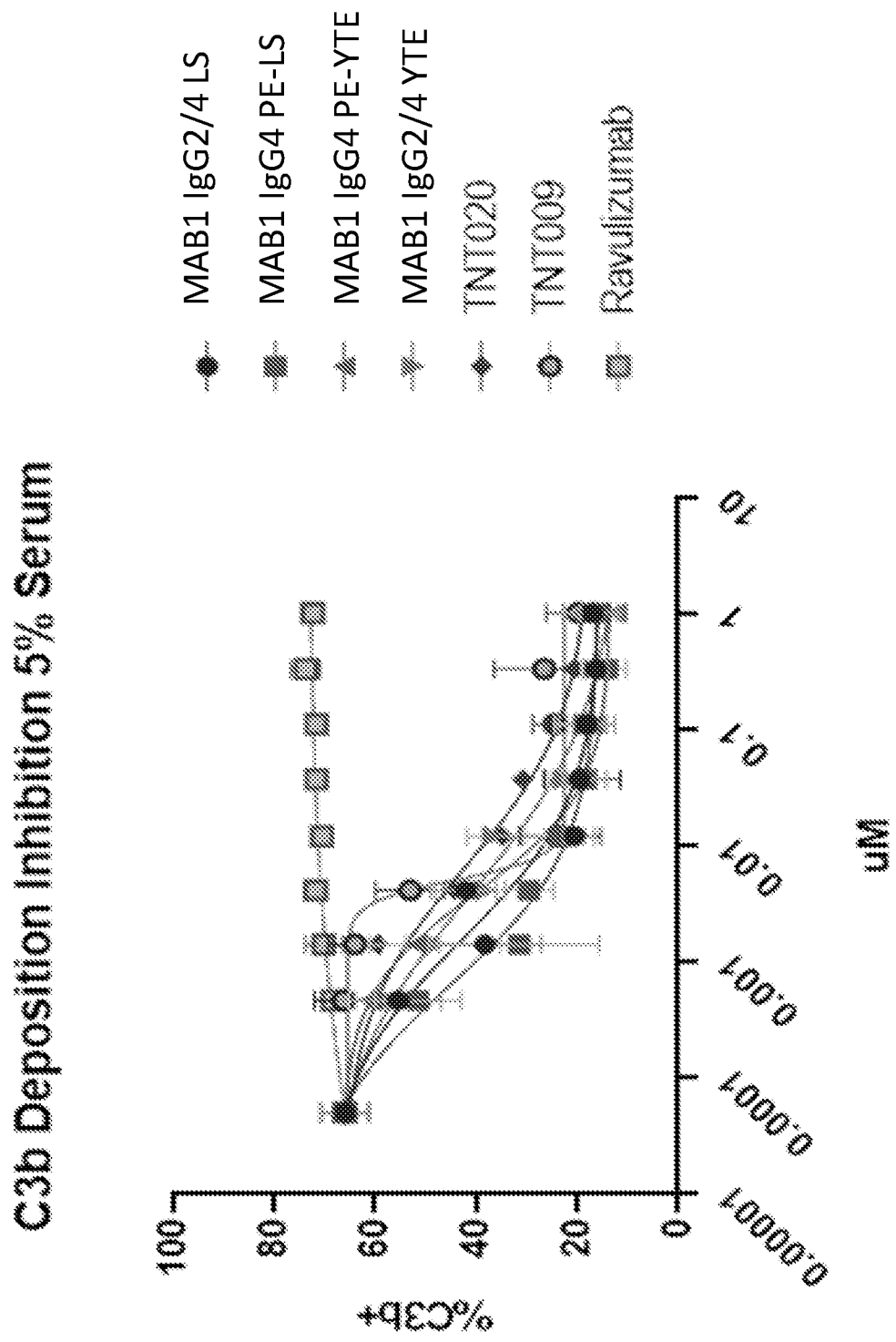


Figure 2

