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(54) **Title:** ANTI-SARS-COV-2-VARIANT-SPIKE GLYCOPROTEIN ANTIBODIES AND ANTIGEN-BINDING FRAGMENTS

(57) **Abstract:** The present disclosure provides mrethods of modifying antibodies and antigen-binding fragments thereof to enhance binding to certain variants of wild-type coronavirus spike protein (e.g., a variant that comprises an E484K substitution) and methods of using such antibodies and fragments for treating or preventing viral infections (*e.g.*, coronavirus infections).

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ANTI-SARS-COV-2-VARIANT-SPIKE GLYCOPROTEIN ANTIBODIES AND ANTIGEN-BINDING FRAGMENTS

SEQUENCE LISTING

[0001] An official copy of the sequence listing is submitted concurrently with the specification electronically via EFS-Web as an ASCII formatted sequence listing with a file name of "10915WO01-Sequence.txt", created on March 4, 2022, and having a size of 933,357 bytes. The sequence listing contained in this ASCII formatted document is part of the specification and is herein incorporated by reference in its entirety.

FIELD OF THE INVENTION

[0002] The present invention relates to antibodies and antigen-binding fragments that bind specifically to coronavirus spike proteins and methods for treating or preventing coronavirus infections with said antibodies and fragments.

BACKGROUND OF THE INVENTION

[0003] Newly identified viruses, such as coronaviruses, can be difficult to treat because they are not sufficiently characterized. The emergence of these newly identified viruses highlights the need for the development of novel antiviral strategies. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a newly-emergent coronavirus which causes a severe acute respiratory disease, COVID-19. SARS-CoV-2 was first identified from an outbreak in Wuhan, China and as of March 20, 2020, the World Health Organization has reported 209,839 confirmed cases in 168 countries, areas, or territories, resulting in 8,778 deaths. Clinical features of COVID-19 include fever, dry cough, and fatigue, and the disease can cause respiratory failure resulting in death.

[0004] Thus far, there has been no vaccine or therapeutic agent to prevent or treat SARS-CoV-2 infection. In view of the continuing threat to human health, there is an urgent need for preventive and therapeutic antiviral therapies for SARS-CoV-2 control. Because this virus uses its spike glycoprotein for interaction with the cellular receptor ACE2 and the serine protease TMPRSS2 for entry into a target cell, this spike protein represents an attractive target for antibody therapeutics. In particular, fully human antibodies that specifically bind to the SARS-

CoV-2-Spike protein (SARS-CoV-2-S) with high affinity and that inhibit virus infectivity could be important in the prevention and treatment of COVID-19. Moreover, novel antibodies designed specifically to enhance binding and/or neutralization against new variants of the SARS-CoV-2 virus (e.g., variants containing an E484K mutation in the spike protein) will become increasingly important as these new variants become more prevalent.

SUMMARY OF THE INVENTION

[0005] There is a need for neutralizing therapeutic anti-SARS-CoV-2-Spike protein (SARS-CoV-2-S) antibodies and their use for treating or preventing viral infection. The present disclosure addresses this need, in part, by providing human anti-SARS-CoV-2-S antibodies, such as those of Table 1, and combinations thereof including, for example, combinations with other therapeutics (e.g., anti-inflammatory agents, antimalarial agents, antiviral agents, or other antibodies or antigen-binding fragments), and methods of use thereof for treating viral infections.

[0006] The present disclosure provides neutralizing human antigen-binding proteins that specifically bind to SARS-CoV-2-S, for example, antibodies or antigen-binding fragments thereof, and methods for modifying antibodies to enhance their binding and/or neutralizing properties, e.g., for variant spike proteins such as those containing an E484k mutation.

[0007] In one aspect, the present disclosure provides a method for modifying an antibody or antigen-binding fragment thereof that binds to a wild-type SARS-CoV-2 spike protein comprising the amino acid sequence set forth in SEQ ID NO: 832, comprising: a) identifying a first amino acid in said antibody or antigen-binding fragment that is in proximity to amino acid E484 of the wild-type SARS-CoV-2 spike protein when the antibody or antigen-binding fragment is bound to the wild-type SARS-CoV-2 spike protein; and b) modifying said first amino acid, thereby generating a modified antibody or antigen-binding fragment thereof, wherein the binding of said modified antibody or antigen-binding fragment to a variant SARS-CoV-2 spike protein comprising the amino acid sequence set forth in SEQ ID NO: 851 is greater than the binding of said antibody or antigen-binding fragment to said variant SARS-CoV-2 spike protein prior to said modifying.

[0008] In one aspect, the present disclosure provides a method for modifying an antibody or antigen-binding fragment thereof that binds to a variant SARS-CoV-2 spike protein comprising the amino acid sequence set forth in SEQ ID NO: 851, comprising: a) identifying a first amino

acid in said antibody or antigen-binding fragment that is in proximity to amino acid K484 of the variant SARS-CoV-2 spike protein when the antibody or antigen-binding fragment is bound to the variant SARS-CoV-2 spike protein; and b) modifying said first amino acid, thereby generating a modified antibody or antigen-binding fragment thereof, wherein the binding of said modified antibody or antigen-binding fragment to the variant SARS-CoV-2 spike protein is greater than the binding of said antibody or antigen-binding fragment to said variant SARS-CoV-2 spike protein prior to said modifying.

[0009] In an embodiment of any of the methods discussed above or herein, a measure of said binding is binding affinity. In some embodiments, a measure of said binding is dissociative half-life.

[00010] In one aspect, the present disclosure provides a method for modifying an antibody or antigen-binding fragment thereof that binds to a wild-type SARS-CoV-2 spike protein comprising the amino acid sequence set forth in SEQ ID NO: 832, comprising: a) identifying a first amino acid in said antibody or antigen-binding fragment that is in proximity to amino acid E484 of the wild-type SARS-CoV-2 spike protein when the antibody or antigen-binding fragment is bound to the wild-type SARS-CoV-2 spike protein; and b) modifying said first amino acid, thereby generating a modified antibody or antigen-binding fragment thereof, wherein said modified antibody or antigen-binding fragment has greater neutralization against a variant SARS-CoV-2 spike protein comprising the amino acid sequence set forth in SEQ ID NO: 851 than said antibody or antigen-binding fragment has neutralization against said variant SARS-CoV-2 spike protein prior to said modifying.

[00011] In one aspect, the present disclosure provides a method for modifying an antibody or antigen-binding fragment thereof that binds to a variant SARS-CoV-2 spike protein comprising the amino acid sequence set forth in SEQ ID NO: 851, comprising: a) identifying a first amino acid in said antibody or antigen-binding fragment that is in proximity to amino acid K484 of the variant SARS-CoV-2 spike protein when the antibody or antigen-binding fragment is bound to the variant SARS-CoV-2 spike protein; and b) modifying said first amino acid, thereby generating a modified antibody or antigen-binding fragment thereof, wherein said modified antibody or antigen-binding fragment has greater neutralization against a variant SARS-CoV-2 spike protein comprising the amino acid sequence set forth in SEQ ID NO: 851 than said

antibody or antigen-binding fragment has neutralization against said variant SARS-CoV-2 spike protein prior to said modifying.

[00012] In an embodiment of any of the methods discussed above or herein, said neutralizing is determined by neutralization of a pseudotyped virus expressing SARS-CoV-2-S or neutralization of SARS-CoV-2 virus.

[00013] In an embodiment of any of the methods discussed above or herein, said modifying comprises substituting a second amino acid for said first amino acid. In some embodiments, said substituting comprises introducing a substitution mutation in a nucleic acid sequence encoding said amino acid. In some embodiments, said first amino acid comprises a positively charged side chain at pH 7.0. In some embodiments, said first amino acid is selected from the group consisting of lysine, arginine, and histidine. In some embodiments, said second amino acid comprises a negatively charged side chain at pH 7.0. In some embodiments, said second amino acid is selected from the group consisting of aspartate and glutamate.

[00014] In an embodiment of any of the methods discussed above or herein, said modifying comprises chemically modifying said amino acid. In some embodiments, said chemically modifying comprises introducing a negative charge.

[00015] In an embodiment of any of the methods discussed above or herein, said proximity comprises 3.5 Å to 4.5 Å between said first amino acid and said amino acid at position 484 of said spike protein. In some embodiments, said proximity comprises about 4.0 Å. In some cases, said fist amino acid forms a salt bridge with said amino acid at position 484 of said spike protein.

[00016] In one aspect, the present disclosure provides a modified antibody or antigen-binding fragment prepared by any of the methods discussed above or herein. In some embodiment, the modified antibody comprises an immunoglobulin constant region. In some cases, the immunoglobulin constant region is an IgG1 constant region. In some embodiments, the modified antibody is a recombinant antibody. In some embodiments the modified antibody is multispecific.

[00017] In one aspect, the present disclosure provides a polynucleotide encoding a heavy chain of the modified antibody or antigen-binding fragment discussed above or herein.

[00018] In one aspect, the present disclosure provides a polynucleotide encoding a light chain of the modified antibody or antigen-binding fragment discussed above or herein.

[00019] In one aspect, the present disclosure provides a vector comprising the polynucleotide discussed above.

[00020] In one aspect, the present disclosure provides a host cell comprising the modified antibody or antigen-binding fragment thereof discussed above or herein, or the polynucleotide or vector discussed above.

[00021] In one aspect, the present disclosure provides a pharmaceutical composition comprising the modified antibody or antigen-binding fragment thereof discussed above or herein, or the polynucleotide, the vector, or host cell discussed above.

[00022] In one aspect, the present disclosure provides a complex comprising the modified antibody or antigen-binding fragment discussed above or herein bound to a SARS-CoV-2 spike protein.

[00023] In one aspect, the present disclosure provides a method for making the modified antibody or antigen-binding fragment discussed above or herein, comprising: (a) introducing into a host cell one or more polynucleotides encoding said antibody or antigen-binding fragment; (b) culturing the host cell under conditions favorable to expression of the one or more polynucleotides; and (c) optionally, isolating the antibody or antigen-binding fragment from the host cell and/or a medium in which the host cell is grown.

[00024] In some embodiments, the host cell is a Chinese hamster ovary cell.

[00025] In various embodiments, any of the features or components of embodiments discussed above or herein may be combined, and such combinations are encompassed within the scope of the present disclosure. Any specific value discussed above or herein may be combined with another related value discussed above or herein to recite a range with the values representing the upper and lower ends of the range, and such ranges are encompassed within the scope of the present disclosure.

DETAILED DESCRIPTION OF THE INVENTION

[00026] Before the present methods are described, it is to be understood that this invention is not limited to particular methods, and experimental conditions described, as such methods and conditions may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting, since the scope of the present invention will be limited only by the appended claims.

[00027] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, preferred methods and materials are now described. All publications mentioned herein are incorporated herein by reference in their entirety.

[00028] The term "coronavirus" or "CoV" refers to any virus of the coronavirus family, including but not limited to SARS-CoV-2, MERS-CoV, and SARS-CoV. SARS-CoV-2 refers to the newly-emerged coronavirus which was identified as the cause of a serious outbreak starting in Wuhan, China, and which is rapidly spreading to other areas of the globe. SARS-CoV-2 has also been known as 2019-nCoV and Wuhan coronavirus. It binds via the viral spike protein to human host cell receptor angiotensin-converting enzyme 2 (ACE2). The spike protein also binds to and is cleaved by TMPRSS2, which activates the spike protein for membrane fusion of the virus.

[00029] The term "CoV-S", also called "S" or "S protein" refers to the spike protein of a coronavirus, and can refer to specific S proteins such as SARS-CoV-2-S, MERS-CoV S, and SARS-CoV S. The SARS-CoV-2-Spike protein is a 1273 amino acid type I membrane glycoprotein which assembles into trimers that constitute the spikes or peplomers on the surface of the enveloped coronavirus particle. The protein has two essential functions, host receptor binding and membrane fusion, which are attributed to the N-terminal (S1) and C-terminal (S2) halves of the S protein. CoV-S binds to its cognate receptor via a receptor binding domain (RBD) present in the S1 subunit. The amino acid sequence of full-length SARS-CoV-2 spike protein is exemplified by the amino acid sequence provided in SEQ ID NO: 832. The term "CoV-S" includes protein variants of CoV spike protein isolated from different CoV isolates as well as recombinant CoV spike protein or a fragment thereof. The term also encompasses CoV spike protein or a fragment thereof coupled to, for example, a histidine tag, mouse or human Fc, or a signal sequence such as ROR1.

[00030] The term "coronavirus infection" or "CoV infection," as used herein, refers to infection with a coronavirus such as SARS-CoV-2, MERS-CoV, or SARS-CoV. The term includes coronavirus respiratory tract infections, often in the lower respiratory tract. Symptoms can include high fever, dry cough, shortness of breath, pneumonia, gastro-intestinal symptoms such

as diarrhea, organ failure (kidney failure and renal dysfunction), septic shock, and death in severe cases.

Viruses

[00031] The present invention includes methods for treating or preventing a viral infection in a subject. The term "virus" includes any virus whose infection in the body of a subject is treatable or preventable by administration of an anti-CoV-S antibody or antigen-binding fragment thereof (*e.g.*, wherein infectivity of the virus is at least partially dependent on CoV-S). In an embodiment of the invention, a "virus" is any virus that expresses spike protein (e.g., CoV-S). The term "virus" also includes a CoV-S-dependent respiratory virus which is a virus that infects the respiratory tissue of a subject (*e.g.*, upper and/or lower respiratory tract, trachea, bronchi, lungs) and is treatable or preventable by administration of an anti-CoV-S antibody or antigen-binding fragment thereof. For example, in an embodiment of the invention, virus includes coronavirus, SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2), SARS-CoV (severe acute respiratory syndrome coronavirus), and MERS-CoV (Middle East respiratory syndrome (MERS) coronavirus). Coronaviruses can include the genera of alphacoronaviruses, betacoronaviruses, gammacoronaviruses, and deltacoronaviruses. In some embodiments, the antibodies or antigen-binding fragments provided herein can bind to and/or neutralize an alphacoronavirus, a betacoronavirus, a gammacoronavirus, and/or a deltacoronavirus. In certain embodiments, this binding and/or neutralization can be specific for a particular genus of coronavirus or for a particular subgroup of a genus. "Viral infection" refers to the invasion and multiplication of a virus in the body of a subject.

[00032] Coronavirus virions are spherical with diameters of approximately 125 nm. The most prominent feature of coronaviruses is the club-shape spike projections emanating from the surface of the virion. These spikes are a defining feature of the virion and give them the appearance of a solar corona, prompting the name, coronaviruses. Within the envelope of the virion is the nucleocapsid. Coronaviruses have helically symmetrical nucleocapsids, which is uncommon among positive-sense RNA viruses, but far more common for negative-sense RNA viruses. SARS-CoV-2, MERS-CoV, and SARS-CoV belong to the coronavirus family. The initial attachment of the virion to the host cell is initiated by interactions between the S protein and its receptor. The sites of receptor binding domains (RBD) within the S1 region of a

coronavirus S protein vary depending on the virus, with some having the RBD at the C-terminus of S1. The S-protein/receptor interaction is the primary determinant for a coronavirus to infect a host species and also governs the tissue tropism of the virus. Many coronaviruses utilize peptidases as their cellular receptor. Following receptor binding, the virus must next gain access to the host cell cytosol. This is generally accomplished by acid-dependent proteolytic cleavage of S protein by a cathepsin, TMPRRS2 or another protease, followed by fusion of the viral and cellular membranes. An exemplary spike protein sequence is given as SEQ ID NO: 832; a variant spike protein sequence containing an E484K mutation is given as SEQ ID NO: 851.

Anti-CoV-S Antibodies and Antigen-Binding Fragments

[00033] The present invention provides antigen-binding proteins, such as antibodies and antigen-binding fragments thereof, that specifically bind to CoV spike protein or an antigenic fragment thereof.

[00034] The term "antibody", as used herein, refers to immunoglobulin molecules comprising four polypeptide chains, two heavy chains (HCs) and two light chains (LCs) inter-connected by disulfide bonds (*i.e.*, "full antibody molecules"), as well as multimers thereof (*e.g.* IgM). Exemplary antibodies include, for example, those listed in Table 1. Each heavy chain comprises a heavy chain variable region ("HCVR" or "V_H") and a heavy chain constant region (comprised of domains C_H1, C_H2 and C_H3). Each light chain is comprised of a light chain variable region ("LCVR or "V_L") and a light chain constant region (C_L). The V_H and V_L regions can be further subdivided into regions of hypervariability, termed complementarity determining regions (CDR), interspersed with regions that are more conserved, termed framework regions (FR). Each V_H and V_L comprises three CDRs and four FRs, arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4. Heavy chain CDRs can also be referred to as HCDRs or CDR-Hs, and numbered as described above (e.g., HCDR1, HCDR2, and HCDR3 or CDR-H1, CDR-H2, and CDR-H3). Likewise, light chain CDRs can be referred to as LCDRs or CDR-Ls, and numbered LCDR1, LCDR2, and LCDR3, or CDR-L1, CDR-L2, and CDR-L3. In certain embodiments of the invention, the FRs of the antibody (or antigen binding fragment thereof) are identical to the human germline sequences, or are naturally or artificially modified. Exemplary human germline sequences include, but are not limited to, VH3-66 and Vk1-33. Thus, the present disclosure provides anti-CoV-S antibodies or antigen-

binding fragments thereof (*e.g.*, anti-SARS-CoV-2-S antibodies or antigen-binding fragments thereof) comprising HCDR and LCDR sequences of Table 1 within a VH3-66 or Vk1-33 variable heavy chain or light chain region. The present disclosure further provides anti-CoV-S antibodies or antigen-binding fragments thereof (*e.g.*, anti-SARS-CoV-2-S antibodies or antigen-binding fragments thereof) comprising HCDR and LCDR sequences of Table 1 within a combination of a light chain selected from IgKV4-1, IgKV 1-5, IgKV1-9, IgKV1-12, IgKV3-15, IgKV1-16, IgKV1-17, IgKV3-20, IgLV3-21, IgKV2-24, IgKV1-33, IgKV1-39, IgLV1-40, IgLV1-44, IgLV1-51, IgLV3-1, IgKV1-6, IgLV2-8, IgKV3-11, IgLV2-11, IgLV2-14, IgLV2-23, or IgLV6-57, and a heavy chain selected from IgHV1-69, IgHV3-64, IgHV4-59, IgHV3-53, IgHV3-48, IgHV4-34, IgHV3-33, IgHV3-30, IgHV3-23, IgHV3-20, IgHV1-18, IgHV3-15, IgHV3-11, IgHV3-9, IgHV1-8, IgHV3-7, IgHV2-5, IgHV1-2, IgHV2-70, IgHV3-66, IgHV5-51, IgHV1-46, IgHV4-39, IgHV4-31, IgHV3-30-3, IgHV2-26, or IgHV7-4-1. The present disclosure further provides anti-CoV-S antibodies or antigen-binding fragments thereof (*e.g.*, anti-SARS-CoV-2-S antibodies or antigen-binding fragments thereof) comprising HCVR and LCVR sequences of Table 1 within a combination of a light chain selected from IgKV4-1, IgKV 1-5, IgKV1-9, IgKV1-12, IgKV3-15, IgKV1-16, IgKV1-17, IgKV3-20, IgLV3-21, IgKV2-24, IgKV1-33, IgKV1-39, IgLV1-40, IgLV1-44, IgLV1-51, IgLV3-1, IgKV1-6, IgLV2-8, IgKV3-11, IgLV2-11, IgLV2-14, IgLV2-23, or IgLV6-57, and a heavy chain selected from IgHV1-69, IgHV3-64, IgHV4-59, IgHV3-53, IgHV3-48, IgHV4-34, IgHV3-33, IgHV3-30, IgHV3-23, IgHV3-20, IgHV1-18, IgHV3-15, IgHV3-11, IgHV3-9, IgHV1-8, IgHV3-7, IgHV2-5, IgHV1-2, IgHV2-70, IgHV3-66, IgHV5-51, IgHV1-46, IgHV4-39, IgHV4-31, IgHV3-30-3, IgHV2-26, or IgHV7-4-1.

[00035] Typically, the variable domains of both the heavy and light immunoglobulin chains comprise three hypervariable regions, also called complementarity determining regions (CDRs), located within relatively conserved framework regions (FR). In general, from N-terminal to C-terminal, both light and heavy chains variable domains comprise FR1, CDR1, FR2, CDR2, FR3, CDR3 and FR4. In an embodiment of the invention, the assignment of amino acids to each domain is 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.

[00036] The present invention includes monoclonal anti-CoV-S antigen-binding proteins, *e.g.*, antibodies and antigen-binding fragments thereof, as well as monoclonal compositions comprising a plurality of isolated monoclonal antigen-binding proteins. The term "monoclonal antibody", as used herein, refers to a 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 that may be present in minor amounts. A "plurality" of such monoclonal antibodies and fragments in a composition refers to a concentration of identical (*i.e.*, as discussed above, in amino acid sequence except for possible naturally occurring mutations that may be present in minor amounts) antibodies and fragments which is above that which would normally occur in nature, *e.g.*, in the blood of a host organism such as a mouse or a human.

[00037] In an embodiment of the invention, an anti-CoV-S antigen-binding protein, *e.g.*, antibody or antigen-binding fragment comprises a heavy chain constant domain, *e.g.*, of the type IgA (*e.g.*, IgA1 or IgA2), IgD, IgE, IgG (*e.g.*, IgG1, IgG2, IgG3 and IgG4) or IgM. In an embodiment of the invention, an antigen-binding protein, *e.g.*, antibody or antigen-binding fragment comprises a light chain constant domain, *e.g.*, of the type kappa or lambda.

[00038] The term "human" antigen-binding protein, such as an antibody, as used herein, includes antibodies having variable and constant regions derived from human germline immunoglobulin sequences whether in a human cell or grafted into a non-human cell, *e.g.*, a mouse cell. See *e.g.*, US8502018, US6596541 or US5789215. The human mAbs of the invention may include amino acid residues not encoded by human germline immunoglobulin sequences (*e.g.*, mutations introduced by random or site-specific mutagenesis *in vitro* or by somatic mutation *in vivo*), for example in the CDRs and, in particular, CDR3. However, the term "human antibody", as used herein, is not intended to include mAbs in which CDR sequences derived from the germline of another mammalian species (*e.g.*, mouse) have been grafted onto human FR sequences. The term includes antibodies recombinantly produced in a non-human mammal or in cells of a non-human mammal. The term is not intended to include antibodies isolated from or generated in a human subject. See below.

[00039] The present invention includes anti-CoV-S chimeric antigen-binding proteins, *e.g.*, antibodies and antigen-binding fragments thereof, and methods of use thereof. As used herein, a "chimeric antibody" is an antibody having the variable domain from a first antibody and the constant domain from a second antibody, where the first and second antibodies are from different species. (US4816567; and Morrison *et al.*, (1984) Proc. Natl. Acad. Sci. USA 81: 6851-6855).

[00040] The present invention includes anti-CoV-S hybrid antigen-binding proteins, *e.g.*, antibodies and antigen-binding fragments thereof, and methods of use thereof. As used herein, a "hybrid antibody" is an antibody having the variable domain from a first antibody and the constant domain from a second antibody, wherein the first and second antibodies are from different animals, or wherein the variable domain, but not the constant region, is from a first animal. For example, a variable domain can be taken from an antibody isolated from a human and expressed with a fixed constant region not isolated from that antibody. Exemplary hybrid antibodies are described in Example 1, which refers to antibody heavy chain variable region and light chain variable region derived PCR products that were cloned into expression vectors containing a heavy constant region and a light constant region, respectively. Hybrid antibodies are synthetic and non-natrually occurring because the variable and constant regions they contain are not isolated from a single natural source.

[00041] The term “recombinant” antigen-binding proteins, such as antibodies or antigen-binding fragments thereof, refers to such molecules created, expressed, isolated or obtained by technologies or methods known in the art as recombinant DNA technology which include, *e.g.*, DNA splicing and transgenic expression. The term includes antibodies expressed in a non-human mammal (including transgenic non-human mammals, *e.g.*, transgenic mice), or a cell (*e.g.*, CHO cells) expression system, or a non-human cell expression system, or isolated from a recombinant combinatorial human antibody library. In some embodiments, a recombinant antibody shares a sequence with an antibody isolated from an organism (*e.g.*, a mouse or a human), but has been expressed via recombinant DNA technology. Such antibodies may have post-translational modifications (*e.g.*, glycosylation) that differ from the antibody as isolated from the organism.

[00042] Recombinant anti-CoV-S antigen-binding proteins, *e.g.*, antibodies and antigen-binding fragments, disclosed herein may also be produced in an *E. coli*/T7 expression system. In this embodiment, nucleic acids encoding the anti-CoV-S antibody immunoglobulin molecules of the

invention (*e.g.*, as found in Table 1) may be inserted into a pET-based plasmid and expressed in the *E. coli*/T7 system. For example, the present invention includes methods for expressing an antibody or antigen-binding fragment thereof or immunoglobulin chain thereof in a host cell (*e.g.*, bacterial host cell such as *E. coli* such as BL21 or BL21DE3) comprising expressing T7 RNA polymerase in the cell which also includes a polynucleotide encoding an immunoglobulin chain that is operably linked to a T7 promoter. For example, in an embodiment of the invention, a bacterial host cell, such as an *E. coli*, includes a polynucleotide encoding the T7 RNA polymerase gene operably linked to a *lac* promoter and expression of the polymerase and the chain is induced by incubation of the host cell with IPTG (isopropyl-beta-D-thiogalactopyranoside). See US4952496 and US5693489 or Studier & Moffatt, Use of bacteriophage T7 RNA polymerase to direct selective high-level expression of cloned genes, J. Mol. Biol. 1986 May 5;189(1): 113-30.

[00043] There are several methods by which to produce recombinant antibodies which are known in the art. One example of a method for recombinant production of antibodies is disclosed in US4816567.

[00044] Transformation can be by any known method for introducing polynucleotides (e.g., DNA or RNA, including mRNA) into a host cell. Methods for introduction of heterologous polynucleotides into mammalian cells are well known in the art and include dextran-mediated transfection, calcium phosphate precipitation, polybrene-mediated transfection, protoplast fusion, electroporation, encapsulation of the polynucleotide(s) in liposomes, lipid nanoparticle technology, biolistic injection and direct microinjection of the DNA into nuclei. In addition, nucleic acid molecules may be introduced into mammalian cells by viral vectors such as lentivirus or adeno-associated virus. Methods of transforming cells are well known in the art. See, for example, U.S. Pat. Nos. 4,399,216; 4,912,040; 4,740,461 and 4,959,455. In some embodiments, an antibody or antigen-binding fragment thereof of the present disclosure can be introduced to a subject in nucleic acid form (e.g, DNA or RNA, including mRNA), such that the subject's own cells produce the antibody. The present disclosure further provides modifications to nucleotide sequences encoding the anti-CoV-S antibodies described herein that result in increased antibody expression, increased antibody stability, increased nucleic acid (e.g., mRNA) stability, or improved affinity or specificity of the antibodies for the CoV spike protein.

[00045] Thus, the present invention includes recombinant methods for making an anti-CoV-S antigen-binding protein, such as an antibody or antigen-binding fragment thereof of the present invention, or an immunoglobulin chain thereof, comprising (i) introducing one or more polynucleotides (*e.g.*, including the nucleotide sequence of any one or more of the sequences of Table 2) encoding light and/or heavy immunoglobulin chains, or CDRs, of the antigen-binding protein, *e.g.*, of Table 1, for example, wherein the polynucleotide is in a vector; and/or integrated into a host cell chromosome and/or is operably linked to a promoter; (ii) culturing the host cell (*e.g.*, CHO or *Pichia* or *Pichia pastoris*) under condition favorable to expression of the polynucleotide and, (iii) optionally, isolating the antigen-binding protein, (*e.g.*, antibody or fragment) or chain from the host cell and/or medium in which the host cell is grown. For example, a polynucleotide can be integrated into a host cell chromosome through targeted insertion with a vector such as adeno-associated virus (AAV), e.g., after cleavage of the chromosome using a gene editing system (e.g., CRISPR (for example, CRISPR-Cas9), TALEN, megaTAL, zinc finger, or Argonaute). Targeted insertions can take place, for example, at host cell loci such as an albumin or immunoglopbulin genomic locus. Alternatively, insertion can be at a random locus, e.g., using a vector such as lentivirus. When making an antigen-binding protein (*e.g.*, antibody or antigen-binding fragment) comprising more than one immunoglobulin chain, *e.g.*, an antibody that comprises two heavy immunoglobulin chains and two light immunoglobulin chains, co-expression of the chains in a single host cell leads to association of the chains, *e.g.*, in the cell or on the cell surface or outside the cell if such chains are secreted, so as to form the antigen-binding protein (*e.g.*, antibody or antigen-binding fragment). The methods include those wherein only a heavy immunoglobulin chain or only a light immunoglobulin chain (*e.g.*, any of those discussed herein including mature fragments and/or variable domains thereof) is expressed. Such chains are useful, for example, as intermediates in the expression of an antibody or antigen-binding fragment that includes such a chain. For example, the present invention also includes anti-CoV-S antigen-binding proteins, such as antibodies and antigen-binding fragments thereof, comprising a heavy chain immunoglobulin (or variable domain thereof or comprising the CDRs thereof) encoded by a polynucleotide comprising a nucleotide sequence set forth in Table 2 and a light chain immunoglobulin (or variable domain thereof or comprising the CDRs thereof) encoded by a nucleotide sequence set forth in Table 2 which are the product of such production methods, and, optionally, the

purification methods set forth herein. For example, in some embodiments, the product of the method is an anti-CoV-S antigen-binding protein which is an antibody or fragment comprising an HCVR comprising an amino acid sequence set forth in Table 1 and an LCVR comprising an amino acid sequence set forth in Table 1, wherein the HCVR and LCVR sequences are selected from a single antibody listed in Table 1. In some embodiments, the product of the method is an anti-CoV-S antigen-binding protein which is an antibody or fragment comprising HCDR1, HCDR2, and HCDR3 comprising amino acid sequences set forth in Table 1 and LCDR1, LCDR2, and LCDR3 comprising amino acid sequences set forth in Table 1, wherein the six CDR sequences are selected from a single antibody listed in Table 1. In some embodiments, the product of the method is an anti-CoV-S antigen-binding protein which is an antibody or fragment comprising a heavy chain comprising an HC amino acid sequence set forth in Table 1 and a light chain comprising an LC amino acid sequence set forth in Table 1.

[00046] Eukaryotic and prokaryotic host cells, including mammalian cells, may be used as hosts for expression of an anti-CoV-S antigen-binding protein. Such host cells are well known in the art and many are available from the American Type Culture Collection (ATCC). These host cells include, *inter alia*, Chinese hamster ovary (CHO) cells, NS0, SP2 cells, HeLa cells, baby hamster kidney (BHK) cells, monkey kidney cells (COS), human hepatocellular carcinoma cells (*e.g.*, Hep G2), A549 cells, 3T3 cells, HEK-293 cells and a number of other cell lines. Mammalian host cells include human, mouse, rat, dog, monkey, pig, goat, bovine, horse and hamster cells. Other cell lines that may be used are insect cell lines (*e.g.*, *Spodoptera frugiperda* or *Trichoplusia ni*), amphibian cells, bacterial cells, plant cells and fungal cells. Fungal cells include yeast and filamentous fungus cells including, for example, *Pichia pastoris*, *Pichia finlandica*, *Pichia trehalophila*, *Pichia koclamae*, *Pichia membranaefaciens*, *Pichia minuta* (*Ogataea minuta*, *Pichia lindneri*), *Pichia opuntiae*, *Pichia thermotolerans*, *Pichia salictaria*, *Pichia guercuum*, *Pichia pijperi*, *Pichia stiptis*, *Pichia methanolica*, *Pichia* sp., *Saccharomyces cerevisiae*, *Saccharomyces* sp., *Hansenula polymorpha*, *Kluyveromyces* sp., *Kluyveromyces lactis*, *Candida albicans*, *Aspergillus nidulans*, *Aspergillus niger*, *Aspergillus oryzae*, *Trichoderma reesei*, *Chrysosporium lucknowense*, *Fusarium* sp., *Fusarium gramineum*, *Fusarium venenatum*, *Physcomitrella patens* and *Neurospora crassa*. The present invention includes an isolated host cell (*e.g.*, a CHO cell) comprising an antigen-binding protein, such as those of Table 1; or a polynucleotide encoding such a polypeptide thereof.

[00047] The term "specifically binds" refers to those antigen-binding proteins (*e.g.*, mAbs) having a binding affinity to an antigen, such as a CoV-S protein (*e.g.*, SARS-CoV-2-S), expressed as K_D, of at least about 10^{-8} M, as measured by real-time, label free bio-layer interferometry assay, for example, at 25°C or 37°C, *e.g.*, an Octet® HTX biosensor, or by surface plasmon resonance, *e.g.*, BIACORE™, or by solution-affinity ELISA. The present invention includes antigen-binding proteins that specifically bind to a CoV-S protein.

[00048] The terms "antigen-binding portion" or "antigen-binding fragment" of an antibody or antigen-binding protein, and the like, as used herein, include any naturally occurring, enzymatically obtainable, synthetic, or genetically engineered polypeptide or glycoprotein that specifically binds an antigen to form a complex. Non-limiting examples of antigen-binding fragments include: (i) Fab fragments; (ii) $F(ab')_2$ fragments; (iii) Fd fragments; (iv) Fv fragments; (v) single-chain Fv (scFv) molecules; (vi) dAb fragments; and (vii) minimal recognition units consisting of the amino acid residues that mimic the hypervariable region of an antibody (*e.g.*, an isolated complementarity determining region (CDR) such as a CDR3 peptide), or a constrained FR3-CDR3-FR4 peptide. Other engineered molecules, such as domain-specific antibodies, single domain antibodies, domain-deleted antibodies, chimeric antibodies, CDR-grafted antibodies, diabodies, triabodies, tetrabodies, minibodies, nanobodies (*e.g.*, as defined in WO08/020079 or WO09/138519) (*e.g.*, monovalent nanobodies, bivalent nanobodies, *etc.*), small modular immunopharmaceuticals (SMIPs), and shark variable IgNAR domains, are also encompassed within the expression "antigen-binding fragment," as used herein. In an embodiment of the invention, the antigen-binding fragment comprises three or more CDRs of an antibody of Table 1 (*e.g.*, CDR-H1, CDR-H2 and CDR-H3; or CDR-L1, CDR-L2 and CDR-L3).

[00049] An antigen-binding fragment of an antibody will, in an embodiment of the invention, comprise at least one variable domain. The variable domain may be of any size or amino acid composition and will generally comprise at least one CDR, which is adjacent to or in frame with one or more framework sequences. In antigen-binding fragments having a V_H domain associated with a V_L domain, the V_H and V_L domains may be situated relative to one another in any suitable arrangement. For example, the variable region may be dimeric and contain V_H - V_H, V_H - V_L or V_L - V_L dimers. Alternatively, the antigen-binding fragment of an antibody may contain a monomeric V_H or V_L domain.

[00050] In certain embodiments, an antigen-binding fragment of an antibody may contain at least one variable domain covalently linked to at least one constant domain. Non-limiting, exemplary configurations of variable and constant domains that may be found within an antigen-binding fragment of an antibody of the present invention include: (i) V_H-C_H1; (ii) V_H-C_H2; (iii) V_H-C_H3; (iv) V_H-C_H1-C_H2; (v) V_H-C_H1-C_H2-C_H3; (vi) V_H-C_H2-C_H3; (vii) V_H-C_L; (viii) V_L-C_H1; (ix) V_L-C_H2; (x) V_L-C_H3; (xi) V_L-C_H1-C_H2; (xii) V_L-C_H1-C_H2-C_H3; (xiii) V_L-C_H2-C_H3; and (xiv) V_L-C_L. In any configuration of variable and constant domains, including any of the exemplary configurations listed above, the variable and constant domains may be either directly linked to one another or may be linked by a full or partial hinge or linker region. A hinge region may consist of at least 2 (*e.g.*, 5, 10, 15, 20, 40, 60 or more) amino acids, which result in a flexible or semi-flexible linkage between adjacent variable and/or constant domains in a single polypeptide molecule. Moreover, an antigen-binding fragment of an antibody of the present invention may comprise a homo-dimer or hetero-dimer (or other multimer) of any of the variable and constant domain configurations listed above in non-covalent association with one another and/or with one or more monomeric V_H or V_L domain (*e.g.*, by disulfide bond(s)).

[00051] Antigen-binding proteins (*e.g.*, antibodies and antigen-binding fragments) may be mono-specific or multi-specific (*e.g.*, bi-specific). Multispecific antigen-binding proteins are discussed further herein.

[00052] In specific embodiments, antibody or antibody fragments of the invention may be conjugated to a moiety such a ligand or a therapeutic moiety ("immunoconjugate"), such as an anti-viral drug, a second anti-influenza antibody, or any other therapeutic moiety useful for treating a viral infection, *e.g.*, influenza viral infection. See below.

[00053] The present invention also provides a complex comprising an anti-CoV-S antigen-binding protein, *e.g.*, antibody or antigen-binding fragment, discussed herein complexed with CoV-S polypeptide or an antigenic fragment thereof and/or with a secondary antibody or antigen-binding fragment thereof (*e.g.*, detectably labeled secondary antibody) that binds specifically to the anti-CoV-S antibody or fragment. In an embodiment of the invention, the antibody or fragment is *in vitro* (*e.g.*, is immobilized to a solid substrate) or is in the body of a subject. In an embodiment of the invention, the CoV-S is *in vitro* (*e.g.*, is immobilized to a solid substrate) or is on the surface of a virus or is in the body of a subject. Immobilized anti-CoV-S antibodies and antigen-binding fragments thereof which are covalently linked to an insoluble

matrix material (*e.g.*, glass or polysaccharide such as agarose or sepharose, *e.g.*, a bead or other particle thereof) are also part of the present invention; optionally, wherein the immobilized antibody is complexed with CoV-S or antigenic fragment thereof or a secondary antibody or fragment thereof.

[00054] "Isolated" antigen-binding proteins, antibodies or antigen-binding fragments thereof, polypeptides, polynucleotides and vectors, are at least partially free of other biological molecules from the cells or cell culture from which they are produced. Such biological molecules include nucleic acids, proteins, other antibodies or antigen-binding fragments, lipids, carbohydrates, or other material such as cellular debris and growth medium. An isolated antibody or antigen-binding fragment may further be at least partially free of expression system components such as biological molecules from a host cell or of the growth medium thereof. Generally, the term "isolated" is not intended to refer to a complete absence of such biological molecules or to an absence of water, buffers, or salts or to components of a pharmaceutical formulation that includes the antibodies or fragments.

[00055] The term “epitope” refers to an antigenic determinant (*e.g.*, a CoV-S polypeptide) that interacts with a specific antigen-binding site of an antigen-binding protein, *e.g.*, a variable region of an antibody molecule, known as a paratope. A single antigen may have more than one epitope. Thus, different antibodies may bind to different areas on an antigen and may have different biological effects. The term “epitope” also refers to a site on an antigen to which B and/or T cells respond. It also refers to a region of an antigen that is bound by an antibody. Epitopes may be defined as structural or functional. Functional epitopes are generally a subset of the structural epitopes and have those residues that directly contribute to the affinity of the interaction. Epitopes may be linear or conformational, that is, composed of non-linear amino acids. In certain embodiments, epitopes may include determinants that are chemically active surface groupings of molecules such as amino acids, sugar side chains, phosphoryl groups, or sulfonyl groups, and, in certain embodiments, may have specific three-dimensional structural characteristics, and/or specific charge characteristics.

[00056] Methods for determining the epitope of an antigen-binding protein, *e.g.*, antibody or fragment or polypeptide, include alanine scanning mutational analysis, peptide blot analysis (Reineke (2004) Methods Mol. Biol. 248: 443-63), peptide cleavage analysis, crystallographic studies and NMR analysis. In addition, methods such as epitope excision, epitope extraction and

chemical modification of antigens can be employed (Tomer (2000) Prot. Sci. 9: 487-496). Another method that can be used to identify the amino acids within a polypeptide with which an antigen-binding protein (*e.g.*, antibody or fragment or polypeptide) (*e.g.*, coversin) interacts is hydrogen/deuterium exchange detected by mass spectrometry. In general terms, the hydrogen/deuterium exchange method involves deuterium-labeling the protein of interest, followed by binding the antigen-binding protein, *e.g.*, antibody or fragment or polypeptide, to the deuterium-labeled protein. Next, the CoV-S protein/ antigen-binding protein complex is transferred to water and exchangeable protons within amino acids that are protected by the antibody complex undergo deuterium-to-hydrogen back-exchange at a slower rate than exchangeable protons within amino acids that are not part of the interface. As a result, amino acids that form part of the protein/ antigen-binding protein interface may retain deuterium and therefore exhibit relatively higher mass compared to amino acids not included in the interface. After dissociation of the antigen-binding protein (*e.g.*, antibody or fragment or polypeptide), the target protein is subjected to protease cleavage and mass spectrometry analysis, thereby revealing the deuterium-labeled residues which correspond to the specific amino acids with which the antigen-binding protein interacts. See, *e.g.*, Ehring (1999) Analytical Biochemistry 267: 252-259; Engen and Smith (2001) Anal. Chem. 73: 256A-265A.

[00057] The term "competes" as used herein, refers to an antigen-binding protein (*e.g.*, antibody or antigen-binding fragment thereof) that binds to an antigen (*e.g.*, CoV-S) and inhibits or blocks the binding of another antigen-binding protein (*e.g.*, antibody or antigen-binding fragment thereof) to the antigen. The term also includes competition between two antigen-binding proteins *e.g.*, antibodies, in both orientations, *i.e.*, a first antibody that binds and blocks binding of second antibody and *vice versa*. In certain embodiments, the first antigen-binding protein (*e.g.*, antibody) and second antigen-binding protein (*e.g.*, antibody) may bind to the same epitope. Alternatively, the first and second antigen-binding proteins (*e.g.*, antibodies) may bind to different, but, for example, overlapping epitopes, wherein binding of one inhibits or blocks the binding of the second antibody, *e.g.*, via steric hindrance. Competition between antigen-binding proteins (*e.g.*, antibodies) may be measured by methods known in the art, for example, by a real-time, label-free bio-layer interferometry assay. Epitope mapping (e.g., via alanine scanning or hydrogen-deuterium exchange (HDX)) can be used to determine whether two or more antibodies are non-competing (e.g., on a spike protein receptor binding domain (RBD) monomer),

competing for the same epitope, or competing but with diverse micro-epitopes (e.g., identified through HDX). In an embodiment of the invention, competition between a first and second anti-CoV-S antigen-binding protein (*e.g.*, antibody) is determined by measuring the ability of an immobilized first anti-CoV-S antigen-binding protein (*e.g.*, antibody) (not initially complexed with CoV-S protein) to bind to soluble CoV-S protein complexed with a second anti-CoV-S antigen-binding protein (*e.g.*, antibody). A reduction in the ability of the first anti-CoV-S antigen-binding protein (*e.g.*, antibody) to bind to the complexed CoV-S protein, relative to uncomplexed CoV-S protein, indicates that the first and second anti-CoV-S antigen-binding proteins (*e.g.*, antibodies) compete. The degree of competition can be expressed as a percentage of the reduction in binding. Such competition can be measured using a real time, label-free bio-layer interferometry assay, *e.g.*, on an Octet RED384 biosensor (Pall ForteBio Corp.), ELISA (enzyme-linked immunosorbent assays) or SPR (surface plasmon resonance).

[00058] Binding competition between anti-CoV-S antigen-binding proteins (*e.g.*, monoclonal antibodies (mAbs)) can be determined using a real time, label-free bio-layer interferometry assay on an Octet RED384 biosensor (Pall ForteBio Corp.). For example, to determine competition between two anti-CoV-S monoclonal antibodies, the anti-CoV-S mAb can be first captured onto anti-hFc antibody coated Octet biosensor tips (Pall ForteBio Corp., # 18-5060) by submerging the tips into a solution of anti-CoV-S mAb (subsequently referred to as "mAb1"). As a positive-control for blocking, the antibody captured biosensor tips can then be saturated with a known blocking isotype control mAb (subsequently referred to as "blocking mAb") by dipping into a solution of blocking mAb. To determine if mAb2 competes with mAb1, the biosensor tips can then be subsequently dipped into a co-complexed solution of CoV-S polypeptide and a second anti-CoV-S mAb (subsequently referred to as "mAb2"), that had been pre-incubated for a period of time and binding of mAb1 to the CoV-S polypeptide can be determined. The biosensor tips can be washed in buffer in between every step of the experiment. The real-time binding response can be monitored during the course of the experiment and the binding response at the end of every step can be recorded.

[00059] For example, in an embodiment of the invention, the competition assay is conducted at 25 °C and pH about 7, *e.g.*, 7.4, *e.g.*, in the presence of buffer, salt, surfactant and a non-specific protein (*e.g.*, bovine serum albumin).

[00060] Typically, an antibody or antigen-binding fragment of the invention which is modified in some way retains the ability to specifically bind to CoV-S, *e.g.*, retains at least 10% of its CoV-S binding activity (when compared to the parental antibody) when that activity is expressed on a molar basis. Preferably, an antibody or antigen-binding fragment of the invention retains at least 20%, 50%, 70%, 80%, 90%, 95% or 100% or more of the CoV-S binding affinity as the parental antibody. It is also intended that an antibody or antigen-binding fragment of the invention can include conservative or non-conservative amino acid substitutions (referred to as "conservative variants" or "function conserved variants" of the antibody) that do not substantially alter its biologic activity.

[00061] A "variant" of a polypeptide, or a "modified" polypeptide, such as an immunoglobulin chain, refers to a polypeptide comprising an amino acid sequence that is at least about 70-99.9% (*e.g.*, 70, 72, 74, 75, 76, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 99.5, 99.9%) identical or similar to a referenced amino acid sequence that is set forth herein; when the comparison is performed by a BLAST algorithm wherein the parameters of the algorithm are selected to give the largest match between the respective sequences over the entire length of the respective reference sequences (*e.g.*, expect threshold: 10; word size: 3; max matches in a query range: 0; BLOSUM 62 matrix; gap costs: existence 11, extension 1; conditional compositional score matrix adjustment).

[00062] A "variant" of a polynucleotide or a "modified" polynucleotide refers to a polynucleotide comprising a nucleotide sequence that is at least about 70-99.9% (*e.g.*, at least about 70, 72, 74, 75, 76, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 99.5, or 99.9%) identical to a referenced nucleotide sequence that is set forth herein (*e.g.*, SEQ ID NO: 1, 9, 17, 19, 21, 29, 37, 39, 41, 49, 57, or 59); when the comparison is performed by a BLAST algorithm wherein the parameters of the algorithm are selected to give the largest match between the respective sequences over the entire length of the respective reference sequences (*e.g.*, expect threshold: 10; word size: 28; max matches in a query range: 0; match/mismatch scores: 1, -2; gap costs: linear).

[00063] Anti-CoV-S antigen-binding proteins, *e.g.*, antibodies and antigen-binding fragments thereof of the present invention, in an embodiment of the invention, include a heavy chain immunoglobulin variable region having at least 70% (*e.g.*, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or greater) amino acid sequence identity to the HCVR amino

acid sequences set forth in Table 1; and/or a light chain immunoglobulin variable region having at least 70% (*e.g.*, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or greater) amino acid sequence identity to the LCVR amino acid sequences set forth in Table 1.

[00064] In addition, a modified anti-CoV-S antigen-binding protein may include a polypeptide comprising an amino acid sequence that is set forth herein except for one or more (*e.g.*, 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10) mutations such as, for example, missense mutations (*e.g.*, conservative substitutions), non-sense mutations, deletions, or insertions. For example, the present invention includes antigen-binding proteins which include an immunoglobulin light chain variant comprising an LCVR amino acid sequence set forth in Table 1 but having one or more of such mutations and/or an immunoglobulin heavy chain variant comprising an HCVR amino acid sequence set forth in Table 1 but having one or more of such mutations. In an embodiment of the invention, a variant anti-CoV-S antigen-binding protein includes an immunoglobulin light chain variant comprising CDR-L1, CDR-L2 and CDR-L3 wherein one or more (*e.g.*, 1 or 2 or 3) of such CDRs has one or more of such mutations (*e.g.*, conservative substitutions) and/or an immunoglobulin heavy chain variant comprising CDR-H1, CDR-H2 and CDR-H3 wherein one or more (*e.g.*, 1 or 2 or 3) of such CDRs has one or more of such mutations (*e.g.*, conservative substitutions). Substitutions can be in a CDR, framework, or constant region.