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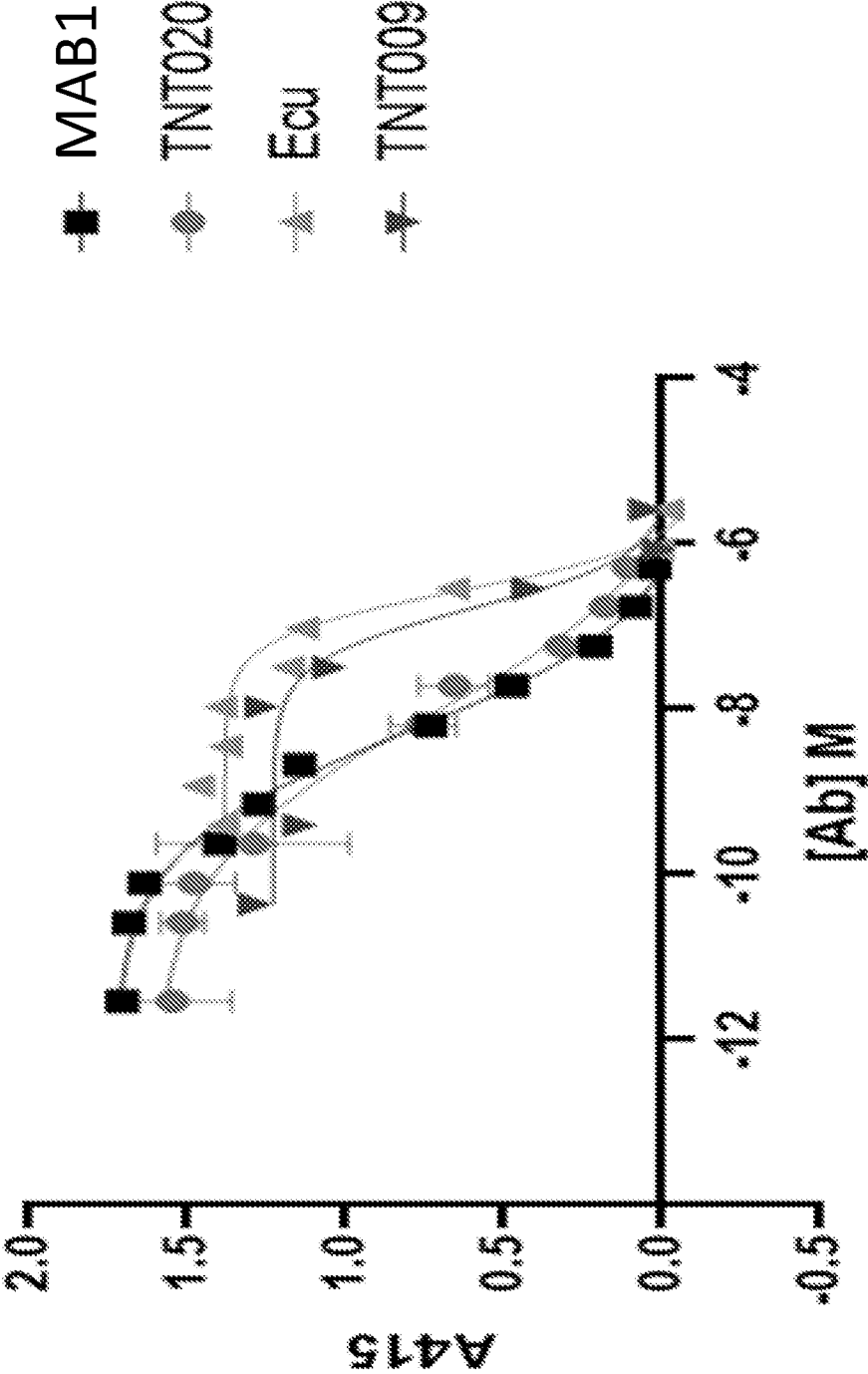