Modified anti-SARS-CoV-2-S antibodies, or antigen-binding fragments thereof, can be generated, for example, through structural analysis of the antibody in complex with the spike glycoprotein. In some embodiments, this structural analysis is through cryo-electron microscophy or protein crystallography. For example, amino acids of an antibody or antigen-binding fragment that interact with amino acid 484 of SEQ ID NO: 832 can be identified and mutated to generate a modified antibody or antigen-binding fragement with enhanced binding (e.g., binding affinity or dissociative half-life) or neutralization of an E484K variant. In some embodiments, this modification comprises a substitution mutation, e.g., in a polynucleic acid encoding the antibody or antigen-binding fragment. This mutation can, for example, comprise mutating a positively charged side chain at pH 7.0 such as lysine, arginine, or histidine to a negatively charged side chain at pH 7.0, such as aspartate or glutamate. In some embodiments, a non-positively charged side chain can be mutated to a negatively-charged side chain (e.g., a nonpolar or polar side chain can be mutated to a negatively-charged side chain). Without wishing to be bound by theory, this change could enhance binding by allowing a salt bridge to form

between the negatively charged side chain and the lysine at position 484 of the variant spike protein, or by allowing one or more new hydrogen bonds to form. An antibody also can be modified, for example, by introducing a chemical modification to an amino acid.

[00065] The invention further provides variant anti-CoV-S antigen-binding proteins, *e.g.*, antibodies or antigen-binding fragments thereof, comprising one or more variant CDRs (*e.g.*, any one or more of CDR-L1, CDR-L2, CDR-L3, CDR-H1, CDR-H2 and/or CDR-H3) that are set forth herein with at least 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 99.9% sequence identity or similarity to, *e.g.*, the heavy chain and light chain CDRs of Table 1.

[00066] Embodiments of the present invention also include variant antigen-binding proteins, *e.g.*, anti-CoV-S antibodies and antigen-binding fragments thereof, that comprise immunoglobulin V_{HS} and V_{LS}; or HCs and LCs, which comprise an amino acid sequence having 70% or more (*e.g.*, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or greater) overall amino acid sequence identity or similarity to the amino acid sequences of the corresponding V_{HS}, V_{LS}, HCs or LCs specifically set forth herein, but wherein the CDR-L1, CDR-L2, CDR-L3, CDR-H1, CDR-H2 and CDR-H3 of such immunoglobulins are not variants and comprise CDR amino acid sequence set forth in Table 1. Thus, in such embodiments, the CDRs within variant antigen-binding proteins are not, themselves, variants.

[00067] Conservatively modified variant anti-CoV-S antibodies and antigen-binding fragments thereof are also part of the present invention. A "conservatively modified variant" or a "conservative substitution" refers to a variant wherein there is one or more substitutions of amino acids in a polypeptide with other amino acids having similar characteristics (*e.g.* charge, side-chain size, hydrophobicity/hydrophilicity, backbone conformation and rigidity, etc.). Such changes can frequently be made without significantly disrupting the biological activity of the antibody or fragment. Those of skill in this art recognize that, in general, single amino acid substitutions in non-essential regions of a polypeptide do not substantially alter biological activity (see, *e.g.*, Watson *et al.* (1987) Molecular Biology of the Gene, The Benjamin/Cummings Pub. Co., p. 224 (4^{th} Ed.)). In addition, substitutions of structurally or functionally similar amino acids are less likely to significantly disrupt biological activity.

[00068] Examples of groups of amino acids that have side chains with similar chemical properties include 1) aliphatic side chains: glycine, alanine, valine, leucine and isoleucine; 2)

aliphatic-hydroxyl side chains: serine and threonine; 3) amide-containing side chains: asparagine and glutamine; 4) aromatic side chains: phenylalanine, tyrosine, and tryptophan; 5) basic side chains: lysine, arginine, and histidine; 6) acidic side chains: aspartate and glutamate, and 7) sulfur-containing side chains: cysteine and methionine. Preferred conservative amino acids substitution groups are: valine-leucine-isoleucine, phenylalanine-tyrosine, lysine-arginine, alanine-valine, glutamate-aspartate, and asparagine-glutamine. Alternatively, a conservative replacement is any change having a positive value in the PAM250 log-likelihood matrix disclosed in Gonnet *et al.* (1992) Science 256: 1443 45.

[00069] Function-conservative variants of the anti-CoV-S antibodies and antigen-binding fragments thereof are also part of the present invention. Any of the variants of the anti-CoV-S antibodies and antigen-binding fragments thereof (as discussed herein) may be "function-conservative variants". Such function-conservative variants may, in some cases, also be characterized as conservatively modified variants. "Function-conservative variants," as used herein, refers to variants of the anti-CoV-S antibodies or antigen-binding fragments thereof in which one or more amino acid residues have been changed without significantly altering one or more functional properties of the antibody or fragment. In an embodiment of the invention, a function-conservative variant anti-CoV-S antibody or antigen-binding fragment thereof of the present invention comprises a variant amino acid sequence and exhibits one or more of the following functional properties:

- Inhibits growth of coronavirus (*e.g.*, SARS-CoV-2, SARS-CoV, and/or MERS-CoV) in ACE2- and/or TMPRSS2-expressing cells (*e.g.*, Calu-3 cells);
- Does not significantly bind to MDCK/Tet-on cells which do not express ACE2 and/or TMPRSS2;
- Limits spread of coronavirus infection (*e.g.*, by SARS-CoV-2, SARS-CoV, and/or MERS-CoV) of cells, *e.g.*, Calu-3, *in vitro*; and/or
- Protects a mouse engineered to express the human TMPRSS2 and/or ACE2 protein from death caused by coronavirus infection (*e.g.*, SARS-CoV-2, SARS-CoV, or MERS-CoV), for example, wherein the mice are infected with an otherwise lethal dose of the virus, optionally when combined with a second therapeutic agent.
- Protects a mouse engineered to express the human TMPRSS2 and/or ACE2 protein from weight loss caused by coronavirus infection (*e.g.*, SARS-CoV-2, SARS-CoV, or

MERS-CoV), for example, wherein the mice are infected with a dose of the virus that would otherwise cause weighht loss, optionally when combined with a second therapeutic agent.

[00070] A "neutralizing" or "antagonist" anti-CoV-S antigen-binding protein, *e.g.*, antibody or antigen-binding fragment, refers to a molecule that inhibits an activity of CoV-S to any detectable degree, *e.g.*, inhibits the ability of CoV-S to bind to a receptor such as ACE2, to be cleaved by a protease such as TMPRSS2, or to mediate viral entry into a host cell or viral reproduction in a host cell.

[00071] Table 1 refers to antigen-binding proteins, such as antibodies and antigen-binding fragments thereof, that comprise the heavy chain or V_H (or a variant thereof) and light chain or V_L (or a variant thereof) as set forth below; or that comprise a V_H that comprises the CDRs thereof (CDR-H1 (or a variant thereof), CDR-H2 (or a variant thereof) and CDR-H3 (or a variant thereof)) and a V_L that comprises the CDRs thereof (CDR-L1 (or a variant thereof), CDR-L2 (or a variant thereof) and CDR-L3 (or a variant thereof)), *e.g.*, wherein the immunoglobulin chains, variable regions and/or CDRs comprise the specific amino acid sequences described below.

[00072] The antibodies described herein also include embodiments wherein the V_H is fused to a wild-type IgG4 (*e.g.*, wherein residue 108 is S) or to IgG4 variants (*e.g.*, wherein residue 108 is P).

[00073] Antibodies and antigen-binding fragments of the present invention comprise immunoglobulin chains including the amino acid sequences set forth herein as well as cellular and *in vitro* post-translational modifications to the antibody. For example, the present invention includes antibodies and antigen-binding fragments thereof that specifically bind to CoV-S comprising heavy and/or light chain amino acid sequences set forth herein (*e.g.*, CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2 and/or CDR-L3) as well as antibodies and fragments wherein one or more amino acid residues is glycosylated, one or more Asn residues is deamidated, one or more residues (*e.g.*, Met, Trp and/or His) is oxidized, the N-terminal Gln is pyroglutamate (pyroE) and/or the C-terminal Lysine is missing.

[00074] The amino acid and nucleotide sequences of exemplary anti-SARS-CoV-2-Spike protein (SARS-CoV-2-S) antibodies are shown in the Table of Exemparly Sequences, below.

Table of Exemplary Sequences

Antibody Designation	Component Part	Sequence	SEQ ID NO
mAb10933	**Amino Acids**		
	HCVR	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYM SWIRQAPGKGLEWVSYITYSGSTIYYADSVKGRF TISRDNAKSSLYLQMNSLRAEDTAVYYCARDRGT TMVPFDYWGQGTLVTVSS	202
	HCDR1	GFTFSDYY	204
	HCDR2	ITYSGSTI	206
	HCDR3	ARDRGTTMVPFDY	208
	LCVR	DIQMTQSPSSLSASVGDRVTITCQASQDITNYLN WYQQKPGKAPKLLIYAASNLETGVPSRFSGSGSG TDFTFTISGLQPEDIATYYCQQYDNLPLTFGGGT KVEIK	210
	LCDR1	QDITNY	212
	LCDR2	AAS	55
	LCDR3	QQYDNLPLT	214
	HC	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYM SWIRQAPGKGLEWVSYITYSGSTIYYADSVKGRF TISRDNAKSSLYLQMNSLRAEDTAVYYCARDRGT TMVPFDYWGQGTLVTVSSASTKGPSVFPLAPSSK STSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICN VNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELL GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVV SVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTIS KAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKG FYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFF LYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQK SLSLSPGK	216
	LC	DIQMTQSPSSLSASVGDRVTITCQASQDITNYLN WYQQKPGKAPKLLIYAASNLETGVPSRFSGSGSG TDFTFTISGLQPEDIATYYCQQYDNLPLTFGGGT KVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLL NNFYPREAKVQWKVDNALQSGNSQESVTEQDSKD STYSLSSTLTLSKADYEKHKVYACEVTHQGLSSP VTKSFNRGEC	218
	Nucleic Acids		
	HCVR	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGG TCAAGCCTGGAGGGTCCCTGAGACTCTCCTGTGC AGCCTCTGGATTCACCTTCAGTGACTACTACATG	201

		AGCTGGATCCGCCAGGCTCCAGGGAAGGGGCTGG AGTGGGTTTCATACATTACTTATAGTGGTAGTAC CATATACTACGCAGACTCTGTGAAGGGCCGATTC ACCATCTCCAGGGACAACGCCAAGAGCTCACTGT ATCTGCAAATGAACAGCCTGAGAGCCGAGGACAC GGCCGTGTATTACTGTGCGAGAGATCGCGGTACA ACTATGGTCCCCTTTGACTACTGGGGCCAGGGAA CCCTGGTCACCGTCTCCTCA	
	HCDR1	GGATTCACCTTCAGTGACTACTAC	203
	HCDR2	ATTACTTATAGTGGTAGTACCATA	205
	HCDR3	GCGAGAGATCGCGGTACAACTATGGTCCCCTTTG ACTAC	207
	LCVR	GACATCCAGATGACCCAGTCTCCATCCTCCCTGT CTGCATCTGTAGGAGACAGAGTCACCATCACTTG CCAGGCGAGTCAGGACATTACCAACTATTTAAAT TGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGC TCCTGATCTACGCTGCATCCAATTTGGAAACAGG GGTCCCATCAAGGTTCAGTGGAAGTGGATCTGGG ACAGATTTTACTTTCACCATCAGCGGCCTGCAGC CTGAAGATATTGCAACATATTACTGTCAACAGTA TGATAATCTCCCTCTCACTTTCGGCGGAGGGACC AAGGTGGAGATCAAA	209
	LCDR1	CAGGACATTACCAACTAT	211
	LCDR2	GCTGCATCC	54
	LCDR3	CAACAGTATGATAATCTCCCTCTCACT	213
	HC	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGG TCAAGCCTGGAGGGTCCCTGAGACTCTCCTGTGC AGCCTCTGGATTCACCTTCAGTGACTACTACATG AGCTGGATCCGCCAGGCTCCAGGGAAGGGGCTGG AGTGGGTTTCATACATTACTTATAGTGGTAGTAC CATATACTACGCAGACTCTGTGAAGGGCCGATTC ACCATCTCCAGGGACAACGCCAAGAGCTCACTGT ATCTGCAAATGAACAGCCTGAGAGCCGAGGACAC GGCCGTGTATTACTGTGCGAGAGATCGCGGTACA ACTATGGTCCCCTTTGACTACTGGGGCCAGGGAA CCCTGGTCACCGTCTCCTCAGCCTCCACCAAGGG CCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAG AGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCC TGGTCAAGGACTACTTCCCCGAACCGGTGACGGT GTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTG CACACCTTCCCGGCTGTCCTACAGTCCTCAGGAC TCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTC CAGCAGCTTGGGCACCCAGACCTACATCTGCAAC GTGAATCACAAGCCCAGCAACACCAAGGTGGACA AGAAAGTTGAGCCCAAATCTTGTGACAAAACTCA	215

		CACATGCCCACCGTGCCCAGCACCTGAACTCCTG GGGGGACCGTCAGTCTTCCTCTTCCCCCCAAAAC CCAAGGACACCCTCATGATCTCCCGGACCCCTGA GGTCACATGCGTGGTGGTGGACGTGAGCCACGAA GACCCTGAGGTCAAGTTCAACTGGTACGTGGACG GCGTGGAGGTGCATAATGCCAAGACAAAGCCGCG GGAGGAGCAGTACAACAGCACGTACCGTGTGGTC AGCGTCCTCACCGTCCTGCACCAGGACTGGCTGA ATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAA AGCCCTCCCAGCCCCCATCGAGAAAACCATCTCC AAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGT ACACCCTGCCCCCATCCCGGGATGAGCTGACCAA GAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGC TTCTATCCCAGCGACATCGCCGTGGAGTGGGAGA GCAATGGGCAGCCGGAGAACAACTACAAGACCAC GCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTC CTCTACAGCAAGCTCACCGTGGACAAGAGCAGGT GGCAGCAGGGGAACGTCTTCTCATGCTCCGTGAT GCATGAGGCTCTGCACAACCACTACACGCAGAAG TCCCTCTCCCTGTCTCCGGGTAAATGA	
	LC	GACATCCAGATGACCCAGTCTCCATCCTCCCTGT CTGCATCTGTAGGAGACAGAGTCACCATCACTTG CCAGGCGAGTCAGGACATTACCAACTATTTAAAT TGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGC TCCTGATCTACGCTGCATCCAATTTGGAAACAGG GGTCCCATCAAGGTTCAGTGGAAGTGGATCTGGG ACAGATTTTACTTTCACCATCAGCGGCCTGCAGC CTGAAGATATTGCAACATATTACTGTCAACAGTA TGATAATCTCCCTCTCACTTTCGGCGGAGGGACC AAGGTGGAGATCAAACGAACTGTGGCTGCACCAT CTGTCTTCATCTTCCCGCCATCTGATGAGCAGTT GAAATCTGGAACTGCCTCTGTTGTGTGCCTGCTG AATAACTTCTATCCCAGAGAGGCCAAAGTACAGT GGAAGGTGGATAACGCCCTCCAATCGGGTAACTC CCAGGAGAGTGTCACAGAGCAGGACAGCAAGGAC AGCACCTACAGCCTCAGCAGCACCCTGACGCTGA GCAAAGCAGACTACGAGAAACACAAAGTCTACGC CTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCC GTCACAAAGAGCTTCAACAGGGGAGAGTGTTAG	217
mAb10934	**Amino Acids**		
	HCVR	EVQLVESGGGLVKPGGSLRLSCAASGITFSNAWM SWVRQAPGKGLEWVGRIKSKTDGGTTDYAAPVKG RFTISRDDSKNTLYLQMNSLKTEDTAVYYCTTAR WDWYFDLWGRGTLVTVSS	220
	HCDR1	GITFSNAW	222
	HCDR2	IKSKTDGGTT	224

	HCDR3	TTARWDWYFDL	226
	LCVR	DIQMTQSPSSLSASVGDRVTITCQASQDIWNYIN WYQQKPGKAPKLLIYDASNLKTGVPSRFSGSGSG TDFTFTISSLQPEDIATYYCQQHDDLPPTFGQGT KVEIK	228
	LCDR1	QDIWNY	230
	LCDR2	DAS	194
	LCDR3	QQHDDLPPT	232
	HC	EVQLVESGGGLVKPGGSLRLSCAASGITFSNAWM SWVRQAPGKGLEWVGRIKSKTDGGTTDYAAPVKG RFTISRDDSKNTLYLQMNSLKTEDTAVYYCTTAR WDWYFDLWGRGTLVTVSSASTKGPSVFPLAPSSK STSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICN VNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELL GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVV SVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTIS KAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKG FYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFF LYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQK SLSLSPGK	234
	LC	DIQMTQSPSSLSASVGDRVTITCQASQDIWNYIN WYQQKPGKAPKLLIYDASNLKTGVPSRFSGSGSG TDFTFTISSLQPEDIATYYCQQHDDLPPTFGQGT KVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLL NNFYPREAKVQWKVDNALQSGNSQESVTEQDSKD STYSLSSTLTLSKADYEKHKVYACEVTHQGLSSP VTKSFNRGEC	236
	Nucleic Acids		
	HCVR	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGG TAAAGCCTGGGGGGTCCCTTAGACTCTCCTGTGC AGCCTCTGGAATCACTTTCAGTAACGCCTGGATG AGTTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGG AGTGGGTTGGCCGTATTAAAAGCAAAACTGATGG TGGGACAACAGACTACGCCGCACCCGTGAAAGGC AGATTCACCATCTCAAGAGATGATTCAAAAAACA CGCTGTATCTACAAATGAACAGCCTGAAAACCGA GGACACAGCCGTGTATTACTGTACCACAGCGAGG TGGGACTGGTACTTCGATCTCTGGGGCCGTGGCA CCCTGGTCACTGTCTCCTCA	219
	HCDR1	GGAATCACTTTCAGTAACGCCTGG	221
	HCDR2	ATTAAAAGCAAAACTGATGGTGGGACAACA	223

	HCDR3	ACCACAGCGAGGTGGGACTGGTACTTCGATCTC	225
	LCVR	GACATCCAGATGACCCAGTCTCCATCCTCCCTGT CTGCATCTGTAGGAGACAGAGTCACCATCACTTG CCAGGCGAGTCAGGACATTTGGAATTATATAAAT TGGTATCAGCAGAAACCAGGGAAGGCCCCTAAGC TCCTGATCTACGATGCATCCAATTTGAAAACAGG GGTCCCATCAAGGTTCAGTGGAAGTGGATCTGGG ACAGATTTTACTTTCACCATCAGCAGCCTGCAGC CTGAAGATATTGCAACATATTACTGTCAACAGCA TGATGATCTCCCTCCGACCTTCGGCCAAGGGACC AAGGTGGAAATCAAA	227
	LCDR1	CAGGACATTTGGAATTAT	229
	LCDR2	GATGCATCC	193
	LCDR3	CAACAGCATGATGATCTCCCTCCGACC	231
	HC	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGG TAAAGCCTGGGGGGTCCCTTAGACTCTCCTGTGC AGCCTCTGGAATCACTTTCAGTAACGCCTGGATG AGTTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGG AGTGGGTTGGCCGTATTAAAAGCAAAACTGATGG TGGGACAACAGACTACGCCGCACCCGTGAAAGGC AGATTCACCATCTCAAGAGATGATTCAAAAAACA CGCTGTATCTACAAATGAACAGCCTGAAAACCGA GGACACAGCCGTGTATTACTGTACCACAGCGAGG TGGGACTGGTACTTCGATCTCTGGGGCCGTGGCA CCCTGGTCACTGTCTCCTCAGCCTCCACCAAGGG CCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAG AGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCC TGGTCAAGGACTACTTCCCCGAACCGGTGACGGT GTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTG CACACCTTCCCGGCTGTCCTACAGTCCTCAGGAC TCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTC CAGCAGCTTGGGCACCCAGACCTACATCTGCAAC GTGAATCACAAGCCCAGCAACACCAAGGTGGACA AGAAAGTTGAGCCCAAATCTTGTGACAAAACTCA CACATGCCCACCGTGCCCAGCACCTGAACTCCTG GGGGGACCGTCAGTCTTCCTCTTCCCCCCAAAAC CCAAGGACACCCTCATGATCTCCCGGACCCCTGA GGTCACATGCGTGGTGGTGGACGTGAGCCACGAA GACCCTGAGGTCAAGTTCAACTGGTACGTGGACG GCGTGGAGGTGCATAATGCCAAGACAAAGCCGCG GGAGGAGCAGTACAACAGCACGTACCGTGTGGTC AGCGTCCTCACCGTCCTGCACCAGGACTGGCTGA ATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAA AGCCCTCCCAGCCCCCATCGAGAAAACCATCTCC AAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGT ACACCCTGCCCCCATCCCGGGATGAGCTGACCAA	233

		GAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGC TTCTATCCCAGCGACATCGCCGTGGAGTGGGAGA GCAATGGGCAGCCGGAGAACAACTACAAGACCAC GCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTC CTCTACAGCAAGCTCACCGTGGACAAGAGCAGGT GGCAGCAGGGGAACGTCTTCTCATGCTCCGTGAT GCATGAGGCTCTGCACAACCACTACACGCAGAAG TCCCTCTCCCTGTCTCCGGGTAAATGA	
	LC	GACATCCAGATGACCCAGTCTCCATCCTCCCTGT CTGCATCTGTAGGAGACAGAGTCACCATCACTTG CCAGGCGAGTCAGGACATTTGGAATTATATAAAT TGGTATCAGCAGAAACCAGGGAAGGCCCCTAAGC TCCTGATCTACGATGCATCCAATTTGAAAACAGG GGTCCCATCAAGGTTCAGTGGAAGTGGATCTGGG ACAGATTTTACTTTCACCATCAGCAGCCTGCAGC CTGAAGATATTGCAACATATTACTGTCAACAGCA TGATGATCTCCCTCCGACCTTCGGCCAAGGGACC AAGGTGGAAATCAAACGAACTGTGGCTGCACCAT CTGTCTTCATCTTCCCGCCATCTGATGAGCAGTT GAAATCTGGAACTGCCTCTGTTGTGTGCCTGCTG AATAACTTCTATCCCAGAGAGGCCAAAGTACAGT GGAAGGTGGATAACGCCCTCCAATCGGGTAACTC CCAGGAGAGTGTCACAGAGCAGGACAGCAAGGAC AGCACCTACAGCCTCAGCAGCACCCTGACGCTGA GCAAAGCAGACTACGAGAAACACAAAGTCTACGC CTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCC GTCACAAAGAGCTTCAACAGGGGAGAGTGTTAG	235
mAb10987	**Amino Acids**		
	HCVR	QVQLVESGGGVVQPGRSLRLSCAASGFTFSNYAM YWVRQAPGKGLEWVAVISYDGSNKYYADSVKGRF TISRDNSKNTLYLQMNSLRTEDTAVYYCASGSDY GDYLLVYWGQGTLVTVSS	640
	HCDR1	GFTFSNYA	642
	HCDR2	ISYDGSNK	499
	HCDR3	ASGSDYGDYLLVY	644
	LCVR	QSALTQPASVSGSPGQSITISCTGTSSDVGGYNY VSWYQQHPGKAPKLMIYDVSKRPSGVSNRFSGSK SGNTASLTISGLQSEDEADYYCNSLTSISTWVFG GGTKLTVL	646
	LCDR1	SSDVGGYNY	648
	LCDR2	DVS	650
	LCDR3	NSLTSISTWV	652
	HC	QVQLVESGGGVVQPGRSLRLSCAASGFTFSNYAM YWVRQAPGKGLEWVAVISYDGSNKYYADSVKGRF	654

		TISRDNSKNTLYLQMNSLRTEDTAVYYCASGSDY GDYLLVYWGQGTLVTVSSASTKGPSVFPLAPSSK STSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICN VNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELL GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVV SVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTIS KAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKG FYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFF LYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQK SLSLSPGK	
	LC	QSALTQPASVSGSPGQSITISCTGTSSDVGGYNY VSWYQQHPGKAPKLMIYDVSKRPSGVSNRFSGSK SGNTASLTISGLQSEDEADYYCNSLTSISTWVFG GGTKLTVLGQPKAAPSVTLFPPSSEELQANKATL VCLISDFYPGAVTVAWKADSSPVKAGVETTTPSK QSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGS TVEKTVAPTECS	656
	Nucleic Acids		
	HCVR	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGG TCCAGCCTGGGAGGTCCCTGAGACTCTCCTGTGC AGCCTCTGGATTCACCTTCAGTAACTATGCTATG TACTGGGTCCGCCAGGCTCCAGGCAAGGGGCTGG AGTGGGTGGCAGTTATATCATATGATGGAAGTAA TAAATACTATGCAGACTCCGTGAAGGGCCGATTC ACCATCTCCAGAGACAATTCCAAGAACACGCTGT ATCTGCAAATGAACAGCCTGAGAACTGAGGACAC GGCTGTGTATTACTGTGCGAGTGGCTCCGACTAC GGTGACTACTTATTGGTTTACTGGGGCCAGGGAA CCCTGGTCACCGTCTCCTCA	639
	HCDR1	GGATTCACCTTCAGTAACTATGCT	641
	HCDR2	ATATCATATGATGGAAGTAATAAA	498
	HCDR3	GCGAGTGGCTCCGACTACGGTGACTACTTATTGG TTTAC	643
	LCVR	CAGTCTGCCCTGACTCAGCCTGCCTCCGTGTCTG GGTCTCCTGGACAGTCGATCACCATCTCCTGCAC TGGAACCAGCAGTGACGTTGGTGGTTATAACTAT GTCTCCTGGTACCAACAACACCCAGGCAAAGCCC CCAAACTCATGATTTATGATGTCAGTAAGCGGCC CTCAGGGGTTTCTAATCGCTTCTCTGGCTCCAAG TCTGGCAACACGGCCTCCCTGACCATCTCTGGGC TCCAGTCTGAGGACGAGGCTGATTATTACTGCAA CTCTTTGACAAGCATCAGCACTTGGGTGTTCGGC GGAGGGACCAAGCTGACCGTCCTA	645
	LCDR1	AGCAGTGACGTTGGTGGTTATAACTAT	647

	LCDR2	GATGTCAGT	649
	LCDR3	AACTCTTTGACAAGCATCAGCACTTGGGTG	651
	HC	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGG TCCAGCCTGGGAGGTCCCTGAGACTCTCCTGTGC AGCCTCTGGATTCACCTTCAGTAACTATGCTATG TACTGGGTCCGCCAGGCTCCAGGCAAGGGGCTGG AGTGGGTGGCAGTTATATCATATGATGGAAGTAA TAAATACTATGCAGACTCCGTGAAGGGCCGATTC ACCATCTCCAGAGACAATTCCAAGAACACGCTGT ATCTGCAAATGAACAGCCTGAGAACTGAGGACAC GGCTGTGTATTACTGTGCGAGTGGCTCCGACTAC GGTGACTACTTATTGGTTTACTGGGGCCAGGGAA CCCTGGTCACCGTCTCCTCAGCCTCCACCAAGGG CCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAG AGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCC TGGTCAAGGACTACTTCCCCGAACCGGTGACGGT GTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTG CACACCTTCCCGGCTGTCCTACAGTCCTCAGGAC TCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTC CAGCAGCTTGGGCACCCAGACCTACATCTGCAAC GTGAATCACAAGCCCAGCAACACCAAGGTGGACA AGAAAGTTGAGCCCAAATCTTGTGACAAAACTCA CACATGCCCACCGTGCCCAGCACCTGAACTCCTG GGGGGACCGTCAGTCTTCCTCTTCCCCCCAAAAC CCAAGGACACCCTCATGATCTCCCGGACCCCTGA GGTCACATGCGTGGTGGTGGACGTGAGCCACGAA GACCCTGAGGTCAAGTTCAACTGGTACGTGGACG GCGTGGAGGTGCATAATGCCAAGACAAAGCCGCG GGAGGAGCAGTACAACAGCACGTACCGTGTGGTC AGCGTCCTCACCGTCCTGCACCAGGACTGGCTGA ATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAA AGCCCTCCCAGCCCCCATCGAGAAAACCATCTCC AAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGT ACACCCTGCCCCCATCCCGGGATGAGCTGACCAA GAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGC TTCTATCCCAGCGACATCGCCGTGGAGTGGGAGA GCAATGGGCAGCCGGAGAACAACTACAAGACCAC GCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTC CTCTACAGCAAGCTCACCGTGGACAAGAGCAGGT GGCAGCAGGGGAACGTCTTCTCATGCTCCGTGAT GCATGAGGCTCTGCACAACCACTACACGCAGAAG TCCCTCTCCCTGTCTCCGGGTAAATGA	653
	LC	CAGTCTGCCCTGACTCAGCCTGCCTCCGTGTCTG GGTCTCCTGGACAGTCGATCACCATCTCCTGCAC TGGAACCAGCAGTGACGTTGGTGGTTATAACTAT GTCTCCTGGTACCAACAACACCCAGGCAAAGCCC CCAAACTCATGATTTATGATGTCAGTAAGCGGCC	655

		CTCAGGGGTTTCTAATCGCTTCTCTGGCTCCAAG TCTGGCAACACGGCCTCCCTGACCATCTCTGGGC TCCAGTCTGAGGACGAGGCTGATTATTACTGCAA CTCTTTGACAAGCATCAGCACTTGGGTGTTCGGC GGAGGGACCAAGCTGACCGTCCTAGGCCAGCCCA AGGCCGCCCCCTCCGTGACCCTGTTCCCCCCCTC CTCCGAGGAGCTGCAGGCCAACAAGGCCACCCTG GTGTGCCTGATCTCCGACTTCTACCCCGGCGCCG TGACCGTGGCCTGGAAGGCCGACTCCTCCCCCGT GAAGGCCGGCGTGGAGACCACCACCCCCTCCAAG CAGTCCAACAACAAGTACGCCGCCTCCTCCTACC TGTCCCTGACCCCCGAGCAGTGGAAGTCCCACCG GTCCTACTCCTGCCAGGTGACCCACGAGGGCTCC ACCGTGGAGAAGACCGTGGCCCCCACCGAGTGCT CCTGA	
mAb10989	**Amino Acids**		
	HCVR	QVQLVQSGAEVKKPGASVKVSCKASGYIFTGYYM HWVRQAPGQGLEWMGWINPNSGGANYAQKFQGRV TLTRDTSITTVYMELSRLRFDDTAVYYCARGSRY DWNQNNWFDPWGQGTLVTVSS	678
	HCDR1	GYIFTGYY	680
	HCDR2	INPNSGGA	682
	HCDR3	ARGSRYDWNQNNWFDP	684
	LCVR	QSALTQPASVSGSPGQSITISCTGTSSDVGTYNY VSWYQQHPGKAPKLMIFDVSNRPSGVSDRFSGSK SGNTASLTISGLQAEDEADYYCSSFTTSSTVVFG GGTKLTVL	686
	LCDR1	SSDVGTYNY	688
	LCDR2	DVS	650
	LCDR3	SSFTTSSTVV	690
	HC	QVQLVQSGAEVKKPGASVKVSCKASGYIFTGYYM HWVRQAPGQGLEWMGWINPNSGGANYAQKFQGRV TLTRDTSITTVYMELSRLRFDDTAVYYCARGSRY DWNQNNWFDPWGQGTLVTVSSASTKGPSVFPLAP SSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTY ICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAP ELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDV SHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTY RVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEK TISKAKGQPREPQVYTLPPSRDELTKNQVSLTCL VKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDG SFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHY TQKSLSLSPGK	692

	LC	QSALTQPASVSGSPGQSITISCTGTSSDVGTYNY VSWYQQHPGKAPKLMIFDVSNRPSGVSDRFSGSK SGNTASLTISGLQAEDEADYYCSSFTTSSTVVFG GGTKLTVLGQPKAAPSVTLFPPSSEELQANKATL VCLISDFYPGAVTVAWKADSSPVKAGVETTTPSK QSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGS TVEKTVAPTECS	694
	Nucleic Acids		
	HCVR	CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGA AGAAGCCTGGGGCCTCAGTGAAGGTCTCCTGCAA GGCTTCTGGATACATCTTCACCGGCTACTATATG CACTGGGTGCGACAGGCCCCTGGACAGGGGCTTG AGTGGATGGGATGGATCAACCCTAACAGTGGTGG CGCAAACTATGCACAGAAGTTTCAGGGCAGGGTC ACCCTGACCAGGGACACGTCCATCACCACAGTCT ACATGGAACTGAGCAGGCTGAGATTTGACGACAC GGCCGTGTATTACTGTGCGAGAGGATCCCGGTAT GACTGGAACCAGAACAACTGGTTCGACCCCTGGG GCCAGGGAACCCTGGTCACCGTCTCCTCA	677
	HCDR1	GGATACATCTTCACCGGCTACTAT	679
	HCDR2	ATCAACCCTAACAGTGGTGGCGCA	681
	HCDR3	GCGAGAGGATCCCGGTATGACTGGAACCAGAACA ACTGGTTCGACCCC	683
	LCVR	CAGTCTGCCCTGACTCAGCCTGCCTCCGTGTCTG GGTCTCCTGGACAGTCGATCACCATCTCCTGCAC TGGAACCAGCAGTGACGTTGGTACTTATAACTAT GTCTCCTGGTACCAACAACACCCAGGCAAAGCCC CCAAACTCATGATTTTTGATGTCAGTAATCGGCC CTCAGGGGTTTCTGATCGCTTCTCTGGCTCCAAG TCTGGCAACACGGCCTCCCTGACCATCTCTGGGC TCCAGGCTGAGGACGAGGCTGATTATTACTGCAG CTCATTTACAACCAGCAGCACTGTGGTTTTCGGC GGAGGGACCAAGCTGACCGTCCTA	685
	LCDR1	AGCAGTGACGTTGGTACTTATAACTAT	687
	LCDR2	GATGTCAGT	649
	LCDR3	AGCTCATTTACAACCAGCAGCACTGTGGTT	689
	HC	CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGA AGAAGCCTGGGGCCTCAGTGAAGGTCTCCTGCAA GGCTTCTGGATACATCTTCACCGGCTACTATATG CACTGGGTGCGACAGGCCCCTGGACAGGGGCTTG AGTGGATGGGATGGATCAACCCTAACAGTGGTGG CGCAAACTATGCACAGAAGTTTCAGGGCAGGGTC ACCCTGACCAGGGACACGTCCATCACCACAGTCT ACATGGAACTGAGCAGGCTGAGATTTGACGACAC	691

		GGCCGTGTATTACTGTGCGAGAGGATCCCGGTAT GACTGGAACCAGAACAACTGGTTCGACCCCTGGG GCCAGGGAACCCTGGTCACCGTCTCCTCAGCCTC CACCAAGGGCCCATCGGTCTTCCCCCTGGCACCC TCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCC TGGGCTGCCTGGTCAAGGACTACTTCCCCGAACC GGTGACGGTGTCGTGGAACTCAGGCGCCCTGACC AGCGGCGTGCACACCTTCCCGGCTGTCCTACAGT CCTCAGGACTCTACTCCCTCAGCAGCGTGGTGAC CGTGCCCTCCAGCAGCTTGGGCACCCAGACCTAC ATCTGCAACGTGAATCACAAGCCCAGCAACACCA AGGTGGACAAGAAAGTTGAGCCCAAATCTTGTGA CAAAACTCACACATGCCCACCGTGCCCAGCACCT GAACTCCTGGGGGGACCGTCAGTCTTCCTCTTCC CCCCAAAACCCAAGGACACCCTCATGATCTCCCG GACCCCTGAGGTCACATGCGTGGTGGTGGACGTG AGCCACGAAGACCCTGAGGTCAAGTTCAACTGGT ACGTGGACGGCGTGGAGGTGCATAATGCCAAGAC AAAGCCGCGGGAGGAGCAGTACAACAGCACGTAC CGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGG ACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGT CTCCAACAAAGCCCTCCCAGCCCCCATCGAGAAA ACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAAC CACAGGTGTACACCCTGCCCCCATCCCGGGATGA GCTGACCAAGAACCAGGTCAGCCTGACCTGCCTG GTCAAAGGCTTCTATCCCAGCGACATCGCCGTGG AGTGGGAGAGCAATGGGCAGCCGGAGAACAACTA CAAGACCACGCCTCCCGTGCTGGACTCCGACGGC TCCTTCTTCCTCTACAGCAAGCTCACCGTGGACA AGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATG CTCCGTGATGCATGAGGCTCTGCACAACCACTAC ACGCAGAAGTCCCTCTCCCTGTCTCCGGGTAAAT GA	
	LC	CAGTCTGCCCTGACTCAGCCTGCCTCCGTGTCTG GGTCTCCTGGACAGTCGATCACCATCTCCTGCAC TGGAACCAGCAGTGACGTTGGTACTTATAACTAT GTCTCCTGGTACCAACAACACCCAGGCAAAGCCC CCAAACTCATGATTTTTGATGTCAGTAATCGGCC CTCAGGGGTTTCTGATCGCTTCTCTGGCTCCAAG TCTGGCAACACGGCCTCCCTGACCATCTCTGGGC TCCAGGCTGAGGACGAGGCTGATTATTACTGCAG CTCATTTACAACCAGCAGCACTGTGGTTTTCGGC GGAGGGACCAAGCTGACCGTCCTAGGCCAGCCCA AGGCCGCCCCCTCCGTGACCCTGTTCCCCCCCTC CTCCGAGGAGCTGCAGGCCAACAAGGCCACCCTG GTGTGCCTGATCTCCGACTTCTACCCCGGCGCCG TGACCGTGGCCTGGAAGGCCGACTCCTCCCCCGT GAAGGCCGGCGTGGAGACCACCACCCCCTCCAAG	693

		CAGTCCAACAACAAGTACGCCGCCTCCTCCTACC TGTCCCTGACCCCCGAGCAGTGGAAGTCCCACCG GTCCTACTCCTGCCAGGTGACCCACGAGGGCTCC ACCGTGGAGAAGACCGTGGCCCCCACCGAGTGCT CCTGA	

Administration of Antibodies

[00075] The present invention provides methods for administering an anti-CoV-S antigen-binding protein of the present invention, *e.g.*, those of Table 1, comprising introducing the antigen-binding protein into the body of a subject (*e.g.*, a human). For example, the method comprises piercing the body of the subject with a needle of a syringe and injecting the antigen-binding protein into the body of the subject, *e.g.*, into the vein, artery, tumor, muscular tissue or subcutis of the subject.

[00076] The present invention provides a vessel (*e.g.*, a plastic or glass vial, *e.g.*, with a cap or a chromatography column, hollow bore needle or a syringe cylinder) comprising an anti-CoV-S antigen-binding protein of the present invention, *e.g.*, those of Table 1.

[00077] The present invention also provides an injection device comprising one or more antigen-binding proteins (*e.g.,* antibody or antigen-binding fragment) that bind specifically to CoV-S, *e.g.*, those of Table 1, or a pharmaceutical composition thereof. The injection device may be packaged into a kit. An injection device is a device that introduces a substance into the body of a subject via a parenteral route, *e.g.*, intramuscular, subcutaneous or intravenous. For example, an injection device may be a syringe (*e.g.*, pre-filled with the pharmaceutical composition, such as an auto-injector) which, for example, includes a cylinder or barrel for holding fluid to be injected (*e.g.*, comprising the antibody or fragment or a pharmaceutical composition thereof), a needle for piecing skin and/or blood vessels for injection of the fluid; and a plunger for pushing the fluid out of the cylinder and through the needle bore. In an embodiment of the invention, an injection device that comprises an antigen-binding protein, *e.g.*, an antibody or antigen-binding fragment thereof, from a combination of the present invention, or a pharmaceutical composition thereof is an intravenous (IV) injection device. Such a device can include the antigen-binding protein or a pharmaceutical composition thereof in a cannula or trocar/needle which may be attached to a tube which may be attached to a bag or reservoir for holding fluid (*e.g.*, saline) introduced into the body of the subject through the cannula or trocar/needle. The antibody or fragment or a pharmaceutical composition thereof may, in an

embodiment of the invention, be introduced into the device once the trocar and cannula are inserted into the vein of a subject and the trocar is removed from the inserted cannula. The IV device may, for example, be inserted into a peripheral vein (*e.g.*, in the hand or arm); the superior *vena cava* or inferior *vena cava*, or within the right atrium of the heart (*e.g.*, a central IV); or into a subclavian, internal jugular, or a femoral vein and, for example, advanced toward the heart until it reaches the superior vena cava or right atrium (*e.g.*, a central venous line). In an embodiment of the invention, an injection device is an autoinjector; a jet injector or an external infusion pump. A jet injector uses a high-pressure narrow jet of liquid which penetrate the epidermis to introduce the antibody or fragment or a pharmaceutical composition thereof to a subject's body. External infusion pumps are medical devices that deliver the antibody or fragment or a pharmaceutical composition thereof into a subject's body in controlled amounts. External infusion pumps may be powered electrically or mechanically. Different pumps operate in different ways, for example, a syringe pump holds fluid in the reservoir of a syringe, and a moveable piston controls fluid delivery, an elastomeric pump holds fluid in a stretchable balloon reservoir, and pressure from the elastic walls of the balloon drives fluid delivery. In a peristaltic pump, a set of rollers pinches down on a length of flexible tubing, pushing fluid forward. In a multi-channel pump, fluids can be delivered from multiple reservoirs at multiple rates.

Preparation of Human Antibodies

[00078] Methods for generating human antibodies in transgenic mice are known in the art. Any such known methods can be used in the context of the present invention to make human antibodies that specifically bind to CoV-S. An immunogen comprising any one of the following can be used to generate antibodies to CoV-S. In certain embodiments of the invention, the antibodies of the invention are obtained from mice immunized with a full length, native CoV-S, or with a live attenuated or inactivated virus, or with DNA encoding the protein or fragment thereof. Alternatively, the CoV-S protein or a fragment thereof may be produced using standard biochemical techniques and modified and used as immunogen. In one embodiment of the invention, the immunogen is a recombinantly produced CoV-S protein or fragment thereof. In certain embodiments of the invention, the immunogen may be a CoV-S polypeptide vaccine. In certain embodiments, one or more booster injections may be administered. In certain

embodiments, the immunogen may be a recombinant CoV-S polypeptide expressed in *E. coli* or in any other eukaryotic or mammalian cells such as Chinese hamster ovary (CHO) cells.

[00079] Using VELOCIMMUNE® technology (see, for example, US 6,596,541, Regeneron Pharmaceuticals, VELOCIMMUNE®) or any other known method for generating monoclonal antibodies, high affinity chimeric antibodies to CoV-S can be initially isolated having a human variable region and a mouse constant region. The VELOCIMMUNE® technology involves generation of a transgenic mouse having a genome comprising human heavy and light chain variable regions operably linked to endogenous mouse constant region loci such that the mouse produces an antibody comprising a human variable region and a mouse constant region in response to antigenic stimulation. The DNA encoding the variable regions of the heavy and light chains of the antibody are isolated and operably linked to DNA encoding the human heavy and light chain constant regions. The DNA is then expressed in a cell capable of expressing the fully human antibody.

[00080] Generally, a VELOCIMMUNE® mouse is challenged with the antigen of interest, and lymphatic cells (such as B-cells) are recovered from the mice that express antibodies. The lymphatic cells may be fused with a myeloma cell line to prepare immortal hybridoma cell lines, and such hybridoma cell lines are screened and selected to identify hybridoma cell lines that produce antibodies specific to the antigen of interest. DNA encoding the variable regions of the heavy chain and light chain may be isolated and linked to desirable isotypic constant regions of the heavy chain and light chain. Such an antibody protein may be produced in a cell, such as a CHO cell. Alternatively, DNA encoding the antigen-specific chimeric antibodies or the variable domains of the light and heavy chains may be isolated directly from antigen-specific lymphocytes.

[00081] Initially, high affinity chimeric antibodies are isolated having a human variable region and a mouse constant region. As in the experimental section below, the antibodies are characterized and selected for desirable characteristics, including affinity, selectivity, epitope, *etc.* The mouse constant regions are replaced with a desired human constant region to generate the fully human antibody of the invention, for example wild-type or modified IgG1 or IgG4. While the constant region selected may vary according to specific use, high affinity antigen-binding and target specificity characteristics reside in the variable region.

Anti-Coronavirus Spike Protein Antibodies Comprising Fc Variants

[00082] According to certain embodiments of the present invention, anti-CoV-S antigen-binding proteins, *e.g.*, antibodies or antigen-binding fragments, are provided comprising an Fc domain comprising one or more mutations, which, for example, enhance or diminish antibody binding to the FcRn receptor, *e.g.*, at acidic pH as compared to neutral pH. For example, the present invention includes anti-CoV-S antibodies comprising a mutation in the C_H2 or a C_H3 region of the Fc domain, wherein the mutation(s) increases the affinity of the Fc domain to FcRn in an acidic environment (*e.g.*, in an endosome where pH ranges from about 5.5 to about 6.0). Such mutations may result in an increase in serum half-life of the antibody when administered to an animal. Non-limiting examples of such Fc modifications include, *e.g.*, a modification at position 250 (*e.g.*, E or Q); 250 and 428 (*e.g.*, L or F); 252 (*e.g.*, L/Y/F/W or T), 254 (*e.g.*, S or T), and 256 (*e.g.*, S/R/Q/E/D or T); or a modification at position 428 and/or 433 (*e.g.*, H/L/R/S/P/Q or K) and/or 434 (*e.g.*, A, W, H, F or Y [N434A, N434W, N434H, N434F or N434Y]); or a modification at position 250 and/or 428; or a modification at position 307 or 308 (*e.g.*, 308F, V308F), and 434. In one embodiment, the modification comprises a 428L (*e.g.*, M428L) and 434S (*e.g.*, N434S) modification; a 428L, 259I (*e.g.*, V259I), and 308F (*e.g.*, V308F) modification; a 433K (*e.g.*, H433K) and a 434 (*e.g.*, 434Y) modification; a 252, 254, and 256 (*e.g.*, 252Y, 254T, and 256E) modification; a 250Q and 428L modification (*e.g.*, T250Q and M428L); and a 307 and/or 308 modification (*e.g.*, 308F or 308P). In yet another embodiment, the modification comprises a 265A (*e.g.*, D265A) and/or a 297A (*e.g.*, N297A) modification.

[00083] For example, the present invention includes anti-CoV-S antigen-binding proteins, *e.g.*, antibodies or antigen-binding fragments, comprising an Fc domain comprising one or more pairs or groups of mutations selected from the group consisting of: 250Q and 248L (*e.g.*, T250Q and M248L); 252Y, 254T and 256E (*e.g.*, M252Y, S254T and T256E); 428L and 434S (*e.g.*, M428L and N434S); 257I and 311I (*e.g.*, P257I and Q311I); 257I and 434H (*e.g.*, P257I and N434H); 376V and 434H (*e.g.*, D376V and N434H); 307A, 380A and 434A (*e.g.*, T307A, E380A and N434A); and 433K and 434F (*e.g.*, H433K and N434F).

[00084] Anti-CoV-S antigen-binding proteins, *e.g.*, antibodies and antigen-binding fragments thereof, that comprise a V_H and/or V_L as set forth herein comprising any possible combinations of the foregoing Fc domain mutations, are contemplated within the scope of the present invention.

[00085] The present invention also includes anti-CoV-S antigen-binding proteins, antibodies or antigen-binding fragments, comprising a V_H set forth herein and a chimeric heavy chain constant (C_H) region, wherein the chimeric C_H region comprises segments derived from the C_H regions of more than one immunoglobulin isotype. For example, the antibodies of the invention may comprise a chimeric C_H region comprising part or all of a C_H2 domain derived from a human IgG1, human IgG2 or human IgG4 molecule, combined with part or all of a C_H3 domain derived from a human IgG1, human IgG2 or human IgG4 molecule. According to certain embodiments, the antibodies of the invention comprise a chimeric C_H region having a chimeric hinge region. For example, a chimeric hinge may comprise an "upper hinge" amino acid sequence (amino acid residues from positions 216 to 227 according to EU numbering) derived from a human IgG1, a human IgG2 or a human IgG4 hinge region, combined with a "lower hinge" sequence (amino acid residues from positions 228 to 236 according to EU numbering) derived from a human IgG1, a human IgG2 or a human IgG4 hinge region. According to certain embodiments, the chimeric hinge region comprises amino acid residues derived from a human IgG1 or a human IgG4 upper hinge and amino acid residues derived from a human IgG2 lower hinge. An antibody comprising a chimeric C_H region as described herein may, in certain embodiments, exhibit modified Fc effector functions without adversely affecting the therapeutic or pharmacokinetic properties of the antibody. (See, *e.g.*, WO2014/022540).