Figure 3

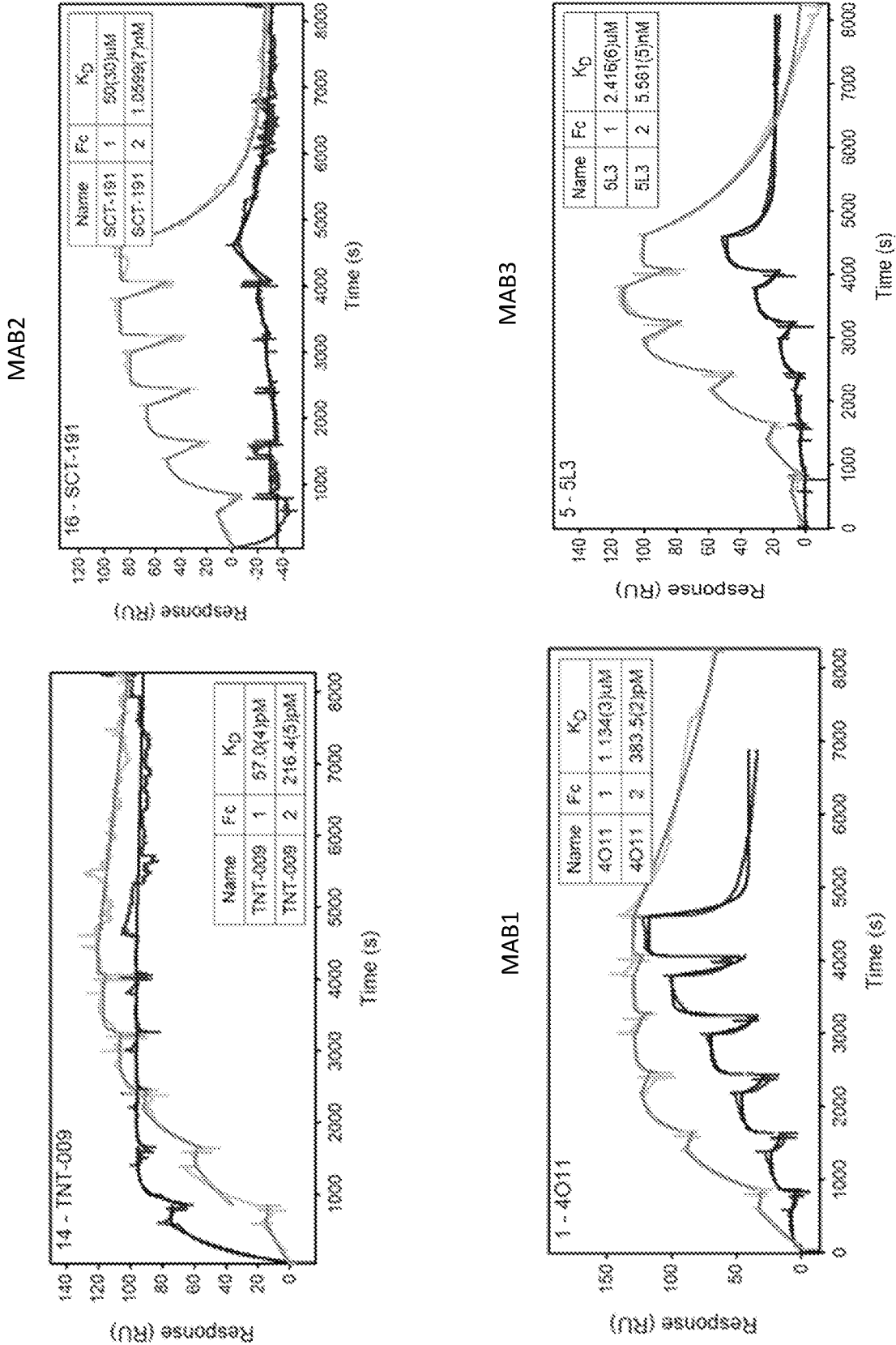


Figure 4