Immunoconjugates

[00086] The invention encompasses an anti-CoV-S antigen-binding proteins, *e.g.*, antibodies or antigen-binding fragments, conjugated to another moiety, *e.g.*, a therapeutic moiety (an "immunoconjugate"), such as a toxoid or an anti-viral drug to treat influenza virus infection. In an embodiment of the invention, an anti-CoV-S antibody or fragment is conjugated to any of the further therapeutic agents set forth herein. As used herein, the term "immunoconjugate" refers to an antigen-binding protein, *e.g.*, an antibody or antigen-binding fragment, which is chemically or biologically linked to a radioactive agent, a cytokine, an interferon, a target or reporter moiety, an enzyme, a peptide or protein or a therapeutic agent. The antigen-binding protein may be linked to the radioactive agent, cytokine, interferon, target or reporter moiety, enzyme, peptide or therapeutic agent at any location along the molecule so long as it is able to bind its target (CoV-S). Examples of immunoconjugates include antibody-drug conjugates and antibody-toxin fusion

proteins. In one embodiment of the invention, the agent may be a second, different antibody that binds specifically to CoV-S. The type of therapeutic moiety that may be conjugated to the anti-CoV-S antigen-binding protein (*e.g.*, antibody or fragment) will take into account the condition to be treated and the desired therapeutic effect to be achieved. See, *e.g.*, Arnon *et al.*, "Monoclonal Antibodies For Immunotargeting Of Drugs In Cancer Therapy", Monoclonal Antibodies And Cancer Therapy, Reisfeld *et al.* (eds.), pp. 243-56 (Alan R. Liss, Inc. 1985); Hellstrom *et al.*, "Antibodies For Drug Delivery", Controlled Drug Delivery (2nd Ed.), Robinson *et al.* (eds.), pp. 623-53 (Marcel Dekker, Inc. 1987); Thorpe, "Antibody Carriers Of Cytotoxic Agents In Cancer Therapy: A Review", Monoclonal Antibodies 1984: Biological And Clinical Applications, Pinchera *et al.* (eds.), pp. 475-506 (1985); "Analysis, Results, And Future Prospective Of The Therapeutic Use Of Radiolabeled Antibody In Cancer Therapy", Monoclonal Antibodies For Cancer Detection And Therapy, Baldwin *et al.* (eds.), pp. 303-16 (Academic Press 1985), and Thorpe *et al.*, "The Preparation And Cytotoxic Properties Of Antibody-Toxin Conjugates", Immunol. Rev., 62: 119-58 (1982).

Multi-specific Antibodies

[00087] The present invention includes anti-CoV-S antigen-binding proteins, *e.g.*, antibodies and antigen-binding fragments thereof, as well as methods of use thereof and methods of making such antigen-binding proteins. The term "anti-CoV-S" antigen-binding proteins, *e.g.*, antibodies or antigen-binding fragments, includes multispecific (*e.g.*, bispecific or biparatopic) molecules that include at least one first antigen-binding domain that specifically binds to CoV-S (*e.g.*, an antigen-binding domain from an antibody of Table 1) and at least one second antigen-binding domain that binds to a different antigen or to an epitope in CoV-S which is different from that of the first antigen-binding domain. In some embodiments, the first antigen-binding domain and the second antigen-binding domain are both selected from the antigen-binding domains of Table 1. In an embodiment of the invention, the first and second epitopes overlap. In another embodiment of the invention, the first and second epitopes do not overlap. For example, in an embodiment of the invention, a multispecific antibody is a bispecific IgG antibody (*e.g.*, IgG1 or IgG4) that includes a first antigen-binding domain that binds specifically to CoV-S including the heavy and light immunoglobulin chain of an antibody of Table 1, and a second antigen-binding domain that binds specifically to a different epitope of CoV-S. In some embodiments, a

bispecific IgG antibody (*e.g.*, IgG1 or IgG4) includes a first antigen-binding domain that binds specifically to CoV-S and a second binding domain that binds to a host cell protein, e.g., ACE2 or TMPRSS2.

[00088] The antibodies of Table 1 include multispecific molecules, *e.g.*, antibodies or antigen-binding fragments, that include the CDR-Hs and CDR-Ls, V_H and V_L, or HC and LC of those antibodies, respectively (including variants thereof as set forth herein).

[00089] In an embodiment of the invention, an antigen-binding domain that binds specifically to CoV-S, which may be included in a multispecific molecule, comprises:

(1)

(i) a heavy chain variable domain sequence that comprises CDR-H1, CDR-H2, and CDR-H3 amino acid sequences set forth in Table 1, and

(ii) a light chain variable domain sequence that comprises CDR-L1, CDR-L2, and CDR-L3 amino acid sequences set forth in Table 1;

or,

(2)

(i) a heavy chain variable domain sequence comprising an amino acid sequence set forth in Table 1, and

(ii) a light chain variable domain sequence comprising an amino acid sequence set forth in Table 1;

or,

(3)

(i) a heavy chain immunoglobulin sequence comprising an amino acid sequence set forth in Table 1, and

(ii) a light chain immunoglobulin sequence comprising an amino acid sequence set forth in Table 1.

[00090] In an embodiment of the invention, the multispecific antibody or fragment includes more than two different binding specificities (*e.g.*, a trispecific molecule), for example, one or more additional antigen-binding domains which are the same or different from the first and/or second antigen-binding domain.

[00091] In one embodiment of the invention, a bispecific antigen-binding fragment comprises a first scFv (*e.g.*, comprising V_H and V_L sequences of Table 1) having binding specificity for a first

epitope (*e.g.*, CoV-S) and a second scFv having binding specificity for a second, different epitope. For example, in an embodiment of the invention, the first and second scFv are tethered with a linker, *e.g.*, a peptide linker (*e.g.*, a GS linker such as $(GGGGS)_n$ (SEQ ID NO: 834) wherein n is, for example, 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10). Other bispecific antigen-binding fragments include an $F(ab)_2$ of a bispecific IgG antibody which comprises the heavy and light chain CDRs of Table 1 and of another antibody that binds to a different epitope.

Therapeutic Methods

[00092] The present invention provides methods for treating or preventing viral infection (*e.g.*, coronavirus infection) by administering a therapeutically effective amount of anti-CoV-S antigen-binding protein, *e.g.*, antibody or antigen-binding fragment, (*e.g.*, of Table 1) to a subject (*e.g.*, a human) in need of such treatment or prevention.

[00093] Coronavirus infection may be treated or prevented, in a subject, by administering an anti-CoV-S antigen-binding protein of the present invention to a subject.

[00094] An effective or therapeutically effective dose of anti-CoV-S antigen-binding protein, *e.g.*, antibody or antigen-binding fragment (*e.g.*, of Table 1), for treating or preventing a viral infection refers to the amount of the antibody or fragment sufficient to alleviate one or more signs and/or symptoms of the infection in the treated subject, whether by inducing the regression or elimination of such signs and/or symptoms or by inhibiting the progression of such signs and/or symptoms. The dose amount may vary depending upon the age and the size of a subject to be administered, target disease, conditions, route of administration, and the like. In an embodiment of the invention, an effective or therapeutically effective dose of antibody or antigen-binding fragment thereof of the present invention, for treating or preventing viral infection, *e.g.*, in an adult human subject, is about 0.01 to about 200 mg/kg, *e.g.*, up to about 150 mg/kg. In an embodiment of the invention, the dosage is up to about 10.8 or 11 grams (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or 11 grams). Depending on the severity of the infection, the frequency and the duration of the treatment can be adjusted. In certain embodiments, the antigen-binding protein of the present invention can be administered at an initial dose, followed by one or more secondary doses. In certain embodiments, the initial dose may be followed by administration of a second or a plurality of subsequent doses of antibody or antigen-binding fragment thereof in an amount that can be approximately the same or less than that of the initial

dose, wherein the subsequent doses are separated by at least 1 day to 3 days; at least one week, at least 2 weeks; at least 3 weeks; at least 4 weeks; at least 5 weeks; at least 6 weeks; at least 7 weeks; at least 8 weeks; at least 9 weeks; at least 10 weeks; at least 12 weeks; or at least 14 weeks.

[00095] As used herein, the term "subject" refers to a mammal (*e.g.*, rat, mouse, cat, dog, cow, pig, sheep, horse, goat, rabbit), preferably a human, for example, in need of prevention and/or treatment of a disease or disorder such as viral infection or cancer. The subject may have a viral infection, *e.g.*, an influenza infection, or be predisposed to developing an infection. Subjects predisposed to developing an infection, or subjects who may be at elevated risk for contracting an infection (*e.g.*, of coronavirus or influenza virus), include subjects with compromised immune systems because of autoimmune disease, subjects receiving immunosuppressive therapy (for example, following organ transplant), subjects afflicted with human immunodeficiency syndrome (HIV) or acquired immune deficiency syndrome (AIDS), subjects with forms of anemia that deplete or destroy white blood cells, subjects receiving radiation or chemotherapy, or subjects afflicted with an inflammatory disorder. Additionally, subjects of very young (*e.g.*, 5 years of age or younger) or old age (*e.g.*, 65 years of age or older) are at increased risk. Moreover, a subject may be at risk of contracting a viral infection due to proximity to an outbreak of the disease, *e.g.* subject resides in a densely-populated city or in close proximity to subjects having confirmed or suspected infections of a virus, or choice of employment, *e.g.* hospital worker, pharmaceutical researcher, traveler to infected area, or frequent flier.

[00096] "Treat" or "treating" means to administer an anti-CoV-S antigen-binding protein, *e.g.*, antibody or antigen-binding fragment of the present invention (*e.g.*, of Table 1), to a subject having one or more signs or symptoms of a disease or infection, *e.g.*, viral infection, for which the antigen-binding protein is effective when administered to the subject at an effective or therapeutically effective amount or dose (as discussed herein).

[00097] The present invention also encompasses prophylactically administering an anti-CoV-S antigen-binding protein, *e.g.*, antibody or antigen-binding fragment thereof of the present invention (*e.g.*, of Table 1), to a subject who is at risk of viral infection so as to prevent such infection. Passive antibody-based immunoprophylaxis has proven an effective strategy for preventing subject from viral infection. See *e.g.*, Berry *et al.*, Passive broad-spectrum influenza immunoprophylaxis. Influenza Res Treat. 2014; 2014:267594. Epub 2014 Sep 22; and Jianqiang

et al., Passive immune neutralization strategies for prevention and control of influenza A infections, Immunotherapy. 2012 February; 4(2): 175–186; Prabhu *et al.*, Antivir Ther. 2009;14(7):911-21, Prophylactic and therapeutic efficacy of a chimeric monoclonal antibody specific for H5 hemagglutinin against lethal H5N1 influenza. "Prevent" or "preventing" means to administer an anti-CoV-S antigen-binding protein, *e.g.*, antibody or antigen-binding fragment of the present invention (*e.g.*, of Table 1), to a subject to inhibit the manifestation of a disease or infection (*e.g.*, viral infection) in the body of a subject, for which the antigen-binding protein is effective when administered to the subject at an effective or therapeutically effective amount or dose (as discussed herein).

[00098] In an embodiment of the invention, a sign or symptom of a viral infection in a subject is survival or proliferation of virus in the body of the subject, *e.g.*, as determined by viral titer assay (*e.g.*, coronavirus propagation in embryonated chicken eggs or coronavirus spike protein assay). Other signs and symptoms of viral infection are discussed herein.

[00099] As noted above, in some embodiments the subject may be a non-human animal, and the antigen-binding proteins (*e.g.*, antibodies and antigen-binding fragments) discussed herein may be used in a veterinary context to treat and/or prevent disease in the non-human animals (*e.g.*, cats, dogs, pigs, cows, horses, goats, rabbits, sheep, and the like).

[000100] The present invention provides a method for treating or preventing viral infection (*e.g.*, coronavirus infection) or for inducing the regression or elimination or inhibiting the progression of at least one sign or symptom of viral infection such as:

- fever or feeling feverish/chills;
- cough;
- sore throat;
- runny or stuffy nose;
- sneezing;
- muscle or body aches;
- headaches;
- fatigue (tiredness);
- vomiting;
- diarrhea;
- respiratory tract infection;

- chest discomfort;
- shortness of breath;
- bronchitis; and/or
- pneumonia,

which sign or symptom is secondary to viral infection, in a subject in need thereof (*e.g.*, a human), by administering a therapeutically effective amount of anti-CoV-S antigen-binding protein (*e.g.*, of Table 1) to the subject, for example, by injection of the protein into the body of the subject.

Combinations and Pharmaceutical Compositions

[000101] To prepare pharmaceutical compositions of the anti-CoV-S antigen-binding proteins, *e.g.*, antibodies and antigen-binding fragments thereof (*e.g.*, of Table 1), antigen-binding protein is 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); Hardman, *et al.* (2001) Goodman and Gilman's The Pharmacological Basis of Therapeutics, McGraw-Hill, New York, N.Y.; Gennaro (2000) Remington: The Science and Practice of Pharmacy, Lippincott, Williams, and Wilkins, New York, N.Y.; 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, N.Y. In an embodiment of the invention, the pharmaceutical composition is sterile. Such compositions are part of the present invention.

[000102] The scope of the present invention includes desiccated, *e.g.*, freeze-dried, compositions comprising an anti-CoV-S antigen-binding proteins, *e.g.*, antibody or antigen-binding fragment thereof (*e.g.*, of Table 1), or a pharmaceutical composition thereof that includes a pharmaceutically acceptable carrier but substantially lacks water.

[000103] In a further embodiment of the invention, a further therapeutic agent that is administered to a subject in association with an anti-CoV-S antigen-binding protein, *e.g.*, antibody or antigen-binding fragment thereof (*e.g.*, of Table 1), disclosed herein is administered

to the subject in accordance with the Physicians' Desk Reference 2003 (Thomson Healthcare; 57th edition (Nov. 1, 2002)).

[000104] The mode of administration can vary. 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.

[000105] The present invention provides methods for administering an anti-CoV-S antigen-binding protein, *e.g.*, antibody or antigen-binding fragment thereof (*e.g.*, of Table 1), comprising introducing the protein into the body of a subject. For example, the method comprises piercing the body of the subject with a needle of a syringe and injecting the antigen-binding protein into the body of the subject, *e.g.*, into the vein, artery, tumor, muscular tissue or subcutis of the subject.

[000106] The present invention provides a vessel (*e.g.*, a plastic or glass vial, *e.g.*, with a cap or a chromatography column, hollow bore needle or a syringe cylinder) comprising any of the anti-CoV-S antigen-binding proteins, *e.g.*, antibodies or antigen-binding fragments thereof (*e.g.*, of Table 1), polypeptides (*e.g.*, an HC, LC, V_H or V_L of Table 1) or polynucleotides (*e.g.*, of Table 2) or vectors set forth herein or a pharmaceutical composition thereof comprising a pharmaceutically acceptable carrier.

[000107] In an embodiment of the present disclosure, an anti-CoV-S antigen-binding protein, *e.g.*, antibody or antigen-binding fragment thereof of the present invention (*e.g.*, of Table 1), is administered in association with one or more further therapeutic agents. A further therapeutic agent includes, but is not limited to: an anti-inflammatory agent, an antimalarial agent, a second antibody or antigen-binding fragment thereof that specifically binds TMPRSS2, and a second antibody or antigen-binding fragment thereof that specifically binds to CoV-S. In some embodiments, an antimalarial agent is chloroquine or hydroxychloroquine. In some embodiments, an anti-inflammatory agent is an antibody such as sarilumab, tocilizumab, or gimsilumab. In some embodiments, the further therapeutic agent is a second antibody or antigen-binding fragment disclosed herein, *e.g.*, of Table 1. In certain embodiments, one, two, three, four, or more antibodies, or antigen-binding fragments thereof, of Table 1 can be administered in combination (e.g., concurrently or sequentially). Particular combinations of antibodies of Table 1 are listed in the Table of Exemplary Antibody Combinations, below (each

number representing a specific combination, e.g., mAb10989 and mAb10987 is Combination 1, mAb10989 and mAb10934 is Combination 2, and so on). In some embodiments, a combination of antibodies can be selected from among those binding to different epitope clusters. For example, certain antibodies described herein belong to epitope clusters as follows: Cluster 1, mAb10987, mAb10922, mAb10936, and mAb10934; Cluster 2, mAb10989, mAb10977, and mAb10933; Cluster 3, mAb10920; Cluster 4, mAb10954, mAb10986, and mAb10964; and Cluster 5, mAb10984. Thus, a combination of two antibodies can be selected from, for example, Cluster 1 and Cluster 2, Cluster 1 and Cluster 3, Cluster 1 and Cluster 4, Cluster 1 and Cluster 5, Cluster 2 and Cluster 3, Cluster 2 and Cluster 4, Cluster 2 and Cluster 5, Cluster 3 and Cluster 4, Cluster 3 and Cluster 5, and Cluster 4 and Cluster 5. In some embodiments, an antibody that specifically binds TMPRSS2 is H1H7017N, as described in International Patent Pub. No. WO/2019/147831.

Table of Exemplary Antibody Combinations

	mAb 10989	mAb 10987	mAb 10934	mAb 10933	mAb 10920	mAb 10922	mAb 10936	mAb 10954	mAb 10964	mAb 10977	mAb 10984	mAb 10986
mAb 10989	X	1	2	3	4	5	6	7	8	9	10	11
mAb 10987	12	X	13	14	15	16	17	18	19	20	21	22
mAb 10934	23	24	X	25	26	27	28	29	30	31	32	33
mAb 10933	34	35	36	X	37	38	39	40	41	42	43	44
mAb 10920	45	46	47	48	X	49	50	51	52	53	54	55
mAb 10922	56	57	58	59	60	X	61	62	63	64	65	66
mAb 10936	67	68	69	70	71	72	X	73	74	75	76	77
mAb 10954	78	79	80	81	82	83	84	X	85	86	87	88
mAb 10964	89	90	91	92	93	94	95	96	X	97	98	99
mAb 10977	100	101	102	103	104	105	106	107	108	X	109	110
mAb 10984	111	112	113	114	115	116	117	118	119	120	X	121
mAb 10986	122	123	124	125	126	127	128	129	130	131	132	X

[000108] In some embodiments, anti-CoV-S antigen-binding proteins (*e.g.*, anti-SARS-CoV-2-S antibodies or antigen-binding fragments thereof) from different human donors may be

combined. The present invention includes a composition comprising two (or more) anti-SARS-CoV-2-S antibodies or antigen-binding fragments comprising variable domains from human subjects, wherein the two (or more) antibodies or antigen-binding fragments are derived from different subjects (*e.g.*, two different human subjects). Antibody variable regions derived from human B cells are discussed, *e.g.*, in Examples 1 and 2 (Table 3), which describes that variable domains cloned from such B cells are combined with a constant region not from those B cells to produce hybrid antibodies. The source (Donor) of such antibody variable regions is shown in the Table of Exemplary Human-Derived Antibody Variable Regions, below. In some embodiments, a composition may comprise a combination of an antibody or antigen-binding fragment thereof with variable domains derived from donor 1 and an antibody or antigen-binding fragment thereof with variable domains derived from donor 2. In some embodiments, a composition may comprise a combination of an antibody or antigen-binding fragment thereof with variable domains derived from donor 1 and an antibody or antigen-binding fragment thereof with variable domains derived from donor 3. In some embodiments, a composition may comprise a combination of an antibody or antigen-binding fragment thereof with variable domains derived from donor 2 and an antibody or antigen-binding fragment thereof with variable domains derived from donor 3. In some embodiments, a composition may comprise a combination of mAb10987 (*e.g.*, an antibody comprising the CDRs, the variable regions, or the heavy and light chain sequences shown in Table 1) from Donor 1, and mAb10989 (*e.g.*, an antibody comprising the CDRs, the variable regions, or the heavy and light chain sequences shown in Table 1) from Donor 3.

Table of Exemplary Human-Derived Antibody Variable Regions

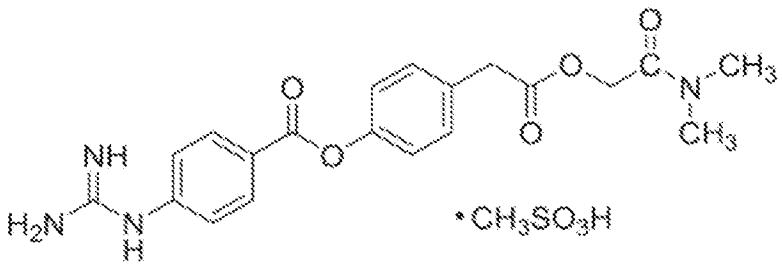
mAb	Donor
mAb10954	Donor 3
mAb10955	Donor 3
mAb10956	Donor 3
mAb10957	Donor 3
mAb10964	Donor 1
mAb10965	Donor 2
mAb10966	Donor 3
mAb10967	Donor 3

mAb10970	Donor 1
mAb10971	Donor 1
mAb10977	Donor 1
mAb10984	Donor 1
mAb10985	Donor 1
mAb10986	Donor 1
mAb10987	Donor 1
mAb10988	Donor 3
mAb10989	Donor 3
mAb10969	Donor 1

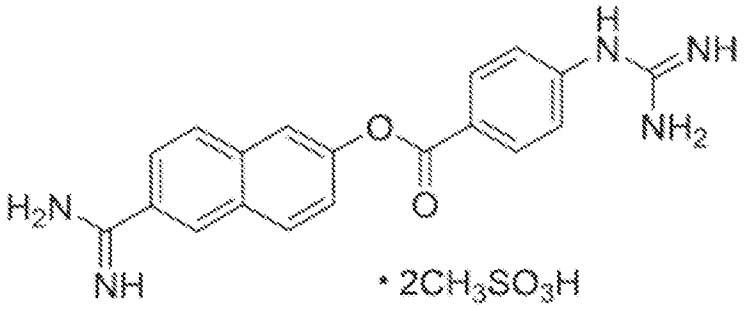
[000109] In some embodiments, the further therapeutic agent is an anti-viral drug and/or a vaccine. As used herein, the term "anti-viral drug" refers to any anti-infective drug or therapy used to treat, prevent, or ameliorate a viral infection in a subject. The term "anti-viral drug" includes, but is not limited to a cationic steroid antimicrobial, leupeptin, aprotinin, ribavirin, or interferon-alpha2b. Methods for treating or preventing virus (*e.g.*, coronavirus) infection in a subject in need of said treatment or prevention by administering an antibody or antigen-binding fragment of Table 1 in association with a further therapeutic agent are part of the present invention.

[000110] For example, in an embodiment of the invention, the further therapeutic agent is a vaccine, *e.g.*, a coronavirus vaccine. In an embodiment of the invention, a vaccine is an inactivated/killed virus vaccine, a live attenuated virus vaccine or a virus subunit vaccine.

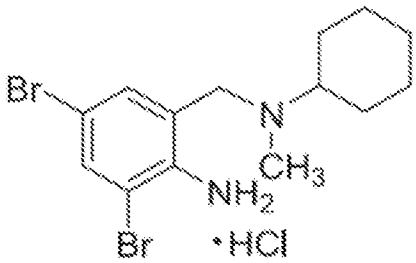
[000111] For example, in an embodiment of the invention, the further therapeutic agent is:



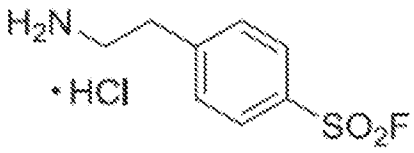
(camostat mesylate);



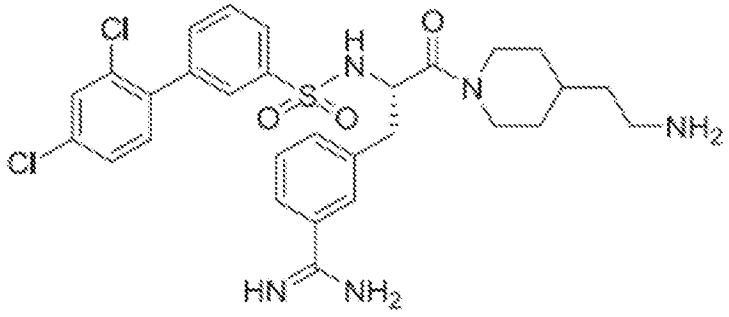
(nafamostat mesylate);



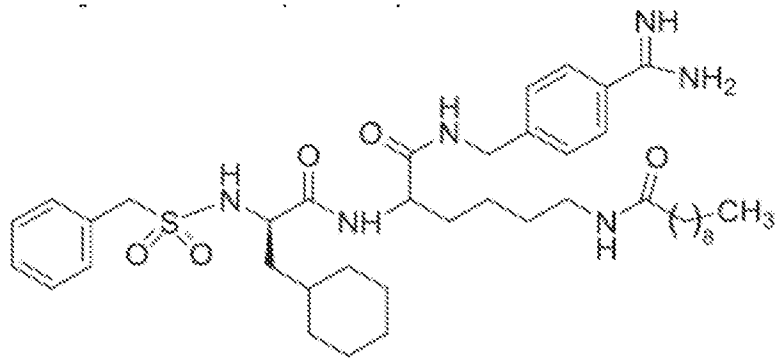
(bromhexine hydrochloride (BHH));



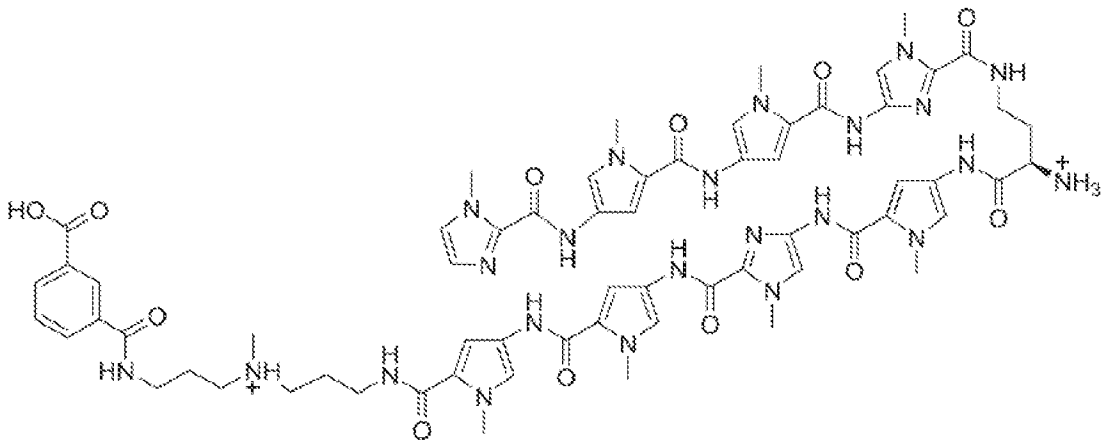
(4-(2-aminomethyl)benzenesulfonyl fluoride hydrochloride (AEBSF));



;



; or



(polyamide). See Shen *et al.* Biochimie 142: 1-10 (2017).

[000112] In an embodiment of the invention, the anti-viral drug is an antibody or antigen-binding fragment that binds specifically to coronavirus, *e.g.*, SARS-CoV-2, SARS-CoV, or MERS-CoV. Exemplary anti-CoV-S antibodies include, but are not limited to: H4sH15188P; H1H15188P; H1H15211P; H1H15177P; H4sH15211P; H1H15260P2; H1H15259P2; H1H15203P; H4sH15260P2; H4sH15231P2; H1H15237P2; H1H15208P; H1H15228P2; H1H15233P2; H1H15264P2; H1H15231P2; H1H15253P2; H1H15215P; and H1H15249P2, as set forth in International patent application publication no. WO/2015/179535, or an antigen-binding fragment thereof, *e.g.*, wherein the antibody or fragment comprises a light chain immunoglobulin that includes CDR-L1, CDR-L2 and CDR-L3 (*e.g.*, the V_L or light chain thereof); and a heavy chain that includes CDR-H1, CDR-H2 and CDR-H3 (*e.g.*, the V_H or heavy chain thereof) of any of the foregoing anti-CoV-S antibodies.

[000113] In a certain embodiment of the invention, the further therapeutic agent is not aprotinin, leupeptin, a cationic steroid antimicrobial, an influenza vaccine (*e.g.*, killed, live,

attenuated whole virus or subunit vaccine), or an antibody against influenza virus (*e.g.*, an anti-hemagglutinin antibody).

[000114] The term "in association with" indicates that the components, an anti-CoV-S antigen-binding protein, *e.g.*, antibody or antigen-binding fragment thereof of the present invention, along with another agent, can be formulated into a single composition, *e.g.*, for simultaneous delivery, or formulated separately into two or more compositions (*e.g.*, a kit). Each component can be administered to a subject at a different time than when the other component is administered; for example, each administration may be given non-simultaneously (*e.g.*, separately or sequentially) at intervals over a given period of time. Moreover, the separate components may be administered to a subject by the same or by a different route (*e.g.*, wherein an anti-CoV-S antibody or antigen-binding fragment thereof.

Kits

[000115] Further provided are kits comprising one or more components that include, but are not limited to, an anti-CoV-S antigen-binding protein, *e.g.*, an antibody or antigen-binding fragment as discussed herein (*e.g.*, of Table 1), in association with one or more additional components including, but not limited to, a further therapeutic agent, as discussed herein. The antigen-binding protein and/or the further therapeutic agent can be formulated as a single composition or separately in two or more compositions, *e.g.*, with a pharmaceutically acceptable carrier, in a pharmaceutical composition.

[000116] In one embodiment of the invention, the kit includes an anti-CoV-S antigen-binding protein, *e.g.*, an antibody or antigen-binding fragment thereof of the invention (*e.g.*, of Table 1), or a pharmaceutical composition thereof in one container (*e.g.*, in a sterile glass or plastic vial) and a further therapeutic agent in another container (*e.g.*, in a sterile glass or plastic vial).

[000117] In another embodiment, the kit comprises a combination of the invention, including an anti-CoV-S antigen-binding protein, *e.g.*, antibody or antigen-binding fragment thereof of the invention (*e.g.*, of Table 1), or pharmaceutical composition thereof in combination with one or more further therapeutic agents formulated together, optionally, in a pharmaceutical composition, in a single, common container.

[000118] If the kit includes a pharmaceutical composition for parenteral administration to a subject, the kit can include a device (*e.g.*, an injection device) for performing such

administration. For example, the kit can include one or more hypodermic needles or other injection devices as discussed above containing the anti-CoV-S antigen-binding protein, *e.g.*, antibody or antigen-binding fragment thereof of the present invention (*e.g.*, of Table 1).

[000119] The kit can include a package insert including information concerning the pharmaceutical compositions and dosage forms in the kit. Generally, such information aids patients and physicians in using the enclosed pharmaceutical compositions and dosage forms effectively and safely. For example, the following information regarding a combination of the invention may be supplied in the insert: pharmacokinetics, pharmacodynamics, clinical studies, efficacy parameters, indications and usage, contraindications, warnings, precautions, adverse reactions, overdosage, proper dosage and administration, how supplied, proper storage conditions, references, manufacturer/distributor information and patent information.

Diagnostic Uses of the Antibodies

[000120] The anti-CoV-S antigen-binding proteins, *e.g.*, antibodies or antigen-binding fragments thereof of the present invention (*e.g.*, of Table 1), may be used to detect and/or measure CoV-S in a sample. Exemplary assays for CoV-S may include, *e.g.*, contacting a sample with an anti-CoV-S antigen-binding protein of the invention, wherein the anti-CoV-S antigen-binding protein is labeled with a detectable label or reporter molecule or used as a capture ligand to selectively isolate CoV-S from samples. The presence of an anti-CoV-S antigen-binding protein complexed with CoV-S indicates the presence of CoV-S in the sample. Alternatively, an unlabeled anti-CoV-S antibody can be used in combination with a secondary antibody which is itself detectably labeled. The detectable label or reporter molecule can be a radioisotope, such as ^{3}H, ^{14}C, ^{32}P, ^{35}S, or ^{125}I; a fluorescent or chemiluminescent moiety such as fluorescein isothiocyanate, or rhodamine; or an enzyme such as alkaline phosphatase, β-galactosidase, horseradish peroxidase, or luciferase. Specific exemplary assays that can be used to detect or measure CoV-S in a sample include neutralization assays, enzyme-linked immunosorbent assay (ELISA), radioimmunoassay (RIA), and fluorescence-activated cell sorting (FACS). Thus, the present invention includes a method for detecting the presence of spike protein polypeptide in a sample comprising contacting the sample with an anti-CoV-S antigen-binding protein and detecting the presence of a CoV-S/anti-CoV-S antigen-binding protein wherein the presence of the complex indicates the presence of CoV-S.

[000121] An anti-CoV-S antigen-binding protein of the invention (*e.g.*, of Table 1) may be used in a Western blot or immune-protein blot procedure for detecting the presence of CoV-S or a fragment thereof in a sample. Such a procedure forms part of the present invention and includes the steps of *e.g.*:

(1) providing a membrane or other solid substrate comprising a sample to be tested for the presence of CoV-S, *e.g.*, optionally including the step of transferring proteins from a sample to be tested for the presence of CoV-S (*e.g.*, from a PAGE or SDS-PAGE electrophoretic separation of the proteins in the sample) onto a membrane or other solid substrate using a method known in the art (*e.g.*, semi-dry blotting or tank blotting); and contacting the membrane or other solid substrate to be tested for the presence of CoV-S or a fragment thereof with an anti-CoV-S antigen-binding protein of the invention.

[000122] Such a membrane may take the form, for example, of a nitrocellulose or vinyl-based (*e.g.*, polyvinylidene fluoride (PVDF)) membrane to which the proteins to be tested for the presence of CoV-S in a non-denaturing PAGE (polyacrylamide gel electrophoresis) gel or SDS-PAGE (sodium dodecyl sulfate polyacrylamide gel electrophoresis) gel have been transferred (*e.g.*, following electrophoretic separation in the gel). Before contacting the membrane with the anti-CoV-S antigen-binding protein, the membrane is optionally blocked, *e.g.*, with non-fat dry milk or the like so as to bind non-specific protein binding sites on the membrane.

(2) washing the membrane one or more times to remove unbound anti-CoV-S antigen-binding protein and other unbound substances; and

(3) detecting the bound anti-CoV-S antigen-binding protein.

[000123] Detection of the bound antigen-binding protein indicates that the CoV-S protein is present on the membrane or substrate and in the sample. Detection of the bound antigen-binding protein may be by binding the antigen-binding protein with a secondary antibody (an anti-immunoglobulin antibody) which is detectably labeled and, then, detecting the presence of the secondary antibody label.

[000124] The anti-CoV-S antigen-binding proteins (*e.g.*, antibodies and antigen-binding fragments (*e.g.*, of Table 1)) disclosed herein may also be used for immunohistochemistry. Such a method forms part of the present invention and comprises, *e.g.*,

(1) contacting tissue to be tested for the presence of CoV-S protein with an anti-CoV-S antigen-binding protein of the invention; and

(2) detecting the antigen-binding protein on or in the tissue.

[000125] If the antigen-binding protein itself is detectably labeled, it can be detected directly. Alternatively, the antigen-binding protein may be bound by a detectably labeled secondary antibody wherein the label is then detected.

EXAMPLES

[000126] The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how to make and use the methods and compositions of the invention and are not intended to limit the scope of what the inventors regard as their invention. Efforts have been made to ensure accuracy with respect to numbers used (*e.g.*, amounts, temperature, *etc.*) but some experimental errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, molecular weight is average molecular weight, temperature is in degrees Centigrade, room temperature is about 25°C, and pressure is at or near atmospheric.

Example 1: Generation of human antibodies to SARS-CoV-2 spike protein (SARS-CoV-2-S)

[000127] Human antibodies to SARS-CoV-2-Spike protein (SARS-CoV-2-S) were generated in a VELOCIMMUNE® mouse comprising DNA encoding human immunoglobulin heavy and kappa light chain variable regions or human immunoglobulin heavy and lambda light chain variable regions. Each mouse was immunized with a vector expressing the SARS-CoV-2-S receptor binding domain (RBD) (amino acids 1-1273 of NCBI accession number (MN908947.3), SEQ ID NO: 832), followed by a booster with a SARS-CoV-2-S vector or a SARS-CoV-2-S protein. The antibody immune response was monitored by a SARS-CoV-2-S-specific immunoassay. When a desired immune response was achieved, lymphocytes were harvested and fused with mouse myeloma cells to preserve their viability and form hybridoma cell lines. The hybridoma cell lines were screened and selected to identify cell lines that produce SARS-CoV-2-S-specific antibodies. Anti-SARS-CoV-2-S antibodies were also isolated directly from antigen-positive mouse B cells without fusion to myeloma cells, as described in U.S. Patent 7582298, herein specifically incorporated by reference in its entirety. Using this method, fully human anti-SARS-CoV-2-S antibodies (*i.e.*, antibodies possessing human variable domains and human constant domains) were obtained.

[000128] Antibody variable regions were also isolated from human blood samples. Whole

blood was received from patients 3-4 weeks after a laboratory-confirmed PCR positive test for SARS-CoV- 2 and symptomatic COVID-19 disease. Red blood cells were lysed using an ammonium chloride based lysis buffer (Life Technologies) and B cells were enriched by negative selection. Single B cells that bound the SARS-CoV-2 spike protein were isolated by fluorescent-activated cell sorting (FACS). Isolated B cells were single-well plated and mixed with antibody light and heavy variable region-specific PCR primers. cDNAs for each single B cell were synthesized via a reverse transcriptase (RT) reaction. Each resulting RT product was then split and transferred into two corresponding wells for subsequent antibody heavy and light chain PCRs. One set of the resulting RT products was first amplified by PCR using a 5' degenerate primer specific for antibody heavy variable region leader sequence or a 5' degenerate primer specific for antibody light chain variable region leader sequence and a 3' primer specific for antibody constant region, to form an amplicon. The amplicons were then amplified again by PCR using a 5' degenerate primer specific for antibody heavy variable region framework 1 or a 5' degenerate primer specific for antibody light chain variable region framework 1 and a 3' primer specific for antibody constant region, to generate amplicons for cloning. The antibody heavy chain and light chain derived PCR products were cloned into expression vectors containing heavy constant region and light constant region, respectively, thereby producing expression vectors for hybrid antibodies. The expression vectors expressing full-length heavy and light chain pairs were transfected into CHO cells to produce antibody proteins for testing.

[000129] Plasmids encoding modified anti-Sars-CoV-2-S antibodies (e.g., to enhance binding and/or neutralization for an E484K variant spike protein) are generated by cloning synthetically-synthesized double-stranded DNA fragments (gBlocks; Integrated DNA Technologies, Coralville, IA) representing the modified anti-Sars-Cov-2-S variable domains (either the heavy chain or the light chain variable domain) into human IgG1 heavy chain or human kappa expression plasmids. Anti-Sars-Cov-2 antibodies are produced in CHO cells after transfection with two expression plasmids encoding a target antigen binding IgG1 heavy chain and the target antigen binding light chain. Antibodies are purified by differential protein A affinity chromatography.

[000130] The biological properties of exemplary antibodies generated in accordance with the methods of this Example are described in detail in the Examples set forth below.

Example 2: Heavy and light chain variable region amino acid and nucleotide sequences

[000131] Table 1 sets forth the amino acid sequence identifiers of the heavy and light chain variable regions and CDRs, as well as the heavy chain and light chain sequences, of exemplary anti-SARS-CoV-2-S antibodies. The corresponding nucleic acid sequence identifiers are set forth in Table 2.

Table 1: Amino Acid Sequence Identifiers

	SEQ ID NOs									
Antibody Designation	**HCVR**	**HCDR 1**	**HCDR 2**	**HCDR 3**	**LCVR**	**LCDR 1**	**LCDR 2**	**LCDR 3**	**HC**	**LC**
mAb10913	2	4	6	8	10	12	14	16	18	20
mAb10915	22	24	26	28	30	32	34	36	38	40
mAb10916	2	4	6	8	10	12	14	16	42	20
mAb10917	44	46	26	49	51	53	55	57	59	61
mAb10918	22	24	26	28	30	32	34	36	63	40
mAb10920	65	67	69	71	73	75	55	77	79	81
mAb10921	83	85	26	87	89	91	55	93	95	97
mAb10922	99	101	103	105	107	109	111	113	115	117
mAb10923	119	121	123	125	127	129	55	131	133	135
mAb10924	137	139	141	143	145	147	149	151	153	155
mAb10925	65	67	69	71	73	75	55	77	157	81
mAb10926	83	85	26	87	89	91	55	93	159	97
mAb10927	99	101	103	105	107	109	111	113	161	117
mAb10928	119	121	123	125	127	129	55	131	163	135
mAb10929	137	139	141	143	145	147	149	151	165	155
mAb10930	167	169	171	173	175	129	55	177	179	181
mAb10931	167	169	171	173	175	129	55	177	183	181
mAb10932	185	187	26	189	191	75	194	196	198	200
mAb10933	202	204	206	208	210	212	55	214	216	218
mAb10934	220	222	224	226	228	230	194	232	234	236
mAb10935	238	24	26	240	242	244	194	246	248	250
mAb10936	252	254	256	258	260	129	55	262	264	266
mAb10937	268	270	272	274	276	129	55	278	280	282
mAb10940	284	169	286	288	290	292	294	296	298	300
mAb10938	302	24	26	304	306	308	194	310	312	314
mAb10939	316	187	319	321	323	325	55	327	329	331
mAb10941	333	85	26	336	338	340	294	296	342	344
mAb10942	185	187	26	189	191	75	194	196	346	200
mAb10943	202	204	206	208	210	212	55	214	348	218

mAb10944	220	222	224	226	228	230	194	232	350	236
mAb10945	238	24	26	240	242	244	194	246	352	250
mAb10946	252	254	256	258	260	129	55	262	354	266
mAb10947	268	270	272	274	276	129	55	278	356	282
mAb10948	302	24	26	304	306	308	194	310	358	314
mAb10949	316	187	319	321	323	325	55	327	360	331
mAb10951	333	85	26	336	338	340	294	296	362	344
mAb10950	284	169	286	288	290	292	294	296	364	300
mAb10954	366	85	26	370	372	244	194	375	377	379
mAb10955	381	383	26	385	387	389	194	310	392	394
mAb10956	396	187	26	399	401	389	194	403	405	407
mAb10957	409	411	26	414	416	53	55	418	420	422
mAb10958	366	85	26	370	372	244	194	375	424	379
mAb10959	381	383	26	385	387	389	194	310	426	394
mAb10960	396	187	26	399	401	389	194	403	428	407
mAb10961	409	411	26	414	416	53	55	418	430	422
mAb10964	432	434	436	438	440	442	55	445	447	449
mAb10965	451	453	26	455	457	459	34	462	464	466
mAb10966	468	187	26	470	472	389	194	474	476	478
mAb10967	480	24	483	485	487	389	194	489	491	493
mAb10969	495	497	499	501	503	389	194	214	506	508
mAb10970	510	24	26	512	514	516	194	518	520	522
mAb10971	524	411	26	528	530	532	55	534	536	538
mAb10973	432	434	436	438	440	442	55	445	540	449
mAb10974	451	453	26	455	457	459	34	462	542	466
mAb10975	468	187	26	470	472	389	194	474	544	478
mAb10976	480	24	483	485	487	389	194	489	546	493
mAb10977	548	550	552	554	556	558	294	560	562	564
mAb10978	495	497	499	501	503	389	194	214	566	508
mAb10979	510	24	26	512	514	516	194	518	568	522
mAb10980	524	411	26	528	530	532	55	534	570	538
mAb10981	548	550	552	554	556	558	294	560	572	564
mAb10982	574	187	576	578	580	582	584	586	588	590
mAb10983	574	187	576	578	580	582	584	586	592	590
mAb10984	594	596	26	598	600	12	14	602	604	606
mAb10985	608	169	610	612	614	616	584	618	620	622
mAb10986	624	626	26	628	630	582	632	634	636	638
mAb10987	640	642	499	644	646	648	650	652	654	656
mAb10988	658	660	662	664	666	668	670	672	674	676

mAb10989	678	680	682	684	686	688	650	690	692	694
mAb10990	594	596	26	598	600	12	14	602	696	606
mAb10991	608	169	610	612	614	616	584	618	698	622
mAb10992	624	626	26	628	630	582	632	634	700	638
mAb10993	640	642	499	644	646	648	650	652	702	656
mAb10994	658	660	662	664	666	668	670	672	704	676
mAb10995	678	680	682	684	686	688	650	690	706	694
mAb10996	708	24	26	711	713	129	55	715	717	719
mAb10997	708	24	26	711	713	129	55	715	721	719
mAb10998	723	187	26	725	727	129	55	729	731	733
mAb10999	723	187	26	725	727	129	55	729	735	733
mAb11000	737	24	26	739	741	743	55	745	747	749
mAb11001	737	24	26	739	741	743	55	745	751	749
mAb11002	753	24	26	755	713	129	55	715	757	719
mAb11003	753	24	26	755	713	129	55	715	759	719
mAb10914	44	46	26	49	51	53	55	57	762	61
mAb11004	764	766	499	768	770	91	55	772	774	776
mAb11005	764	766	499	768	770	91	55	772	778	776
mAb11006	780	782	26	784	786	53	55	788	790	792
mAb11007	780	782	26	784	786	53	55	788	794	792
mAb11008	796	24	26	798	800	53	55	802	804	806
mAb11009	796	24	26	798	800	53	55	802	808	806
mAb11010	810	812	814	816	818	129	820	822	824	826
mAb11011	810	812	814	816	818	129	820	822	828	826

Table 2: Nucleic Acid Sequence Identifiers

	SEQ ID NOs									
Antibody Designation	**HCVR**	**HCDR 1**	**HCDR 2**	**HCDR 3**	**LCVR**	**LCDR 1**	**LCDR 2**	**LCDR 3**	**HC**	**LC**
mAb10913	1	3	5	7	9	11	13	15	17	19
mAb10915	21	23	25	27	29	31	33	35	37	39
mAb10916	1	3	5	7	9	11	13	15	41	19
mAb10917	43	45	47	48	50	52	54	56	58	60
mAb10918	21	23	25	27	29	31	33	35	62	39
mAb10920	64	66	68	70	72	74	54	76	78	80
mAb10921	82	84	47	86	88	90	54	92	94	96
mAb10922	98	100	102	104	106	108	110	112	114	116
mAb10923	118	120	122	124	126	128	54	130	132	134

mAb10924	136	138	140	142	144	146	148	150	152	154
mAb10925	64	66	68	70	72	74	54	76	156	80
mAb10926	82	84	47	86	88	90	54	92	158	96
mAb10927	98	100	102	104	106	108	110	112	160	116
mAb10928	118	120	122	124	126	128	54	130	162	134
mAb10929	136	138	140	142	144	146	148	150	164	154
mAb10930	166	168	170	172	174	128	54	176	178	180
mAb10931	166	168	170	172	174	128	54	176	182	180
mAb10932	184	186	47	188	190	192	193	195	197	199
mAb10933	201	203	205	207	209	211	54	213	215	217
mAb10934	219	221	223	225	227	229	193	231	233	235
mAb10935	237	23	47	239	241	243	193	245	247	249
mAb10936	251	253	255	257	259	128	54	261	263	265
mAb10937	267	269	271	273	275	128	54	277	279	281
mAb10940	283	168	285	287	289	291	293	295	297	299
mAb10938	301	23	47	303	305	307	193	309	311	313
mAb10939	315	317	318	320	322	324	54	326	328	330
mAb10941	332	334	47	335	337	339	293	295	341	343
mAb10942	184	186	47	188	190	192	193	195	345	199
mAb10943	201	203	205	207	209	211	54	213	347	217
mAb10944	219	221	223	225	227	229	193	231	349	235
mAb10945	237	23	47	239	241	243	193	245	351	249
mAb10946	251	253	255	257	259	128	54	261	353	265
mAb10947	267	269	271	273	275	128	54	277	355	281
mAb10948	301	23	47	303	305	307	193	309	357	313
mAb10949	315	317	318	320	322	324	54	326	359	330
mAb10951	332	334	47	335	337	339	293	295	361	343
mAb10950	283	168	285	287	289	291	293	295	363	299
mAb10954	365	367	368	369	371	373	193	374	376	378
mAb10955	380	382	47	384	386	388	193	390	391	393
mAb10956	395	397	47	398	400	388	193	402	404	406
mAb10957	408	410	412	413	415	52	54	417	419	421
mAb10958	365	367	368	369	371	373	193	374	423	378
mAb10959	380	382	47	384	386	388	193	390	425	393
mAb10960	395	397	47	398	400	388	193	402	427	406
mAb10961	408	410	412	413	415	52	54	417	429	421
mAb10964	431	433	435	437	439	441	443	444	446	448
mAb10965	450	452	47	454	456	458	460	461	463	465
mAb10966	467	397	412	469	471	388	193	473	475	477

mAb10967	479	481	482	484	486	388	193	488	490	492
mAb10969	494	496	498	500	502	388	193	504	505	507
mAb10970	509	481	412	511	513	515	193	517	519	521
mAb10971	523	525	526	527	529	531	54	533	535	537
mAb10973	431	433	435	437	439	441	443	444	539	448
mAb10974	450	452	47	454	456	458	460	461	541	465
mAb10975	467	397	412	469	471	388	193	473	543	477
mAb10976	479	481	482	484	486	388	193	488	545	492
mAb10977	547	549	551	553	555	557	293	559	561	563
mAb10978	494	496	498	500	502	388	193	504	565	507
mAb10979	509	481	412	511	513	515	193	517	567	521
mAb10980	523	525	526	527	529	531	54	533	569	537
mAb10981	547	549	551	553	555	557	293	559	571	563
mAb10982	573	186	575	577	579	581	583	585	587	589
mAb10983	573	186	575	577	579	581	583	585	591	589
mAb10984	593	595	47	597	599	11	13	601	603	605
mAb10985	607	168	609	611	613	615	583	617	619	621
mAb10986	623	625	47	627	629	581	631	633	635	637
mAb10987	639	641	498	643	645	647	649	651	653	655
mAb10988	657	659	661	663	665	667	669	671	673	675
mAb10989	677	679	681	683	685	687	649	689	691	693
mAb10990	593	595	47	597	599	11	13	601	695	605
mAb10991	607	168	609	611	613	615	583	617	697	621
mAb10992	623	625	47	627	629	581	631	633	699	637
mAb10993	639	641	498	643	645	647	649	651	701	655
mAb10994	657	659	661	663	665	667	669	671	703	675
mAb10995	677	679	681	683	685	687	649	689	705	693
mAb10996	707	709	47	710	712	128	54	714	716	718
mAb10997	707	709	47	710	712	128	54	714	720	718
mAb10998	722	186	47	724	726	128	54	728	730	732
mAb10999	722	186	47	724	726	128	54	728	734	732
mAb11000	736	23	47	738	740	742	54	744	746	748
mAb11001	736	23	47	738	740	742	54	744	750	748
mAb11002	752	23	47	754	712	128	54	714	756	718
mAb11003	752	23	47	754	712	128	54	714	758	718
mAb10914	760	45	47	48	50	52	54	56	761	60
mAb11004	763	765	498	767	769	90	54	771	773	775
mAb11005	763	765	498	767	769	90	54	771	777	775
mAb11006	779	781	47	783	785	52	54	787	789	791

mAb11007	779	781	47	783	785	52	54	787	793	791
mAb11008	795	709	47	797	799	52	54	801	803	805
mAb11009	795	709	47	797	799	52	54	801	807	805
mAb11010	809	811	813	815	817	128	819	821	823	825
mAb11011	809	811	813	815	817	128	819	821	827	825

[000132] Antibodies disclosed herein have fully human variable regions but can have mouse constant regions (e.g., a mouse IgG1 Fc or a mouse IgG2 Fc (a or b isotype)) or human constant regions (e.g., a human IgG1 Fc or a human IgG4 Fc). As will be appreciated by a person of ordinary skill in the art, an antibody having a particular Fc isotype can be converted to an antibody with a different Fc isotype (*e.g.*, an antibody with a mouse IgG1 Fc can be converted to an antibody with a human IgG4, etc.), but in any event, the variable domains (including the CDRs) – which are indicated by the numerical identifiers shown in Tables 1 and 2 will remain the same, and the binding properties to antigen are expected to be identical or substantially similar regardless of the nature of the constant domain.

[000133] As described above, the antibodies were obtained from hybridomas generated from VELOCIMMUNE® mice, by direct isolation from antigen-positive VELOCIMMUNE® mouse B cells, or derived from variable regions cloned from antigen-positive human B cells. A summary of these sources is shown in Table 3.

Table 3: Antibody/Variable Region sources

Antibody	**Source**
mAb10913	mouse B cells
mAb10915	mouse B cells
mAb10916	mouse B cells
mAb10917	mouse B cells
mAb10918	mouse B cells
mAb10920	mouse B cells
mAb10921	mouse B cells
mAb10922	mouse B cells

mAb10923	mouse B cells
mAb10924	mouse B cells
mAb10925	mouse B cells
mAb10926	mouse B cells
mAb10927	mouse B cells
mAb10928	mouse B cells
mAb10929	mouse B cells
mAb10930	mouse B cells
mAb10931	mouse B cells
mAb10932	mouse B cells
mAb10933	mouse B cells
mAb10934	mouse B cells
mAb10935	mouse B cells
mAb10936	mouse B cells
mAb10937	mouse B cells
mAb10940	mouse B cells
mAb10938	mouse B cells
mAb10939	mouse B cells
mAb10941	mouse B cells
mAb10942	mouse B cells
mAb10943	mouse B cells
mAb10944	mouse B cells
mAb10945	mouse B cells
mAb10946	mouse B cells

mAb10947	mouse B cells
mAb10948	mouse B cells
mAb10949	mouse B cells
mAb10951	mouse B cells
mAb10950	mouse B cells
mAb10954	human B cells
mAb10955	human B cells
mAb10956	human B cells
mAb10957	human B cells
mAb10958	human B cells
mAb10959	human B cells
mAb10960	human B cells
mAb10961	human B cells
mAb10964	human B cells
mAb10965	human B cells
mAb10966	human B cells
mAb10967	human B cells
mAb10969	human B cells
mAb10970	human B cells
mAb10971	human B cells
mAb10973	human B cells
mAb10974	human B cells
mAb10975	human B cells
mAb10976	human B cells

mAb10977	human B cells
mAb10978	human B cells
mAb10979	human B cells
mAb10980	human B cells
mAb10981	human B cells
mAb10982	mouse B cells
mAb10983	mouse B cells
mAb10984	human B cells
mAb10985	human B cells
mAb10986	human B cells
mAb10987	human B cells
mAb10988	human B cells
mAb10989	human B cells
mAb10990	human B cells
mAb10991	human B cells
mAb10992	human B cells
mAb10993	human B cells
mAb10994	human B cells
mAb10995	human B cells
mAb10996	hybridoma
mAb10997	hybridoma
mAb10998	hybridoma
mAb10999	hybridoma
mAb11000	hybridoma

mAb11001	hybridoma
mAb11002	hybridoma
mAb11003	hybridoma
mAb10914	mouse B cells
mAb11004	hybridoma
mAb11005	hybridoma
mAb11006	hybridoma
mAb11007	hybridoma
mAb11008	hybridoma
mAb11009	hybridoma
mAb11010	hybridoma
mAb11011	hybridoma

Example 3: Luminex binding of anti-SARS-CoV-2-S antibodies to wild-type and variant spike glycoproteins

[000134] A Luminex binding assay was performed in order to determine the binding of 43 anti-SARS-COV-2-S antibodies to the SARS-CoV-2 spike glycoprotein receptor-binding domain (RBD) with a C-terminal myc-myc-hexahistidine tag (SARS-CoV-2(RBD)(R319-F541).mmH) and SARS-CoV-2 spike glycoprotein RBD with an E484K substitution and a hexahistidine tag ((E484K)-His Recombinant Protein) (SinoBiologicals, Cat No. 40592-V08H84). For this assay, proteins were amine-coupled to Luminex microspheres as follows: approximately 10 million MagPlex microspheres (MagPLex Microspheres, Luminex, Cat. No. MC10043 and MC10118), were resuspended by vortexing in 500 µL 0.1M $NaPO_4$, pH 6.2 (activation buffer) and then magnetically separated to remove the supernatant. Microspheres were protected from light, as they are light sensitive. The microspheres were resuspended in 160 µL of activation buffer and the carboxylate groups (-COOH) were activated by addition of 20 µL of 50 mg/mL of N-hydroxysuccinimide (NHS, Thermo Scientific, Cat. No. 24525) followed by addition of 20 µL of

50 mg/mL 1-ethyl-3-[3-dimethylaminopropyl]carbodiimide (EDC, ThermoScientific, Cat. No. 22980) at 25°C. After 10 minutes, the pH of the reaction was reduced to 5.0 with the addition of 600 µL of 50 mM MES, pH 5.0 (coupling buffer), and the microspheres were vortexed and magnetically separated to remove supernatant. The activated microspheres were immediately mixed with 500 µL of 25 µg/mL of the protein antigen in coupling buffer and incubated for two hours at 25 °C. The coupling reaction was quenched by the addition of 50 µL of 1M Tris-HCl, pH 8.0 and the microspheres were vortexed, magnetically separated, and washed three times with 800 µL of PBS 0.005% Tween20 0.05%), to remove uncoupled proteins and other reaction components. Microspheres were resuspended in 1 mL of PBS 2% BSA 0.05% Na Azide at 10 million microspheres/mL.

[000135] Microspheres with amine-coupled proteins were mixed at 2700 beads/ml, and 75 µL of microspheres were plated per well on a 96 well filter plate (EMD Millipore, Cat. No: MSBVN1250) and mixed with 25 µL of individual anti-SARS-CoV-2 supernatant containing antibody. Samples and microspheres were incubated for two hours at 25oC and then washed twice with 200 µL of DPBS with 0.05% Tween 20. To detect bound antibody levels to individual microspheres, 100 µL of 2.5 µg/mL R-Phycoerythrin conjugated goat F(ab')2 anti-human kappa (Southern Biotech, Cat# 2063-09) in blocking buffer or 100 µL R-Phycoerythrin conjugated goat IgG anti-human lambda (Southern Biotech, Cat# 2070-09) in blocking buffer was added and incubated for 30 minutes at 25 °C. After 30 minutes, the samples were washed twice with 200 µl of washing buffer and resuspended in 150 µL of wash buffer. The plates were read in a Luminex FlexMap 3D and Luminex xPonent software version 4.3.

[000136] The results of the Luminex binding are shown in Tables 4, 5, and 6 as median fluorescence intensity (MFI) signal intensities. Table 4 shows that 21 anti-SARS-CoV-2 antibodies bound to SARS-CoV-2 RBD and RBD (E484K) proteins with similar binding signal intensities: mAb10937, mAb10935, mAb10966, mAb11004, mAb10956, mAb10932, mAb11010, mAb10957, mAb10955, mAb10954, mAb10938, mAb10984, mAb10939, mAb10971, mAb10982, mAb10967, mAb10986, mAb10969, mAb10965, mAb10985, mAb10922. Table 5 shows that 17 anti-SARS-CoV-2 antibodies have enhanced binding for SARS-CoV2 RBD protein over the RBD (E484K) protein: mAb10964, mAb11008, mAb11000, mAb10998, mAb10970, mAb10915, mAb10914, mAb10941, mAb10940, mAb10930, mAb10923, mAb10921, mAb11006, mAb10998, mAb10930, mAb10996 and mAb10936. Table

6 shows that 5 anti-SARS-CoV-2 antibodies bound to SARS-CoV2 RBD but did not demonstrate binding to RBD (E484K) protein: mAb11002, mAb10920, mAb10977, mAb10924 and mAb10913.

Table 4: Antibodies binding to SARS-CoV-2-S RBD and RBD (E484K) proteins with similar binding signal intensities

Sample	**Concentration (µg/ml)**	SARS-CoV-2(RBD)(R319-F541).mmH Mean Fluorescent Intensity	SARS-CoV-2 Spike RBD**(E484K)**-His Recombinant Protein (Sino 40592-V08H84) Mean Fluorescent Intensity
mAb10937	20	31453	31007
mAb10937	5	19027	22474
mAb10937	1	6223	8985
mAb10937	0.2	4590	5147
mAb10935	20	32573	31533
mAb10935	5	5094	5144
mAb10935	1	6978	7895
mAb10935	0.2	1107	1599
mAb10966	20	31483	28633
mAb10966	5	29070	25301
mAb10966	1	21739	16798
mAb10966	0.2	2746	1326
mAb11004	20	29460	29322
mAb11004	5	28288	28036
mAb11004	1	18729	15753
mAb11004	0.2	3906	3364
mAb10956	20	30139	24552
mAb10956	5	24864	22383
mAb10956	1	16910	16853
mAb10956	0.2	3342	2812
mAb10932	20	34481	27043
mAb10932	5	13131	10155
mAb10932	1	8042	8962
mAb10932	0.2	2115	1053

mAb11010	20	29328	28882
mAb11010	5	12886	8079
mAb11010	1	5323	5622
mAb11010	0.2	1822	909
mAb10957	20	25318	26140
mAb10957	5	14295	10456
mAb10957	1	8968	6194
mAb10957	0.2	2744	2439
mAb10955	20	33909	31316
mAb10955	5	15256	10330
mAb10955	1	11271	10678
mAb10955	0.2	2027	1914
mAb10954	20	28254	24313
mAb10954	5	19602	13685
mAb10954	1	14278	10016
mAb10954	0.2	2512	1844
mAb10938	20	32424	31122
mAb10938	5	3195	1695
mAb10938	1	5501	5055
mAb10938	0.2	1679	1575
mAb10984	20	26231	24458
mAb10984	5	25226	18646
mAb10984	1	10646	11189
mAb10984	0.2	5344	6463
mAb10939	20	29454	29317
mAb10939	5	17067	12494
mAb10939	1	16977	12832
mAb10939	0.2	2042	1942
mAb10971	20	33041	32401
mAb10971	5	8755	6786
mAb10971	1	8355	6574
mAb10971	0.2	2854	2596
mAb10982	20	26370	23848
mAb10982	5	12154	8534
mAb10982	1	8575	6839
mAb10982	0.2	4154	2542
mAb10967	20	27968	27420
mAb10967	5	13827	9485
mAb10967	1	7061	6815
mAb10967	0.2	2003	1192
mAb10986	20	27026	24688
mAb10986	5	10274	7612
mAb10986	1	6744	5122
mAb10986	0.2	1786	1663

mAb10969	20	29591	27751
mAb10969	5	10224	7907
mAb10969	1	3157	3416
mAb10969	0.2	2001	1407
mAb10965	20	35075	33236
mAb10965	5	8794	5430
mAb10965	1	13752	12963
mAb10965	0.2	3183	1898
mAb10985	20	28938	27705
mAb10985	5	9835	6432
mAb10985	1	5793	5804
mAb10985	0.2	990	592
mAb10922	20	30802	29979
mAb10922	5	9078	6886
mAb10922	1	12606	10448
mAb10922	0.2	2579	1413

Table 5: Antibodies binding to SARS-CoV-2-S RBD with reduced binding to RBD (E484K) proteins

Sample	**Concentration (µg/ml)**	SARS-CoV-2(RBD)(R319-F541).mmH Mean Fluorescent Intensity	SARS-CoV-2 Spike RBD**(E484K)**-His Recombinant Protein (Sino 40592-V08H84) Mean Fluorescent Intensity
mAb10964	20	30573	27511
mAb10964	5	14993	9277
mAb10964	1	14771	7886
mAb10964	0.2	1192	767
mAb11008	20	32642	30322
mAb11008	5	10926	7547
mAb11008	1	6941	4607
mAb11008	0.2	1465	864
mAb11000	20	37768	26588
mAb11000	5	29024	18131
mAb11000	1	24129	7598
mAb11000	0.2	7057	1411

mAb10998	20	33505	24772
mAb10998	5	29231	18453
mAb10998	1	23555	7770
mAb10998	0.2	6317	1381
mAb10970	20	34275	33178
mAb10970	5	26186	16059
mAb10970	1	12392	6619
mAb10970	0.2	5318	1923
mAb10915	20	28517	31350
mAb10915	5	20062	10899
mAb10915	1	11746	4675
mAb10915	0.2	2890	1055
mAb10914	20	34036	31624
mAb10914	5	13926	9882
mAb10914	1	8864	4702
mAb10914	0.2	2188	1771
mAb10941	20	31979	25181
mAb10941	5	4314	2002
mAb10941	1	6356	3978
mAb10941	0.2	833	500
mAb10940	20	33658	28985
mAb10940	5	9722	5114
mAb10940	1	5467	3986
mAb10940	0.2	1965	779
mAb10930	20	25531	19993
mAb10930	5	22739	13019
mAb10930	1	15184	3853
mAb10930	0.2	3875	746
mAb10923	20	33149	27622
mAb10923	5	29368	10704
mAb10923	1	15095	2407
mAb10923	0.2	2749	355
mAb10921	20	27478	23878
mAb10921	5	16775	7097
mAb10921	1	12412	5044
mAb10921	0.2	2591	1062
mAb11006	20	31990	28951
mAb11006	5	10877	5294
mAb11006	1	7806	3770
mAb11006	0.2	1084	1591
mAb10998	20	32104	23170
mAb10998	5	10034	2801
mAb10998	1	13449	3407
mAb10998	0.2	4810	575

mAb10930	20	27306	19594
mAb10930	5	8673	1379
mAb10930	1	11953	1985
mAb10930	0.2	1503	455
mAb10996	20	36149	16611
mAb10996	5	16913	1660
mAb10996	1	6912	326
mAb10996	0.2	2938	120
mAb10936	20	29472	5765
mAb10936	5	27496	1533
mAb10936	1	17166	510
mAb10936	0.2	5102	230

Table 6: Antibodies with specific binding to SARS-CoV-2-S RBD but not to RBD (E484K) proteins

Sample	**Concentration (µg/ml)**	SARS-CoV-2(RBD)(R319-F541).mmH Mean Fluorescent Intensity	SARS-CoV-2 Spike RBD**(E484K)**-His Recombinant Protein (Sino 40592-V08H84) Mean Fluorescent Intensity
mAb11002	20	33041	3380
mAb11002	5	19936	160
mAb11002	1	12463	79
mAb11002	0.2	5101	36
mAb10920	20	33087	1510
mAb10920	5	11923	70
mAb10920	1	5234	57
mAb10920	0.2	3129	31
mAb10977	20	35989	264
mAb10977	5	1423	47
mAb10977	1	6286	66
mAb10977	0.2	2885	39
mAb10924	20	33505	419
mAb10924	5	31897	281
mAb10924	1	21222	53
mAb10924	0.2	3639	36

mAb10913	20	28834	153
mAb10913	5	4318	44
mAb10913	1	10492	71
mAb10913	0.2	1136	34

Example 4: Characterization of hybridoma supernatants by binding ELISA

[000137] An ELISA binding assay is performed to identify antibody supernatants that bind to the SARS-CoV-2-Spike protein receptor binding domain (RBD), or to the E484K variant protein. A protein composed of the wild-type or E484K RBD of SARS-CoV-2 (amino acids 319-541) expressed with a 6X histidine tag and two myc epitope tags at the C-terminus (SARS-CoV-2-S-RBD-mmH; see also NCBI Accession Number MN908947.3) is coated at 1 μg/ml on a 96-well plate in PBS buffer overnight at 4°C. Nonspecific binding sites are subsequently blocked using a 0.5% (w/v) solution of BSA in PBS. Antibody supernatants or media alone are diluted 1:40 or 1 :50 in the PSA+0.5% BSA blocking buffer and transferred to the washed microtiter plates. After one hour of incubation at room temperature, the wells are washed, and plate-bound supernatant is detected with either goat-anti-human IgG antibody conjugated with horseradish peroxidase (HRP) (Jackson Immunoresearch), or anti-mouse IgG antibody conjugated with horseradish peroxidase (HRP) (Jackson Immunoresearch). The plates are then developed using TMB substrate solution (BD Biosciences) according to manufacturer's recommendation and absorbance at 450nm was measured on a Victor X5 plate reader.

[000138] Experiments also can be carried out using the following procedure. A monoclonal anti-Penta-His antibody (Qiagen) is coated at 1μg/ml in PBS on a 96-well microtiter plate overnight at 4 °C. The hACE2-His receptor is added at 0.2ug/ml in PBS and bound for two hours at room temperature (RT). Nonspecific binding sites are subsequently blocked using a 0.5% (w/v) solution of BSA in PBS. In other microtiter plates, a constant amount of 100pM of SARS-CoV-2 RBD-hFc or SARS-CoV-2 RBD(E484K)-hFc protein is bound with anti-SARS-COV-2 antibodies and an isotype IgG1 antibody control at dilutions from 0.0008nM to 50nM in PBS +0.5% BSA. After a one-hour incubation, the mixture solutions are transferred to the microtiter plate coated hACE2-His. After 1.5 hours of incubation at RT, the wells are washed, and plate-bound SARS-COV-2 is detected with goat-anti-human IgG antibody conjugated with horseradish peroxidase (HRP) (Jackson). The plates are then developed using TMB substrate solution (BD

Biosciences, #555214) according to manufacturer's recommendation and absorbance at 450nm was measured on a Victor X5 plate reader.

[000139] Binding data are analyzed using a sigmoidal dose-response model within Prism™ software (GraphPad). The calculated IC50 value, defined as the concentration of antibody required to block 50% of SARS-CoV-2 RBD-hFc or SARS-CoV-2 RBD(E484K)-hFc binding to plate-coated hACE2-His, is used as an indicator of blocking potency. Percent blocking is defined based on the background-corrected binding signal observed at the highest antibody concentration tested using this formula:

$$\% \text{ Blocking} = 100 - \left(\frac{[\text{Experimental Signal}_{(\text{highest Ab conc})} - \text{Background Signal}_{(\text{buffer})}]}{[\text{Maximum Signal}_{(\text{hEGF.mFc alone})} - \text{Background Signal}_{(\text{buffer})}]} \times 100 \right)$$

[000140] Antibodies that block binding less than or equal to 50% at the highest concentration tested can be classified as non-blockers.

[000141] Antibodies that have been modified to enhance binding to E484K variant spike protein show increased binding to the variant spike protein and/or reduced binding of the spike protein to hACE2 as compared to the corresponding antibodies prior to modification.

Example 5: Antibody binding to SARS-CoV-2-S-expressing virus-like particle

[000142] To investigate the ability of a panel of anti-SARS-CoV-2-S monoclonal antibodies to bind the SARS-CoV-2 spike glycoprotein, an in vitro binding assay utilizing SARS-CoV-2 spike protein-expressing viral-like particles (VLPs) in an electrochemiluminescence based detection platform (MSD) is used.

[000143] To transiently express the SARS-CoV-2 spike protein (wild-type: NCBI Accession number MN908947.3, amino acids 16-1211; SEQ ID NO: 833; E484K variant: SEQ ID NO: 851), Vesicular stomatitis virus (VSV) lacking glycoprotein G (VSV delta G) is pseudotyped with SARS-CoV-2 spike protein (VSV-SARS-CoV-2-S) and generated in HEK293T cells. As a negative binding control, VSV delta G is pseudotyped with VSV G protein (VSV-G).

[000144] Experiments are carried out according to following procedure. The types of VLPs described above are diluted in PBS, seeded into 96-well carbon electrode plates (MULTI-ARRAY high bind plate, MSD), and incubated overnight at 4 °C to allow the VLPs to adhere. Nonspecific binding sites are blocked by 2% BSA (w/v) in PBS for 1 hour at room temperature.

Supernatants containing antibodies produced from SARS CoV-2-immunized mice or infected human sera, along with media-only controls which are diluted 1:10 or 1:20 in 1x PBS + 0.5% BSA buffer, are added to the plate-bound particles. The plates are then incubated for 1 hour at room temperature with shaking, after which the plates are washed with 1x PBS to remove the unbound antibodies using an AquaMax2000 plate washer (MDS Analytical Technologies). The plate-bound antibodies are detected with a SULFO-TAGTM-conjugated anti-human IgG antibody (Jackson Immunoresearch) or a SULFO-TAGTM-conjugated anti-mouse IgG antibody (Jackson Immunoresearch) for 1 hour at room temperature. After washes, the plates are developed with the Read Buffer (MSD) according to manufacturer's recommended procedure and the luminescent signals are recorded with a SECTOR Imager 600 (Meso Scale Development) instrument. Direct binding signals (in RLU) are captured, and a ratio of SARS-CoV-2-S-expressing VLPs to the irrelevant VLP was calculated.

[000145] The ability of the anti-SARS-CoV-2-S monoclonal antibodies to bind to SARS-CoV-2-S-expressing VLPs compared with binding to irrelevant VSV-expressing VLPs is assessed using an immunobinding assay, as described above. Single-point binding to the immobilized VLPs on 96-well High Bind plates (MSD) is performed with an antibody supernatant dilution of 1:10 or 1:20, bound for 1 hour, and detected using SULFO-TAGTM-conjugated anti-human IgG or anti-mouse IgG antibody. The binding signals from electrochemiluminescence are recorded on a Sector Imager 600 (MSD). RLU values are determined for the antibody binding to VLPs. Ratios are calculated comparing the SARS-CoV-2-S-expressing VLP binding signals to control VLPs.

[000146] A signal observed from SARS-COV-2-S-expressing VLPs indicates binding, while comparison with negative VLPs provides a relative background. Media alone samples provide baseline signals of secondary antibody binding to samples with no supernatant. Antibodies modified to enhance binding to the E484K variant spike protein show increased binding as compared to the anitbodies from which they are modified.

Example 6: Antibody neutralization of VSV-SARS-CoV-2-S pseudovirus infectivity

[000147] To investigate the ability of a panel of anti-SARS-CoV-2-S monoclonal antibodies to neutralize SARS-CoV-2, an in vitro neutralization assay utilizing VSV-SARS-CoV-2-S pseudovirus is used.

[000148] As described above, VSV pseudotype viruses are generated by transiently transfecting 293T cells with a plasmid encoding for SARS-CoV-2 spike protein (wild-type or E484K). Cells are seeded in 15 cm plates at $1.2x10^7$ cells per plate in DMEM complete media one day prior to transfection with 15 µg/plate spike protein DNA using 125 µL Lipofectamine LTX, 30 µL PLUS reagent, and up to 3 mL Opti-Mem. 24 hours post transfection, the cells are washed with 10 mL PBS, then infected with an MOI of 0.1 $VSV^{\Delta G:mNeon}$ virus in 10 mL Opti-Mem. Virus is incubated on cells for 1 hour, with gentle rocking every 10 minutes. Cells are washed 3 times with 10 mL PBS, then overlaid with 20 mL Infection media before incubation at 37 C, 5% CO_2 for 24 hours. Supernatant is collected into 250 mL centrifuge tubes on ice, then centrifuged at 3000 rpm for 5 minutes to pellet any cellular debris, aliquoted on ice, then frozen to -80 °C. Infectivity is tested on Vero cells prior to use in neutralization assays. This material will be referred to as VSV-SARS-CoV-2-S or VSV-SARS-CoV-2-S(E484K).

Neutralization assay with VSV-SARS-CoV-2-S and VSV-SARS-CoV-2-S(E484K)

[000149] On day 1, Vero cells are seeded at 80% confluency in T225 flasks. To seed cells, media is removed from the cells, the cells are washed with 20mL PBS (Gibco: 20012-043), and 5mL TrypLE is added and incubated for ~5 minutes at 37 °C until the cells are dislodged. 5 mL of complete DMEM is added to inactivate the trypsin, and pipetted up and down to distribute the cells. To count the resuspended cells, 20,000 Vero cells are plated in 100 µL prewarmed Complete DMEM per well in a 96 Well Black Polystyrene Microplate (Corning: 3904).

[000150] On day 2, VSV-SARS-CoV-2-S and VSV-SARS-CoV-2-S(E484K) are thawed on ice and diluted 1:1 with infection media.

[000151] In a V-bottom 96 well plate, a dilution of each supernatant is generated in 60ul infection media. For media (negative) controls, 60 µl of diluted conditioned media is added to the wells. 60 µL of diluted VSV-SARS-CoV-2-S or VSV-SARS-CoV-2-S(E484K) is added to every well except the media control wells. To those wells, 60 µL of infection media is added. Pseudoviruses are then incubated with supernatant dilutions for 30 minutes at room temperature. Media is removed from the Vero cell plates, 100 µL of supernatant/pseudovirus mixtures are transferred to the cells, and the plate is incubated at 37 °C, 5% CO_2 for 24 hours. The final supernatant dilutions of 1:4 and 1:20, and for some samples 1:100, are used to assess neutralization of VSV-SARS-CoV-2-S or VSV-SARS-CoV-2-S(E484K) pseudoviruses.

[000152] On day 3, after the 24 hr incubation, supernatant is removed from the cell wells and

replaced with 100 µL of PBS. The plates are then read on a SpectraMax i3 with MiniMax imaging cytometer.

[000153] The ability of the anti-SARS-CoV-2-S antibodies to neutralize VSV-based SARS-CoV-2-S-expressing pseudotyped virus is assessed using a neutralization fluorescence focus assay. The neutralization potency of antibody at each dilution is represented as a percentage compared to mock supernatant control. Antibodies modified to enhance binding to the E484K variant spike protein showed increased binding as compared to the antibodies from which they are modified.

[000154] In addition to testing neutralization capacity with non-replicating VSV-SARS-CoV-2-S virus, antibodies also can be tested with SARS-CoV-2 virus (wild-type and E484K variants). Monoclonal antibodies and antibody combinations are serially diluted in DMEM (Quality Biological), supplemented with 10% (v/v) heat inactivated fetal bovine serum (Sigma), 1% (v/v) penicillin/streptomycin (Gemini Bio-products) and 1% (v/v) L-glutamine (2 mM final concentration, Gibco) (VeroE6 media) to a final volume of 250 µL. Next, 250 µL of VeroE6 media containing SARS-CoV-2 (WA-1) (1000 PFU/mL) is added to each serum dilution and to 250 µL media as an untreated control. The virus-antibody mixtures are incubated for 60 min at 37 °C. Following incubation, virus titers of the mixtures are determined by plaque assay. Finally, 50% plaque reduction neutralization titer (PRNT50) values (the serum dilutions at which plaque formation was reduced by 50% relative to that of the untreated control) are calculated using a 4-parameter logistic curve fit to the percent neutralization data (GraphPad Software, La Jolla, CA).

[000155] Individual monoclonal antibody half maximal inhibitory concentration (IC50) against VSV-SARS-CoV-2 spike protein (S)-expressing pseudovirus encoding the Wuhan-Hu-1 (NCBI Accession Number MN908947.3) sequence of spike protein (S-wt) and the E484K variant spike protein (SEQ ID NO: 851) are determined in Vero cells. Antibodies modified to enhance neutralization of the E484K variant spike protein show enhanced neutralization as compared to the antibodies from which they are modified.

Example 7: Biacore binding kinetics of anti-SARS-CoV-2-S monoclonal antibodies

[000156] Equilibrium dissociation constants (K_D) for different SARS-CoV-2-S antibodies from primary supernatants from CHOt cells or from hybridomas are determined using a real-time surface plasmon resonance-based Biacore T200/Biacore 8K biosensor. All binding studies are

performed in 10mM HEPES, 150mM NaCl, 3mM EDTA, and 0.05% v/v Surfactant Tween-20, pH 7.4 (HBS-ET) running buffer at 25 °C. The Biacore CM5 sensor chip surface is first derivatized by amine coupling with either mouse anti-human Fc specific mAb or rabbit anti-mouse Fcγ monoclonal antibody (GE, Catalog # BR-1008-38) to capture anti-SARS-CoV-2 antibodies. Binding studies are performed on a human SARS-CoV-2 RBD extracellular domain expressed with a C-terminal myc-myc-hexahistidine tag (SARS-COV-2 RBD-MMH), SARS-CoV-2 RBD extracellular domain expressed with a C-terminal mouse IgG2a (SARS-COV-2 RBD-mFc), or SARS-CoV-2 RBD extracellular domain expressed with a C-terminal human IgG1 (SARS-COV-2 RBD-hFc), each of which is generated with wild-type and E484K variant sequences. Single concentrations of SARS-COV-2 RBD-MMH, (100nM); SARS-COV-2 RBD-mFc (50nM), or SARS-COV-2 RBD-hFc (50nM), prepared in HBS-ET running buffer, are injected for 1.5 minutes at a flow rate of 30µL/min while the dissociation of antibody-bound different SARS-CoV-2 RBD reagents is monitored for 2 minutes in HBS-ET running buffer. At the end of each cycle, the SARS-CoV-2 RBD antibody capture surface is regenerated using either a 10 sec injection of 20mM phosphoric acid for the mouse anti-human Fc specific monoclonal antibody surface or a 40 sec injection of 10mM Glycine, HCl, pH1.5 for the rabbit anti-mouse Fcγ specific polyclonal antibody. The association rate (k_a) and dissociation rate (k_d) are determined by fitting the real-time binding sensorgrams to a 1:1 binding model with mass transport limitation using BiaEvaluation software v3.1 or Biacore Insight Evaluation software v2.0. or curve-fitting software. Binding dissociation equilibrium constant (K_D) and dissociative half-life (t½) were calculated from the kinetic rates as:

$$\mathbf{K_D\ (M)} = \frac{kd}{ka}, \quad \textbf{and} \quad \mathbf{t½\ (min)} = \frac{\ln(2)}{60*kd}$$

[000157] Antibodies modified to enhance binding to the E484K variant spike protein show enhanced binding kinetics (e.g., a lower K_D and/or a higher t½) as compared to the antibodies from which they are modified.

Example 8: Structure determination of antibody-bound spike protein

[000158] To determine amino acids that are in proximity to amino acid 484 of the spike protein, structural analysis is performed via cryo-electron microscopy (cryoEM). Fab fragments are isolated using FabALACTICA kit (Genovis). 600 µg of the Fab is mixed with 300 µg of

SARS-CoV-2-S RBD or SARS-CoV-2-S(E484K) RBD and incubated on ice for ~1 hour then injected into a Superdex 200 increase gel filtration column equilibrated to 50 mM Tris pH 7.5, 150 mM NaCl. Peak fractions containing the mAb10933 Fab - mAb10987 Fab - RBD complex are collected and concentrated using a 10 kDa MWCO centrifugal filter. For cryoEM grid preparation, the protein sample is diluted to 1.5 mg/mL and 0.15% PMAL-C8 amphipol is added. 3.5 μL of protein is deposited onto a freshly plasma cleaned UltrAufoil grid (1.2/1.3, 300 mesh). Excess solution is blotted away using filter paper and plunge-frozen into liquid ethane using a Vitrobot Mark IV. The cryoEM grid is transferred to a Titan Krios (Thermo Fisher) equipped with a K3 detector (Gatan). Movies are collected using EPU (Thermo Fisher) at 105,000x magnification, corresponding to a pixel size of 0.85 Å. A dose rate of 15 electrons per pixel per second is used and each movie is 2 seconds, corresponding to a total dose of ~40 electrons per $Å^2$.

[000159] All cryoEM data processing is carried out using cryoSPARC v2.14.2. Movies are aligned using patch motion correction and patch CTF estimation. Aligned micrographs are selected for further processing on the basis of estimated defocus values and CTF fit resolutions. An initial set of particles picked using blob picker are subjected to 2D classification to generate templates for template picking. Particles picked by template picking are subjected to multiple rounds of 2D classification to remove unbound fabs and particles containing an incomplete complex. Ab initio reconstruction with three classes generate a single class containing particles that correspond to the Fab-RBD complex. Heterogenous refinement of the particles in this class followed by non-uniform refinement results in a final resolution map containing particles that are used for model building. Into this map, models of the RBD (taken from PDB code 6M17) and the two Fabs are manually placed. These models are then manually rebuilt using Coot and real-space refined against the map using Phenix.

[000160] CDR amino acids identified as being in proximity to amino acid 484 of the spike protein can then be modified as described previously herein, e.g., using gBlocks

Example 9: Anti-SARS-CoV-2-S antibodies binding to spike protein-expressing cells

[000161] To investigate the ability of a panel of anti-SARS-CoV-2-S monoclonal antibodies to bind to SARS-CoV-2-S expressing cells, an in vitro binding assay utilizing SARS-CoV-2-S or

SARS-CoV-2-S(E484K) expressing cells in an electrochemiluminescence based detection platform (MSD) is used.

[000162] Jurkat/Tet3G/hCD20/Tet-3G inducible cells are engineered to transiently express the SARS-CoV-2 Spike Protein (Accession number MN908947.3, amino acids 16-1211, Jurkat/Tet3G/hCD20/Tet-On 3G Inducible COVID-19 Spike Protein High Sorted) (wild-type or E484K), and flow cytometry sorted for selection of high expression of the SARS-CoV-2 protein. Parental Jurkat/Tet3G/hCD20/Tet-3G are also included in the experiments as a negative binding control.

[000163] Experiments are carried out according to following procedure. Cells from the two lines described above are induced with 1 μg/ml doxycycline at 37 °C for 36 hours prior to harvest, spun down, washed with PBS, then diluted in PBS, seeded into the 96-well carbon electrode plates (MULTI-ARRAY high bind plate, MSD), and incubated overnight at 4 °C to allow the cells to adhere. Nonspecific binding sites are blocked by 2% BSA (w/v) in PBS for one hour at room temperature. To the plate-bound cells, anti-SARS-CoV-2 antibodies and a non-binding human IgG1 control, diluted in PBS + 0.5% BSA at a range of concentrations from 0.0008nM to 50nM, and buffer with no antibody are added in duplicate and the plates incubated for one hour at room temperature with shaking. The plates are then washed with 1X PBS to remove the unbound antibodies using an AquaMax2000 plate washer (MDS Analytical Technologies). The plate-bound antibodies are detected with a SULFO-TAGTM-conjugated anti-human IgG antibody (Jackson Immunoresearch) for one hour at room temperature. After washes, the plates are developed with the Read Buffer (MSD) according to manufacturer's recommended procedure and the luminescent signals were recorded with a SECTOR Imager 600 (Meso Scale Development) instrument. The direct binding signals (in RLU) are captured for SARS-CoV-2-S expressing cells and a negative control cell line.

[000164] The ability of the anti-SARS-CoV-2 monoclonal antibodies to bind to SARS-CoV-2 spike protein-expressing cells and E484K variant SARS-CoV-2 spike protein-expressing cells compared with binding to parental cells is assessed using an immunobinding assay. Binding to the immobilized cells on 96-well high bind plates (MSD) is performed with a series of antibody dilutions and the bound antibodies were detected using SULFO-TAGTM-conjugated anti-human IgG. The binding signals from electrochemiluminescence are recorded on a Sector Imager 600 (MSD). All antibodies display a concentration-dependent binding and the ratio of the binding on

spike expressing cells to the parental cells are analyzed at the concentration of 5.5nM and 0.20nM.

[000165] Antibodies modified to enhance binding to the E484K variant spike protein show an increase in binding to E484K variant spike protein-expressing cells as compared to the antibodies from which they are modified.

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[000166] 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 to relate to each and every individual publication, database entry (*e.g.*, Genbank sequences or GeneID entries), patent application, or patent identified 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.

We claim:

1. A method for modifying an antibody or antigen-binding fragment thereof that binds to a wild-type SARS-CoV-2 spike protein comprising the amino acid sequence set forth in SEQ ID NO: 832, comprising:

a) identifying a first amino acid in said antibody or antigen-binding fragment that is in proximity to amino acid E484 of the wild-type SARS-CoV-2 spike protein when the antibody or antigen-binding fragment is bound to the wild-type SARS-CoV-2 spike protein; and

b) modifying said first amino acid, thereby generating a modified antibody or antigen-binding fragment thereof, wherein the binding of said modified antibody or antigen-binding fragment to a variant SARS-CoV-2 spike protein comprising the amino acid sequence set forth in SEQ ID NO: 851 is greater than the binding of said antibody or antigen-binding fragment to said variant SARS-CoV-2 spike protein prior to said modifying.

2. A method for modifying an antibody or antigen-binding fragment thereof that binds to a variant SARS-CoV-2 spike protein comprising the amino acid sequence set forth in SEQ ID NO: 851, comprising:

a) identifying a first amino acid in said antibody or antigen-binding fragment that is in proximity to amino acid K484 of the variant SARS-CoV-2 spike protein when the antibody or antigen-binding fragment is bound to the variant SARS-CoV-2 spike protein; and

b) modifying said first amino acid, thereby generating a modified antibody or antigen-binding fragment thereof, wherein the binding of said modified antibody or antigen-binding fragment to the variant SARS-CoV-2 spike protein is greater than the binding of said antibody or antigen-binding fragment to said variant SARS-CoV-2 spike protein prior to said modifying.

3. The method of claim 1 or 2, wherein a measure of said binding is binding affinity.

4. The method of claim 1 or 2, wherein a measure of said binding is dissociative half-life.

5. A method for modifying an antibody or antigen-binding fragment thereof that binds to a wild-type SARS-CoV-2 spike protein comprising the amino acid sequence set forth in SEQ ID NO: 832, comprising:

a) identifying a first amino acid in said antibody or antigen-binding fragment that is in proximity to amino acid E484 of the wild-type SARS-CoV-2 spike protein when the antibody or antigen-binding fragment is bound to the wild-type SARS-CoV-2 spike protein; and

b) modifying said first amino acid, thereby generating a modified antibody or antigen-binding fragment thereof, wherein said modified antibody or antigen-binding fragment has greater neutralization against a variant SARS-CoV-2 spike protein comprising the amino acid sequence set forth in SEQ ID NO: 851 than said antibody or antigen-binding fragment has neutralization against said variant SARS-CoV-2 spike protein prior to said modifying.

6. A method for modifying an antibody or antigen-binding fragment thereof that binds to a variant SARS-CoV-2 spike protein comprising the amino acid sequence set forth in SEQ ID NO: 851, comprising:

a) identifying a first amino acid in said antibody or antigen-binding fragment that is in proximity to amino acid K484 of the variant SARS-CoV-2 spike protein when the antibody or antigen-binding fragment is bound to the variant SARS-CoV-2 spike protein; and

b) modifying said first amino acid, thereby generating a modified antibody or antigen-binding fragment thereof, wherein said modified antibody or antigen-binding fragment has greater neutralization against a variant SARS-CoV-2 spike protein comprising the amino acid sequence set forth in SEQ ID NO: 851 than said antibody or antigen-binding fragment has neutralization against said variant SARS-CoV-2 spike protein prior to said modifying.

7. The method of claim 5 or 6, wherein said neutralizing is determined by neutralization of a pseudotyped virus expressing SARS-CoV-2-S or neutralization of SARS-CoV-2 virus.

8. The method of any one of claims 1-7, wherein said modifying comprises substituting a second amino acid for said first amino acid.

9. The method of claim 8, wherein said substituting comprises introducing a substitution mutation in a nucleic acid sequence encoding said amino acid.

10. The method of claim 8 or 9, wherein said first amino acid comprises a positively charged side chain at pH 7.0.

11. The method of claim 10, wherein said first amino acid is selected from the group consisting of lysine, arginine, and histidine.

12. The method of any one of claims 8-11, wherein said second amino acid comprises a negatively charged side chain at pH 7.0.

13. The method of claim 12, wherein said second amino acid is selected from the group consisting of aspartate and glutamate.

14. The method of any one of claims 1-7, wherein said modifying comprises chemically modifying said amino acid.

15. The method of claim 14, wherein said chemically modifying comprises introducing a negative charge.

16. The method of any one of the above claims, wherein said proximity comprises 3.5 Å to 4.5 Å between said first amino acid and said amino acid at position 484 of said spike protein.

17. The method of claim 16, wherein said proximity comprises about 4.0 Å.

18. The method of claim 16 or 17, wherein said fist amino acid forms a salt bridge with said amino acid at position 484 of said spike protein.

19. The modified antibody or antigen-binding fragment of any one of claims 1-18.

20. The modified antibody or antigen-binding fragment of claim 19, wherein said modified antibody comprises an immunoglobulin constant region.

21. The modified antibody of claim 20, wherein said immunoglobulin constant region is an IgG1 constant region.

22. The modified antibody of claim 19 which is a recombinant antibody.

23. The modified antibody of claim 19 which is multispecific.

24. A polynucleotide encoding a heavy chain of the modified antibody or antigen-binding fragment of any one of claims 19-23.

25. A polynucleotide encoding a light chain of the modified antibody or antigen-binding fragment of any one of claims 19-23.

26. A vector comprising the polynucleotide of claim 24 or 25.

27. A host cell comprising the modified antibody or antigen-binding fragment thereof of any one of claims 19-23, the polynucleotide of claim 24 or 25, or the vector of claim 26.

28. A pharmaceutical composition comprising the modified antibody or antigen-binding fragment thereof of any one of claims 19-23, the polynucleotide of claim 24 or 25, the vector of claim 26, or the host cell of claim 27.

29. A complex comprising the modified antibody or antigen-binding fragment of any one of claims 19-23 bound to a SARS-CoV-2 spike protein.

30. A method for making the modified antibody or antigen-binding fragment of any one of claims 19-23, comprising:

(a) introducing into a host cell one or more polynucleotides encoding said antibody or antigen-binding fragment;

(b) culturing the host cell under conditions favorable to expression of the one or more polynucleotides; and

(c) optionally, isolating the antibody or antigen-binding fragment from the host cell and/or a medium in which the host cell is grown.

31. The method of claim 30, wherein the host cell is a Chinese hamster ovary cell.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2022/018918

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61P31/14 C07K16/10
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61P C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Cheng Mary Hongying ET AL: "Impact of South African 501.V2 Variant on SARS-CoV-2 Spike Infectivity and Neutralization: A Structure-based Computational Assessment", bioRxiv, 11 January 2021 (2021-01-11), pages 0-0, XP055926780, DOI: 10.1101/2021.01.10.426143 Retrieved from the Internet: URL:https://www.biorxiv.org/content/10.1101/2021.01.10.426143v1.full.pdf [retrieved on 2022-05-31] figure 3; table 1 -/--	1-31

[x] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"X" document of particular relevance;; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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Date of the actual completion of the international search	Date of mailing of the international search report
2 June 2022	17/06/2022

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Cilensek, Zoran

1

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	& Cheng Mary Hongying ET AL: "Supplementary Material Impact of South African 501.V2 Variant on SARS-CoV-2 Spike Infectivity and Neutralization: A Structure-based Computational Assessment", bioRxiv, 11 January 2021 (2021-01-11), XP055926911, DOI: 10.1101/2021.01.10.426143 Retrieved from the Internet: URL:https://www.biorxiv.org/content/biorxiv/early/2021/01/11/2021.01.10.426143/DC1/embed/media-1.pdf?download=true [retrieved on 2022-06-01] figures S2,S3 -----	
A	Yuan Meng ET AL: "Structural and functional ramifications of antigenic drift in recent SARS-CoV-2 variants", bioRxiv, 17 February 2021 (2021-02-17), XP055926445, DOI: 10.1101/2021.02.16.430500 Retrieved from the Internet: URL:https://www.researchgate.net/publication/349403607_Structural_and_functional_ramifications_of_antigenic_drift_in_recent_SARS-CoV-2_variants/fulltext/602e6ab3a6fdcc37a835fbaa/Structural-and-functional-ramifications-of-antigenic-drift-in-recent-SARS-CoV-2-variants.pdf [retrieved on 2022-05-31] figures 2C,4A -----	1-31
A	Wang Wei Bu ET AL: "E484K mutation in SARS-CoV-2 RBD enhances binding affinity with hACE2 but reduces interactions with neutralizing antibodies and nanobodies: Binding free energy calculation studies", bioRxiv, 17 February 2021 (2021-02-17), XP055926450, DOI: 10.1101/2021.02.17.431566 Retrieved from the Internet: URL:https://www.biorxiv.org/content/10.1101/2021.02.17.431566v1.full.pdf [retrieved on 2022-05-31] figure 3; table 4 ----- -/--	1-31

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	ZHOU DAMING ET AL: "Evidence of escape of SARS-CoV-2 variant B.1.351 from natural and vaccine-induced sera", CELL, ELSEVIER, AMSTERDAM NL, vol. 184, no. 9, 23 February 2021 (2021-02-23), page 2348, XP086555062, ISSN: 0092-8674, DOI: 10.1016/J.CELL.2021.02.037 [retrieved on 2021-02-23] the whole document	1-31
A	CHEN RITA E ET AL: "Resistance of SARS-CoV-2 variants to neutralization by monoclonal and serum-derived polyclonal antibodies", NATURE MEDICINE, NATURE PUBLISHING GROUP US, NEW YORK, vol. 27, no. 4, 4 March 2021 (2021-03-04), pages 717-726, XP037424509, ISSN: 1078-8956, DOI: 10.1038/S41591-021-01294-W [retrieved on 2021-03-04] the whole document	1-31
A	SUPASA PIYADA ET AL: "Reduced neutralization of SARS-CoV-2 B.1.1.7 variant by convalescent and vaccine sera", CELL, ELSEVIER, AMSTERDAM NL, vol. 184, no. 8, 18 February 2021 (2021-02-18), page 2201, XP086538660, ISSN: 0092-8674, DOI: 10.1016/J.CELL.2021.02.033 [retrieved on 2021-02-18] the whole document	1-31
A	JAMES W. STAVE ET AL.: "Antibody and Antigen Contact Residues Define Epitope and Paratope size and Structure", THE JOURNAL OF IMMUNOLOGY, vol. 191, 1 January 2013 (2013-01-01), pages 1428-1435, XP055303910, the whole document	1-31

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INTERNATIONAL SEARCH REPORT

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Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:

   a. [X] forming part of the international application as filed:

      [X] in the form of an Annex C/ST.25 text file.

      [ ] on paper or in the form of an image file.

   b. [ ] furnished together with the international application under PCT Rule 13ter.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

   c. [ ] furnished subsequent to the international filing date for the purposes of international search only:

      [ ] in the form of an Annex C/ST.25 text file (Rule 13ter.1(a)).

      [ ] on paper or in the form of an image file (Rule 13ter.1(b) and Administrative Instructions, Section 713).

2. [ ] In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments: