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(57) Abstract: The present invention relates to antibodies, and antigen binding fragments thereof, that bind to the spike (S) protein of coronaviruses. The antibodies, and antigen binding fragments thereof, broadly target coronaviruses, including different alpha- and betacoronaviruses. The invention also relates to nucleic acids that encode, and to cells that express such antibodies and antibody fragments. In addition, the invention relates to the use of the antibodies and antibody fragments in the treatment and diagnosis of coronavirus infection. Furthermore, a recombinant peptide, polypeptide or protein comprising the epitope, to which the antibodies bind to, is provided, which may be useful in vaccination.

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ANTIBODIES BROADLY TARGETING CORONAVIRUSES AND USES THEREOF

The present invention relates to the field of antibodies against coronaviruses, in particular to antibodies binding to the spike (S) protein of coronaviruses, in particular of multiple alpha- and betacoronaviruses. The present invention also relates to the use of such antibodies, e.g. in the treatment of coronavirus infection. Furthermore, the present invention relates to recombinant (poly)peptides comprising the epitope to which the antibodies bind to, as well as its use, e.g. in vaccination.

Coronaviruses cause a number of pathological conditions in humans, including common cold, severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), and coronavirus disease 2019 (COVID-19). Symptoms of coronavirus infections range from relatively harmless to severe symptoms. For example, infection with MERS CoV can kill more than 30% of infected humans. Major symptoms of coronavirus infection include symptoms of common cold, such as fever and a sore throat, as well as pneumonia and bronchitis. Other coronavirus-induced diseases have a unique pathogenesis, such as severe acute respiratory syndrome (SARS), including upper and lower respiratory tract infections.

In 2020, coronavirus SARS-CoV-2 spread rapidly around the world, leading to the COVID-19 pandemic. Symptoms of COVID-19 are highly variable, ranging from none to severe illness and death. As of 8 January 2021, more than 88 million cases have been confirmed, with more than 1.89 million deaths attributed to COVID-19. The responses to the pandemic around the world have resulted in global social and economic disruption, including the largest global recession since the Great Depression. Recent reports of different variants of SARS-CoV-2 have raised concern about the impact and spreading of viral changes. For example, the VOC-202012/01 variant initially detected in the United Kingdom has meanwhile been detected in

at least 40 other countries/territories/areas, and the 501Y.V2 variant initially detected in South African in at least six other countries/territories/areas.

To date, seven strains of human coronaviruses (six species with one species subdivided into two different strains) are known, namely, human coronavirus OC43 (HCoV-OC43), human coronavirus HKU1 (HCoV-HKU1), human coronavirus 229E (HCoV-229E), human coronavirus NL63 (HCoV-NL63), Middle East respiratory syndrome-related coronavirus (MERS-CoV), Severe acute respiratory syndrome coronavirus (SARS-CoV) and Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). In general, the term "coronavirus" refers to any member of the subfamily Orthocoronavirinae of the family Coronaviridae, which includes the four genera, namely Alphacoronavirus, Betacoronavirus, Deltacoronavirus, and Gammacoronavirus. While human coronavirus 229E (HCoV-229E) and human coronavirus NL63 (HCoV-NL63) belong to alphacoronaviruses (α-CoV), human coronavirus OC43 (HCoV-OC43), human coronavirus HKU1 (HCoV-HKU1), Middle East respiratory syndrome-related coronavirus (MERS-CoV), Severe acute respiratory syndrome coronavirus (SARS-CoV) and Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) belong to betacoronaviruses (β-CoV).

Coronaviruses are enveloped viruses having a viral envelope made up of a lipid bilayer in which the membrane (M), envelope (E) and spike (S) structural proteins are anchored. The spike (S) proteins required for interaction with host cells. It forms trimers ("spikes") giving coronaviruses their characteristic shape. The S protein mediates receptor binding and membrane fusion between the virus and host cell. Structurally, the S protein contains an S1 and S2 subunit, with the S1 subunit forming the "head" of the spike containing the receptor binding domain (RBD) and the S2 subunit forming the "stem", which anchors the spike in the viral envelope and which contains the fusion peptide (FP) for fusion with the host cell.

Antibodies against coronaviruses, such as SARS-CoV-2, represent a promising tool for combatting diseases caused by coronaviruses, such as COVID-19. They can be passively transferred into individuals before or after viral infection to prevent or treat disease. Currently, various antibodies targeting, for example, SARS-CoV-2 are in preclinical development and clinical trials, such as P2C-1F11, CC6.29, CC6.30, CC12.1, n3088 and n3130, Vh–Fc ab8,

4A8, 5–24, 2–17 and 4–8, 2–43 and 2–51, SAB-185, VIR-7831, LY-CoV555, REGN-COV-2 (REGN10933 + REGN10987), H11-D4 and H11-H4, IE2, 2F2, 3F11, 4D8 and 5F8, Ty1, S304, S309 and S315 (for review see Jiang, S., Zhang, X., Yang, Y. et al. Neutralizing antibodies for the treatment of COVID-19. Nat Biomed Eng 4, 1134–1139 (2020). https://doi.org/10.1038/s41551-020-00660-2). In November 2020, an emergency use authorization (EUA) was issued by the FDA for casirivimab (REGN10933) and imdevimab (REGN10987) to be administered in combination (REGN-COV-2) for treatment of COVID-19.

However, casirivimab/imdevimab as well as the large majority of the anti-coronavirus antibodies currently in development bind to the receptor binding domain (RBD) of the spike protein, which is known to be more divergent. In particular, viral escape mutants can develop, which exhibit mutations in the RBD, thereby escaping the recognition of antibodies targeting the RBD (Greaney AJ, Starr TN, Gilchuk P, et al. Complete Mapping of Mutations to the SARS-CoV-2 Spike Receptor-Binding Domain that Escape Antibody Recognition [published online ahead of print, 2020 Nov 19]. *Cell Host Microbe*. 2020; S1931-3128(20)30624-7. doi:10.1016/j.chom.2020.11.007). Indeed, it was recently shown that the vast majority of antibodies targeting the RBD of the SARS-CoV-2 spike protein lost their *in-vitro* neutralizing activity against the recently emerged SARS-CoV-2 Omicron (B.1.1.529.1) variant (Cameroni, Elisabetta et al. "Broadly neutralizing antibodies overcome SARS-CoV-2 Omicron antigenic shift." *bioRxiv : the preprint server for biology* 2021.12.12.472269. 14 Dec. 2021, doi:10.1101/2021.12.12.472269. Preprint.). This study demonstrates that targeting conserved epitopes can result not only in breadth but also in protection against viral evolution. Therefore, there is a need for antibodies targeting epitopes in the more conserved regions of the coronavirus S protein, so as to improve the antibodies' broad-spectrum activity and efficacy and to provide protection against existing and future variants of coronaviruses, such as SARS-CoV-2.

In view of the above, it is the object of the present invention to provide antibodies that broadly target coronaviruses, in particular antibodies binding to different strains of coronaviruses, e.g. to various alpha- and betacoronaviruses. In particular, it is an object of the present invention to provide antibodies binding to conserved regions of the coronavirus spike protein, for example to the fusion peptide.

This object is achieved by means of the subject-matter set out below and in the appended claims.

Although the present invention is described in detail below, it is to be understood that this invention is not limited to the particular methodologies, protocols and reagents described herein as these may vary. It is also to be understood that the terminology used herein is not intended to limit the scope of the present invention which will be limited only by the appended claims. Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art.

In the following, the elements of the present invention will be described. These elements are listed with specific embodiments, however, it should be understood that they may be combined in any manner and in any number to create additional embodiments. The variously described examples and embodiments should not be construed to limit the present invention to only the explicitly described embodiments. This description should be understood to support and encompass embodiments which combine the explicitly described embodiments with any number of the disclosed elements. Furthermore, any permutations and combinations of all described elements in this application should be considered disclosed by the description of the present application unless the context indicates otherwise.

Throughout this specification and the claims which follow, unless the context requires otherwise, the term "comprise", and variations such as "comprises" and "comprising", will be understood to imply the inclusion of a stated member, integer or step but not the exclusion of any other non-stated member, integer or step. The term "consist of" is a particular embodiment of the term "comprise", wherein any other non-stated member, integer or step is excluded. In the context of the present invention, the term "comprise" encompasses the term "consist of". The term "comprising" thus encompasses "including" as well as "consisting" *e.g.*, a composition "comprising" X may consist exclusively of X or may include something additional *e.g.*, X + Y.

The terms "a" and "an" and "the" and similar reference used in the context of describing the invention (especially in the context of the claims) are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. Recitation of ranges of values herein is merely intended to serve as a shorthand method of referring individually to each separate value falling within the range. Unless otherwise indicated herein, each individual value is incorporated into the specification as if it were individually recited herein. No language in the specification should be construed as indicating any non-claimed element essential to the practice of the invention.

The word "substantially" does not exclude "completely" *e.g.*, a composition which is "substantially free" from Y may be completely free from Y. Where necessary, the word "substantially" may be omitted from the definition of the invention.

The term "about" in relation to a numerical value x means x ± 10%, for example, x ± 5%, or x ± 7%, or x ± 10%, or x ± 12%, or x ± 15%, or x ± 20%.

The term "disease" as used herein is intended to be generally synonymous, and is used interchangeably with, the terms "disorder" and "condition" (as in medical condition), in that all reflect an abnormal condition of the human or animal body or of one of its parts that impairs normal functioning, is typically manifested by distinguishing signs and symptoms, and causes the human or animal to have a reduced duration or quality of life.

As used herein, reference to "treatment" of a subject or patient is intended to include prevention, prophylaxis, attenuation, amelioration and therapy. The terms "subject" or "patient" are used interchangeably herein to mean all mammals including humans. Examples of subjects include humans, cows, dogs, cats, horses, goats, sheep, pigs, and rabbits. In some embodiments, the patient is a human.

Doses are often expressed in relation to the bodyweight. Thus, a dose which is expressed as [g, mg, or other unit]/kg (or g, mg etc.) usually refers to [g, mg, or other unit] "per kg (or g, mg etc.) bodyweight", even if the term "bodyweight" is not explicitly mentioned.

The term "binding" and similar reference usually means "specifically binding", which does not encompass non-specific sticking.

As used herein, the term "antibody" encompasses various forms of antibodies including, without being limited to, whole antibodies, antibody fragments (such as antigen binding fragments), human antibodies, chimeric antibodies, humanized antibodies, recombinant antibodies and genetically engineered antibodies (variant or mutant antibodies) as long as the characteristic properties according to the invention are retained. In some embodiments, the antibody is a human antibody. In some embodiments, the antibody is a monoclonal antibody. For example, the antibody may be a human monoclonal antibody.

As described above, the term "antibody" generally also includes antibody fragments. Fragments of the antibodies may retain the antigen-binding activity of the antibodies. Such fragments are referred to as "antigen-binding fragments". Antigen-binding fragments include, but are not limited to, single chain antibodies, Fab, Fab', F(ab')2, Fv or scFv. Fragments of the antibodies can be obtained from the antibodies by methods that include digestion with enzymes, such as pepsin or papain, and/or by cleavage of disulfide bonds by chemical reduction. Alternatively, fragments of the antibodies can be obtained by recombinant means, for example by cloning and expressing a part (fragment) of the sequences of the heavy and/or light chain. The invention also encompasses single-chain Fv fragments (scFv) derived from the heavy and light chains of an antibody of the invention. For example, the invention includes a scFv comprising the CDRs from an antibody of the invention. Also included are heavy or light chain monomers and dimers, single domain heavy chain antibodies, single domain light chain antibodies, as well as single chain antibodies, *e.g.*, single chain Fv in which the heavy and light chain variable domains are joined by a peptide linker. Antibody fragments of the invention may be contained in a variety of structures known to the person skilled in the art. In addition, the sequences of the invention may be a component of multispecific molecules in which the sequences of the invention target the epitopes of the invention and other regions of the molecule bind to other targets. Although the specification, including the claims, may, in some places, refer explicitly to antigen binding fragment(s), antibody fragment(s), variant(s) and/or derivative(s) of antibodies, it is understood that the term

"antibody" includes all categories of antibodies, namely, antigen binding fragment(s), antibody fragment(s), variant(s) and derivative(s) of antibodies.

Human antibodies are well-known in the state of the art (van Dijk, M. A., and van de Winkel, J. G., *Curr. Opin. Chem. Biol.* 5 (2001) 368-374). Human antibodies can also be produced in transgenic animals (e.g., mice) that are capable, upon immunization, of producing a full repertoire or a selection of human antibodies in the absence of endogenous immunoglobulin production. Transfer of the human germ-line immunoglobulin gene array in such germ-line mutant mice will result in the production of human antibodies upon antigen challenge (see, e.g., Jakobovits, A., et al., *Proc. Natl. Acad. Sci. USA* 90 (1993) 2551-2555; Jakobovits, A., et al., *Nature* 362 (1993) 255-258; Bruggemann, M., et al., *Year Immunol.* 7 (1993) 3340). Human antibodies can also be produced in phage display libraries (Hoogenboom, H. R., and Winter, G., *J. Mol. Biol.* 227 (1992) 381-388; Marks, J. D., et al., *J. Mol. Biol.* 222 (1991) 581-597). The techniques of Cole et al. and Boerner et al. are also available for the preparation of human monoclonal antibodies (Cole et al., *Monoclonal Antibodies and Cancer Therapy,* Alan R. Liss, p. 77 (1985); and Boerner, P., et al., *J. Immunol.* 147 (1991) 86-95). In some embodiments, human monoclonal antibodies are prepared by using improved EBV-B cell immortalization as described in Traggiai E, Becker S, Subbarao K, Kolesnikova L, Uematsu Y, Gismondo MR, Murphy BR, Rappuoli R, Lanzavecchia A. (2004): An efficient method to make human monoclonal antibodies from memory B cells: potent neutralization of SARS coronavirus. Nat Med. 10(8):871-5. As used herein, the term "variable region" (variable region of a light chain (V_L), variable region of a heavy chain (V_H)) denotes each of the pair of light and heavy chains which is involved directly in binding the antibody to the antigen. Typically, a human antibody comprises human variable region (VH/VL) sequences as well as human constant region sequences. It is understood that a human antibody may carry one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) mutations (mutated amino acids), in comparison to a corresponding human reference antibody occurring in nature. Such mutations may be introduced, for example, by site-directed mutagenesis known in the art. For example, one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) mutations may be introduced into the Fc region of the antibody, e.g. to modify its half-life, complement and/or Fc receptor binding functionalities. In some instances, one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8,

9, 10 or more) mutations may be introduced in the VH and/or VL sequences, e.g. to modify the antibody's binding to the antigen.

Antibodies of the invention can be of any isotype (*e.g.*, IgA, IgG, IgM i.e. an α, γ or μ heavy chain). For example, the antibody is of the IgG type. Within the IgG isotype, antibodies may be IgG1, IgG2, IgG3 or IgG4 subclass, for example IgG1. Antibodies of the invention may have a κ or a λ light chain. In some embodiments, the antibody is of IgG1 type and has a κ light chain.

Antibodies according to the present invention may be provided in purified form. Typically, the antibody will be present in a composition that is substantially free of other polypeptides *e.g.*, where less than 90% (by weight), usually less than 60% and more usually less than 50% of the composition is made up of other polypeptides.

Antibodies according to the present invention may be immunogenic in human and/or in non-human (or heterologous) hosts *e.g.*, in mice. For example, the antibodies may have an idiotope that is immunogenic in non-human hosts, but not in a human host. Antibodies of the invention for human use include those that cannot be easily isolated from hosts such as mice, goats, rabbits, rats, non-primate mammals, etc. and cannot generally be obtained by humanization or from xeno-mice.

As used herein, a "neutralizing antibody" is one that can neutralize, *i.e.*, prevent, inhibit, reduce, impede or interfere with, the ability of a pathogen to initiate and/or perpetuate an infection in a host. The terms "neutralizing antibody" and "an antibody that neutralizes" or "antibodies that neutralize" are used interchangeably herein. These antibodies can be used alone, or in combination, as prophylactic or therapeutic agents upon appropriate formulation, in association with active vaccination, as a diagnostic tool, or as a production tool as described herein.

As used herein, the term "mutation" relates to a change in the nucleic acid sequence and/or in the amino acid sequence in comparison to a reference sequence, e.g. a corresponding genomic sequence. A mutation, e.g. in comparison to a genomic sequence, may be, for

example, a (naturally occurring) somatic mutation, a spontaneous mutation, an induced mutation, e.g. induced by enzymes, chemicals or radiation, or a mutation obtained by site-directed mutagenesis (molecular biology methods for making specific and intentional changes in the nucleic acid sequence and/or in the amino acid sequence). Thus, the terms "mutation" or "mutating" shall be understood to also include physically making a mutation, e.g. in a nucleic acid sequence or in an amino acid sequence. A mutation includes substitution, deletion and insertion of one or more nucleotides or amino acids as well as inversion of several successive nucleotides or amino acids. To achieve a mutation in an amino acid sequence, a mutation may be introduced into the nucleotide sequence encoding said amino acid sequence in order to express a (recombinant) mutated polypeptide. A mutation may be achieved e.g., by altering, e.g., by site-directed mutagenesis, a codon of a nucleic acid molecule encoding one amino acid to result in a codon encoding a different amino acid, or by synthesizing a sequence variant, e.g., by knowing the nucleotide sequence of a nucleic acid molecule encoding a polypeptide and by designing the synthesis of a nucleic acid molecule comprising a nucleotide sequence encoding a variant of the polypeptide without the need for mutating one or more nucleotides of a nucleic acid molecule.

Several documents are cited throughout the text of this specification. Each of the documents cited herein (including all patents, patent applications, scientific publications, manufacturer's specifications, instructions, etc.), whether supra or infra, are hereby incorporated by reference in their entirety. Nothing herein is to be construed as an admission that the invention is not entitled to antedate such disclosure by virtue of prior invention.

It is to be understood that this invention is not limited to the particular methodology, protocols and reagents described herein as these 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 limit the scope of the present invention which will be limited only by the appended claims. Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art.

Antibodies and antigen-binding fragments thereof

In a first aspect the present invention provides an (isolated) antibody, or an antigen-binding fragment thereof, which (specifically) binds to the spike (S) protein of different sarbecoviruses.

As used herein, the term "coronavirus" refers to viruses of the subfamily Orthocoronavirinae, which belongs to the family Coronaviridae, a family of enveloped, positive-strand RNA viruses. The subfamily Orthocoronavirinae includes four genera, namely, alphacoronavirus, betacoronavirus, gammacoronavirus and deltacoronavirus.

In the genus of alphacoronaviruses, two species infecting humans are known, namely, human coronavirus 229E (also referred to herein as "229E") and human coronavirus NL63 (also referred to herein as "NL63").

The genus of betacoronaviruses includes the subgenus of sarbecoviruses, which comprises the species severe acute respiratory syndrome (SARS)-related coronavirus. This species includes the human infecting strains SARS-CoV-1 (also referred to herein as "SARS-CoV") and SARS-CoV-2 (with its variants), as well as bat SARS-like coronavirus WIV-1 (also referred to as „WIV-1" or „WIV1"). Further human infecting betacoronaviruses belong to the subgenus embecovirus, which includes, among others, the species human coronavirus HKU1 (also referred to herein as "HKU1") and the species betacoronavirus 1 including the human-infecting strain human coronavirus OC43 (also referred to herein as "OC43"). Another human infecting betacoronavirus is the species Middle East respiratory syndrome (MERS)-related coronavirus (also referred to herein as "MERS" or "MERS CoV"), which belong to the subgenus merbecovirus of betacoronaviruses.

So far, no human infecting coronaviruses are known in the genera gammacoronavirus and deltacoronavirus, which also include various subgenera including various species. For example, the genus gammacoronavirus includes the subgenus igacovirus with the species avian coronavirus, also referred to as avian infectious bronchitis virus ("IBV"). The genus deltacoronavirus includes, for example, the subgenus buldecovirus with the species porcine deltacoronavirus (also referred to as "PdCV" or "(porcine) coronvirus HKU15").

The antibody, or antigen-binding fragment thereof, binding to the spike protein of different sarbecoviruses may bind, for example, to at least two different viruses of the group SARS-CoV-1, SARS-CoV-2 and WIV-1. Preferably, the antibody, or the antigen-binding fragment thereof, binds to the spike (S) protein of SARS-CoV-1 and a SARS-CoV-2 virus. In some embodiments, the antibody, or the antigen-binding fragment thereof, binds to the spike (S) protein of SARS-CoV-1 and WIV-1. In some embodiments, the antibody, or the antigen-binding fragment thereof, binds to the spike (S) protein of SARS-CoV-2 and WIV-1. In particular, the antibody, or the antigen-binding fragment thereof, may bind to the spike (S) protein of SARS-CoV-1, a SARS-CoV-2 virus and WIV-1. In general, pan-sarbecovirus antibodies target epitopes conserved among sarbecoviruses. Such antibodies targeting conserved epitopes are very likely to bind to different variants of sarbecoviruses, e.g. different variants of SARS-CoV-2.

As demonstrated in the appended examples, the exemplified antibodies of the present invention CLM20_A7, CLM20_B8, CLM20_C9, CLM20_B8_UCA, CLM99_G12, CLM99_D10, CLM99_E3, CLM13_G9, CLM20_Bis_B3, ISR42_E7, CSC3_H1, E371_F8, E2418_G12, E2121_B7, E1373_G3 and CSC3_H1_UCA bind to the spike protein of at least two different sarbecoviruses, in particular to SARS-CoV-1 and SARS-CoV-2. Accordingly, the antibody, or the antigen-binding fragment thereof, binding to the spike (S) protein of different sarbecoviruses, such as to the spike (S) protein of SARS-CoV-1 and a SARS-CoV-2 virus, may comprise (i) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 9, SEQ ID NO: 10, and SEQ ID NO: 11, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 12, SEQ ID NO: 13 or 14, and SEQ ID NO: 15, respectively; or (ii) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 20, SEQ ID NO: 21, and SEQ ID NO: 22, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 12, SEQ ID NO: 23 or 24, and SEQ ID NO: 25, respectively; or (iii) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 28, SEQ ID NO: 29, and SEQ ID NO: 30, respectively, and light

chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 12, SEQ ID NO: 31 or 32, and SEQ ID NO: 33, respectively; or (iv) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 36, SEQ ID NO: 37, and SEQ ID NO: 38, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 39, SEQ ID NO: 40 or 41, and SEQ ID NO: 42, respectively; or (v) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 45, SEQ ID NO: 46, and SEQ ID NO: 47, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 48, SEQ ID NO: 40 or 49, and SEQ ID NO: 42, respectively; or (vi) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 52, SEQ ID NO: 37, and SEQ ID NO: 38, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 53, SEQ ID NO: 40 or 41, and SEQ ID NO: 42, respectively; or (vii) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 56, SEQ ID NO: 57, and SEQ ID NO: 58, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 59, SEQ ID NO: 60 or 61, and SEQ ID NO: 62, respectively; or (viii) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 65, SEQ ID NO: 66, and SEQ ID NO: 67, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 68, SEQ ID NO: 40 or 69, and SEQ ID NO: 70, respectively; or (ix) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 207, SEQ ID NO: 208, and SEQ ID NO: 209, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 210, SEQ ID NO: 211 or 212, and SEQ ID NO: 213, respectively; or (x) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 216, SEQ ID NO: 217, and SEQ ID NO: 218, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences

of SEQ ID NO: 219, SEQ ID NO: 220 or 221, and SEQ ID NO: 222, respectively; or (xi) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 225, SEQ ID NO: 226, and SEQ ID NO: 227, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 228, SEQ ID NO: 229 or 230, and SEQ ID NO: 231, respectively; or (xii) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 234, SEQ ID NO: 235, and SEQ ID NO: 236, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 237, SEQ ID NO: 211 or 238, and SEQ ID NO: 239, respectively; or (xiii) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 242, SEQ ID NO: 243, and SEQ ID NO: 244, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 245, SEQ ID NO: 31 or 32, and SEQ ID NO: 246, respectively; or (xiv) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 249, SEQ ID NO: 250, and SEQ ID NO: 251, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 252, SEQ ID NO: 253 or 254, and SEQ ID NO: 255, respectively; or (xv) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 258, SEQ ID NO: 259 and SEQ ID NO: 260, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 219, SEQ ID NO: 220 or 221, and SEQ ID NO: 261, respectively.

Preferably, the antibody, or the antigen-binding fragment thereof, binding to the spike (S) protein of different sarbecoviruses, such as to the spike (S) protein of SARS-CoV-1 and a SARS-CoV-2 virus, may comprise (i) heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 9, SEQ ID NO: 10, and SEQ ID NO: 11, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 12, SEQ ID NO: 13 or 14, and SEQ ID NO: 15, respectively; or (ii) heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 20, SEQ ID NO: 21, and SEQ ID NO: 22, respectively, and light chain CDR1,

CDR2, and CDR3 sequences according to SEQ ID NO: 12, SEQ ID NO: 23 or 24, and SEQ ID NO: 25, respectively; or (iii) heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 28, SEQ ID NO: 29, and SEQ ID NO: 30, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 12, SEQ ID NO: 31 or 32, and SEQ ID NO: 33, respectively; or (iv) heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 36, SEQ ID NO: 37, and SEQ ID NO: 38, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 39, SEQ ID NO: 40 or 41, and SEQ ID NO: 42, respectively; or (v) heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 45, SEQ ID NO: 46, and SEQ ID NO: 47, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 48, SEQ ID NO: 40 or 49, and SEQ ID NO: 42, respectively; or (vi) heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 52, SEQ ID NO: 37, and SEQ ID NO: 38, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 53, SEQ ID NO: 40 or 41, and SEQ ID NO: 42, respectively; or (vii) heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 56, SEQ ID NO: 57, and SEQ ID NO: 58, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 59, SEQ ID NO: 60 or 61, and SEQ ID NO: 62, respectively; or (viii) heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 65, SEQ ID NO: 66, and SEQ ID NO: 67, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 68, SEQ ID NO: 40 or 69, and SEQ ID NO: 70, respectively; or (ix) heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 207, SEQ ID NO: 208, and SEQ ID NO: 209, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 210, SEQ ID NO: 211 or 212, and SEQ ID NO: 213, respectively; or (x) heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 216, SEQ ID NO: 217, and SEQ ID NO: 218, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 219, SEQ ID NO: 220 or 221, and SEQ ID NO: 222, respectively; or (xi) heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 225, SEQ ID NO: 226, and SEQ ID NO: 227, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 228, SEQ ID NO: 229 or 230, and SEQ ID NO: 231, respectively; or (xii) heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 234, SEQ ID NO: 235, and SEQ ID NO: 236, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 237, SEQ ID NO: 211 or 238, and SEQ ID NO: 239, respectively; or (xiii) heavy

chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 242, SEQ ID NO: 243, and SEQ ID NO: 244, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 245, SEQ ID NO: 31 or 32, and SEQ ID NO: 246, respectively; or (xiv) heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 249, SEQ ID NO: 250, and SEQ ID NO: 251, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 252, SEQ ID NO: 253 or 254, and SEQ ID NO: 255, respectively; or (xv) heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 258, SEQ ID NO: 259 and SEQ ID NO: 260, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 219, SEQ ID NO: 220 or 221, and SEQ ID NO: 261, respectively.

Preferably, the antibody, or the antigen-binding fragment thereof, binds to the spike (S) protein of sarbecoviruses and non-sarbecovirus betacoronaviruses. In particular, the antibody, or the antigen-binding fragment thereof, may bind to the spike (S) protein of sarbecoviruses and human-infecting non-sarbecovirus betacoronaviruses. As described above, examples of human infecting non-sarbecovirus betacoronaviruses include HKU1, OC43 and MERS coronavirus.

In some embodiments the antibody, or the antigen-binding fragment thereof, binds to the spike (S) protein of HKU1 coronavirus, SARS-CoV-1 and SARS-CoV-2. As demonstrated in the appended examples, the exemplified antibodies of the present invention CLM20_A7, CLM20_B8, CLM20_C9, CLM20_B8_UCA, CLM99_G12, CLM99_D10, CLM99_E3, CLM20_Bis_B3, ISR42_E7, CSC3_H1, E371_F8, E2418_G12, E1373_G3 and CSC3_H1_UCA bind to the spike protein of sarbecoviruses and (human-infecting) non-sarbecovirus betacoronaviruses, in particular to HKU1, SARS-CoV-1 and SARS-CoV-2. Accordingly, the antibody, or the antigen-binding fragment thereof, binding to the spike (S) protein of sarbecoviruses and (human-infecting) non-sarbecovirus betacoronaviruses, such as to the spike (S) protein of HKU1, SARS-CoV-1 and a SARS-CoV-2 virus, may comprise (i) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 9, SEQ ID NO: 10, and SEQ ID NO: 11, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 12, SEQ ID NO: 13 or 14, and SEQ ID NO:

15, respectively; or (ii) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 20, SEQ ID NO: 21, and SEQ ID NO: 22, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 12, SEQ ID NO: 23 or 24, and SEQ ID NO: 25, respectively; or (iii) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 28, SEQ ID NO: 29, and SEQ ID NO: 30, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 12, SEQ ID NO: 31 or 32, and SEQ ID NO: 33, respectively; or (iv) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 36, SEQ ID NO: 37, and SEQ ID NO: 38, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 39, SEQ ID NO: 40 or 41, and SEQ ID NO: 42, respectively; or (v) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 45, SEQ ID NO: 46, and SEQ ID NO: 47, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 48, SEQ ID NO: 40 or 49, and SEQ ID NO: 42, respectively; or (vi) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 52, SEQ ID NO: 37, and SEQ ID NO: 38, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 53, SEQ ID NO: 40 or 41, and SEQ ID NO: 42, respectively; or (vii) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 65, SEQ ID NO: 66, and SEQ ID NO: 67, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 68, SEQ ID NO: 40 or 69, and SEQ ID NO: 70, respectively; or (viii) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 207, SEQ ID NO: 208, and SEQ ID NO: 209, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 210, SEQ ID NO: 211 or 212, and SEQ ID NO: 213, respectively; or (ix) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID

NO: 216, SEQ ID NO: 217, and SEQ ID NO: 218, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 219, SEQ ID NO: 220 or 221, and SEQ ID NO: 222, respectively; or (x) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 225, SEQ ID NO: 226, and SEQ ID NO: 227, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 228, SEQ ID NO: 229 or 230, and SEQ ID NO: 231, respectively; or (xi) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 234, SEQ ID NO: 235, and SEQ ID NO: 236, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 237, SEQ ID NO: 211 or 238, and SEQ ID NO: 239, respectively; or (xii) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 249, SEQ ID NO: 250, and SEQ ID NO: 251, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 252, SEQ ID NO: 253 or 254, and SEQ ID NO: 255, respectively; or (xiii) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 258, SEQ ID NO: 259 and SEQ ID NO: 260, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 219, SEQ ID NO: 220 or 221, and SEQ ID NO: 261, respectively.

Preferably, the antibody, or the antigen-binding fragment thereof, binding to the spike (S) protein of sarbecoviruses and (human-infecting) non-sarbecovirus betacoronaviruses, such as to the spike (S) protein of HKU1, SARS-CoV-1 and a SARS-CoV-2 virus, may comprise (i) heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 9, SEQ ID NO: 10, and SEQ ID NO: 11, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 12, SEQ ID NO: 13 or 14, and SEQ ID NO: 15, respectively; or (ii) heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 20, SEQ ID NO: 21, and SEQ ID NO: 22, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 12, SEQ ID NO: 23 or 24, and SEQ ID NO: 25, respectively; or (iii) heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 28, SEQ ID NO:

29, and SEQ ID NO: 30, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 12, SEQ ID NO: 31 or 32, and SEQ ID NO: 33, respectively; or (iv) heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 36, SEQ ID NO: 37, and SEQ ID NO: 38, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 39, SEQ ID NO: 40 or 41, and SEQ ID NO: 42, respectively; or (v) heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 45, SEQ ID NO: 46, and SEQ ID NO: 47, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 48, SEQ ID NO: 40 or 49, and SEQ ID NO: 42, respectively; or (vi) heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 52, SEQ ID NO: 37, and SEQ ID NO: 38, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 53, SEQ ID NO: 40 or 41, and SEQ ID NO: 42, respectively; or (vii) heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 65, SEQ ID NO: 66, and SEQ ID NO: 67, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 68, SEQ ID NO: 40 or 69, and SEQ ID NO: 70, respectively; or (viii) heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 207, SEQ ID NO: 208, and SEQ ID NO: 209, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 210, SEQ ID NO: 211 or 212, and SEQ ID NO: 213, respectively; or (ix) heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 216, SEQ ID NO: 217, and SEQ ID NO: 218, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 219, SEQ ID NO: 220 or 221, and SEQ ID NO: 222, respectively; or (x) heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 225, SEQ ID NO: 226, and SEQ ID NO: 227, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 228, SEQ ID NO: 229 or 230, and SEQ ID NO: 231, respectively; or (xi) heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 234, SEQ ID NO: 235, and SEQ ID NO: 236, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 237, SEQ ID NO: 211 or 238, and SEQ ID NO: 239, respectively; or (xii) heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 249, SEQ ID NO: 250, and SEQ ID NO: 251, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 252, SEQ ID NO: 253 or 254, and SEQ ID NO: 255, respectively; or (xiii) heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 258, SEQ ID NO: 259

and SEQ ID NO: 260, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 219, SEQ ID NO: 220 or 221, and SEQ ID NO: 261, respectively.

In some embodiments the antibody, or the antigen-binding fragment thereof, binds to the spike (S) protein of HKU1 coronavirus, OC43 coronavirus, SARS-CoV-1 and SARS-CoV-2. As demonstrated in the appended examples, the exemplified antibodies of the present invention CLM20_A7, CLM20_B8, CLM20_C9, CLM20_B8_UCA, CLM99_G12, CLM99_D10, CLM99_E3, CLM20_Bis_B3, ISR42_E7, CSC3_H1, E371_F8, E2418_G12 and CSC3_H1_UCA bind to the spike protein of sarbecoviruses and (human-infecting) non-sarbecovirus betacoronaviruses, in particular to HKU1, OC43, SARS-CoV-1 and SARS-CoV-2. Accordingly, the antibody, or the antigen-binding fragment thereof, binding to the spike (S) protein of sarbecoviruses and (human-infecting) non-sarbecovirus betacoronaviruses, such as to the spike (S) protein of HKU1, OC43, SARS-CoV-1 and a SARS-CoV-2 virus, may comprise (i) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 9, SEQ ID NO: 10, and SEQ ID NO: 11, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 12, SEQ ID NO: 13 or 14, and SEQ ID NO: 15, respectively; or (ii) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 20, SEQ ID NO: 21, and SEQ ID NO: 22, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 12, SEQ ID NO: 23 or 24, and SEQ ID NO: 25, respectively; or (iii) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 28, SEQ ID NO: 29, and SEQ ID NO: 30, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 12, SEQ ID NO: 31 or 32, and SEQ ID NO: 33, respectively; or (iv) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 36, SEQ ID NO: 37, and SEQ ID NO: 38, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 39, SEQ ID NO: 40 or 41, and SEQ ID NO: 42, respectively; or (v) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID

NO: 45, SEQ ID NO: 46, and SEQ ID NO: 47, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 48, SEQ ID NO: 40 or 49, and SEQ ID NO: 42, respectively; or (vi) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 52, SEQ ID NO: 37, and SEQ ID NO: 38, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 53, SEQ ID NO: 40 or 41, and SEQ ID NO: 42, respectively; or (vii) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 65, SEQ ID NO: 66, and SEQ ID NO: 67, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 68, SEQ ID NO: 40 or 69, and SEQ ID NO: 70, respectively; or (viii) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 207, SEQ ID NO: 208, and SEQ ID NO: 209, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 210, SEQ ID NO: 211 or 212, and SEQ ID NO: 213, respectively; or (ix) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 216, SEQ ID NO: 217, and SEQ ID NO: 218, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 219, SEQ ID NO: 220 or 221, and SEQ ID NO: 222, respectively; or (x) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 225, SEQ ID NO: 226, and SEQ ID NO: 227, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 228, SEQ ID NO: 229 or 230, and SEQ ID NO: 231, respectively; or (xi) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 234, SEQ ID NO: 235, and SEQ ID NO: 236, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 237, SEQ ID NO: 211 or 238, and SEQ ID NO: 239, respectively; or (xii) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 258, SEQ ID NO: 259 and SEQ ID NO: 260, respectively, and light chain CDR1, CDR2,

and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 219, SEQ ID NO: 220 or 221, and SEQ ID NO: 261, respectively.

Preferably, the antibody, or the antigen-binding fragment thereof, binding to the spike (S) protein of sarbecoviruses and (human-infecting) non-sarbecovirus betacoronaviruses, such as to the spike (S) protein of HKU1, OC43, SARS-CoV-1 and a SARS-CoV-2 virus, may comprise (i) heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 9, SEQ ID NO: 10, and SEQ ID NO: 11, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 12, SEQ ID NO: 13 or 14, and SEQ ID NO: 15, respectively; or (ii) heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 20, SEQ ID NO: 21, and SEQ ID NO: 22, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 12, SEQ ID NO: 23 or 24, and SEQ ID NO: 25, respectively; or (iii) heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 28, SEQ ID NO: 29, and SEQ ID NO: 30, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 12, SEQ ID NO: 31 or 32, and SEQ ID NO: 33, respectively; or (iv) heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 36, SEQ ID NO: 37, and SEQ ID NO: 38, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 39, SEQ ID NO: 40 or 41, and SEQ ID NO: 42, respectively; or (v) heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 45, SEQ ID NO: 46, and SEQ ID NO: 47, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 48, SEQ ID NO: 40 or 49, and SEQ ID NO: 42, respectively; or (vi) heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 52, SEQ ID NO: 37, and SEQ ID NO: 38, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 53, SEQ ID NO: 40 or 41, and SEQ ID NO: 42, respectively; or (vii) heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 65, SEQ ID NO: 66, and SEQ ID NO: 67, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 68, SEQ ID NO: 40 or 69, and SEQ ID NO: 70, respectively; or (viii) heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 207, SEQ ID NO: 208, and SEQ ID NO: 209, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 210, SEQ ID NO: 211 or 212, and SEQ ID NO: 213, respectively; or (ix) heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 216, SEQ ID NO: 217, and SEQ ID NO: 218, respectively, and light chain CDR1,

CDR2, and CDR3 sequences according to SEQ ID NO: 219, SEQ ID NO: 220 or 221, and SEQ ID NO: 222, respectively; or (x) heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 225, SEQ ID NO: 226, and SEQ ID NO: 227, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 228, SEQ ID NO: 229 or 230, and SEQ ID NO: 231, respectively; or (xi) heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 234, SEQ ID NO: 235, and SEQ ID NO: 236, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 237, SEQ ID NO: 211 or 238, and SEQ ID NO: 239, respectively; or (xii) heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 258, SEQ ID NO: 259 and SEQ ID NO: 260, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 219, SEQ ID NO: 220 or 221, and SEQ ID NO: 261, respectively.

Preferably the antibody, or the antigen-binding fragment thereof, binds to the spike (S) protein of HKU1 coronavirus, OC43 coronavirus, MERS coronavirus, SARS-CoV-1 and SARS-CoV-2 (i.e., to all known human infecting betacoronaviruses). As demonstrated in the appended examples, the exemplified antibodies of the present invention CLM20_A7, CLM20_B8, CLM20_C9, CLM20_B8_UCA, CLM99_G12, CLM99_D10, CLM99_E3, ISR42_E7, CSC3_H1, E371_F8, E2418_G12 and CSC3_H1_UCA bind to the spike protein of sarbecoviruses and (human-infecting) non-sarbecovirus betacoronaviruses, in particular to HKU1, OC43, MERS-CoV, SARS-CoV-1 and SARS-CoV-2. Accordingly, the antibody, or the antigen-binding fragment thereof, binding to the spike (S) protein of sarbecoviruses and (human-infecting) non-sarbecovirus betacoronaviruses, such as to the spike (S) protein of HKU1, OC43, MERS-CoV, SARS-CoV-1 and a SARS-CoV-2 virus, may comprise (i) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 9, SEQ ID NO: 10, and SEQ ID NO: 11, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 12, SEQ ID NO: 13 or 14, and SEQ ID NO: 15, respectively; or (ii) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 20, SEQ ID NO: 21, and SEQ ID NO: 22, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 12, SEQ ID NO: 23 or 24, and SEQ ID NO: 25, respectively; or (iii) heavy chain CDR1, CDR2, and CDR3 sequences

having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 28, SEQ ID NO: 29, and SEQ ID NO: 30, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 12, SEQ ID NO: 31 or 32, and SEQ ID NO: 33, respectively; or (iv) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 36, SEQ ID NO: 37, and SEQ ID NO: 38, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 39, SEQ ID NO: 40 or 41, and SEQ ID NO: 42, respectively; or (v) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 45, SEQ ID NO: 46, and SEQ ID NO: 47, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 48, SEQ ID NO: 40 or 49, and SEQ ID NO: 42, respectively; or (vi) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 52, SEQ ID NO: 37, and SEQ ID NO: 38, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 53, SEQ ID NO: 40 or 41, and SEQ ID NO: 42, respectively; or (vii) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 207, SEQ ID NO: 208, and SEQ ID NO: 209, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 210, SEQ ID NO: 211 or 212, and SEQ ID NO: 213, respectively; or (viii) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 216, SEQ ID NO: 217, and SEQ ID NO: 218, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 219, SEQ ID NO: 220 or 221, and SEQ ID NO: 222, respectively; or (ix) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 225, SEQ ID NO: 226, and SEQ ID NO: 227, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 228, SEQ ID NO: 229 or 230, and SEQ ID NO: 231, respectively; or (x) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID

NO: 234, SEQ ID NO: 235, and SEQ ID NO: 236, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 237, SEQ ID NO: 211 or 238, and SEQ ID NO: 239, respectively; or (xi) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 258, SEQ ID NO: 259 and SEQ ID NO: 260, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 219, SEQ ID NO: 220 or 221, and SEQ ID NO: 261, respectively.

Preferably, the antibody, or the antigen-binding fragment thereof, binding to the spike (S) protein of sarbecoviruses and (human-infecting) non-sarbecovirus betacoronaviruses, such as to the spike (S) protein of HKU1, OC43, MERS-CoV, SARS-CoV-1 and a SARS-CoV-2 virus, may comprise (i) heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 9, SEQ ID NO: 10, and SEQ ID NO: 11, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 12, SEQ ID NO: 13 or 14, and SEQ ID NO: 15, respectively; or (ii) heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 20, SEQ ID NO: 21, and SEQ ID NO: 22, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 12, SEQ ID NO: 23 or 24, and SEQ ID NO: 25, respectively; or (iii) heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 28, SEQ ID NO: 29, and SEQ ID NO: 30, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 12, SEQ ID NO: 31 or 32, and SEQ ID NO: 33, respectively; or (iv) heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 36, SEQ ID NO: 37, and SEQ ID NO: 38, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 39, SEQ ID NO: 40 or 41, and SEQ ID NO: 42, respectively; or (v) heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 45, SEQ ID NO: 46, and SEQ ID NO: 47, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 48, SEQ ID NO: 40 or 49, and SEQ ID NO: 42, respectively; or (vi) heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 52, SEQ ID NO: 37, and SEQ ID NO: 38, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 53, SEQ ID NO: 40 or 41, and SEQ ID NO: 42, respectively; or (vii) heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 207, SEQ ID NO: 208, and SEQ ID NO: 209, respectively, and light chain CDR1,

CDR2, and CDR3 sequences according to SEQ ID NO: 210, SEQ ID NO: 211 or 212, and SEQ ID NO: 213, respectively; or (viii) heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 216, SEQ ID NO: 217, and SEQ ID NO: 218, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 219, SEQ ID NO: 220 or 221, and SEQ ID NO: 222, respectively; or (ix) heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 225, SEQ ID NO: 226, and SEQ ID NO: 227, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 228, SEQ ID NO: 229 or 230, and SEQ ID NO: 231, respectively; or (x) heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 234, SEQ ID NO: 235, and SEQ ID NO: 236, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 237, SEQ ID NO: 211 or 238, and SEQ ID NO: 239, respectively; or (xi) heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 258, SEQ ID NO: 259 and SEQ ID NO: 260, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 219, SEQ ID NO: 220 or 221, and SEQ ID NO: 261, respectively.

More preferably, the antibody, or the antigen-binding fragment thereof, binds to the spike (S) protein of an alphacoronavirus and to the spike (S) protein of a betacoronavirus. Such broad binding activity across different genera of coronaviruses typically requires binding to an epitope, which is strongly conserved, even across different genera of coronaviruses. An example of a strongly conserved region in the spike protein of different coronavirus genera is the fusion peptide. Without being bound to any theory, it is assumed that such a strong conservation implies that mutations in the strongly conserved regions can easily abolish or reduce important functionalities, such that mutations in those strongly conserved regions are not well tolerated. In other words, strongly conserved regions of the spike protein may be strongly conserved because escape mutants may come at a cost of viral fitness. Therefore, it is unlikely, even for (escape) variants of a coronavirus to acquire mutations in regions of the spike protein, which are strongly conserved, in particular across different genera of coronaviruses.

In some embodiments, the antibody, or the antigen-binding fragment thereof, binding to the spike (S) protein of an alphacoronavirus and to the spike (S) protein of a betacoronavirus binds to the spike (S) protein of 229E coronavirus, NL63 coronavirus, HKU1 coronavirus, OC43

coronavirus, MERS coronavirus, SARS-CoV-1 and SARS-CoV-2 (i.e., to the spike protein of all known human infecting coronaviruses). As demonstrated in the appended examples, the exemplified antibodies of the present invention CLM20_A7, CLM20_B8, CLM20_C9, CLM20_B8_UCA, ISR42_E7, CSC3_H1, E371_F8, E2418_G12 and CSC3_H1_UCA bind to the spike protein of an alphacoronavirus and to the spike (S) protein of a betacoronavirus, in particular to HKU1, OC43, MERS-CoV, SARS-CoV-1, SARS-CoV-2, 229E and NL63. Accordingly, the antibody, or the antigen-binding fragment thereof, binding to the spike (S) protein of an alphacoronavirus and to the spike (S) protein of a betacoronavirus, such as to the spike (S) protein of 229E coronavirus, NL63 coronavirus, HKU1 coronavirus, OC43 coronavirus, MERS coronavirus, SARS-CoV-1 and SARS-CoV-2, may comprise (i) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 9, SEQ ID NO: 10, and SEQ ID NO: 11, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 12, SEQ ID NO: 13 or 14, and SEQ ID NO: 15, respectively; or (ii) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 20, SEQ ID NO: 21, and SEQ ID NO: 22, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 12, SEQ ID NO: 23 or 24, and SEQ ID NO: 25, respectively; or (iii) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 28, SEQ ID NO: 29, and SEQ ID NO: 30, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 12, SEQ ID NO: 31 or 32, and SEQ ID NO: 33, respectively; or (iv) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 207, SEQ ID NO: 208, and SEQ ID NO: 209, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 210, SEQ ID NO: 211 or 212, and SEQ ID NO: 213, respectively; or (v) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 216, SEQ ID NO: 217, and SEQ ID NO: 218, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 219, SEQ ID NO: 220 or 221, and SEQ ID NO: 222, respectively; or (vi) heavy

chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 225, SEQ ID NO: 226, and SEQ ID NO: 227, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 228, SEQ ID NO: 229 or 230, and SEQ ID NO: 231, respectively; or (vii) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 234, SEQ ID NO: 235, and SEQ ID NO: 236, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 237, SEQ ID NO: 211 or 238, and SEQ ID NO: 239, respectively; or (viii) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 258, SEQ ID NO: 259 and SEQ ID NO: 260, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 219, SEQ ID NO: 220 or 221, and SEQ ID NO: 261, respectively.

Preferably, the antibody, or the antigen-binding fragment thereof, binding to the spike (S) protein of an alphacoronavirus and to the spike (S) protein of a betacoronavirus, such as to the spike (S) protein of 229E coronavirus, NL63 coronavirus, HKU1 coronavirus, OC43 coronavirus, MERS coronavirus, SARS-CoV-1 and SARS-CoV-2, may comprise (i) heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 9, SEQ ID NO: 10, and SEQ ID NO: 11, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 12, SEQ ID NO: 13 or 14, and SEQ ID NO: 15, respectively; or (ii) heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 20, SEQ ID NO: 21, and SEQ ID NO: 22, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 12, SEQ ID NO: 23 or 24, and SEQ ID NO: 25, respectively; or (iii) heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 28, SEQ ID NO: 29, and SEQ ID NO: 30, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 12, SEQ ID NO: 31 or 32, and SEQ ID NO: 33, respectively; or (iv) heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 207, SEQ ID NO: 208, and SEQ ID NO: 209, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 210, SEQ ID NO: 211 or 212, and SEQ ID NO: 213, respectively; or (v) heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 216, SEQ ID NO: 217,

and SEQ ID NO: 218, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 219, SEQ ID NO: 220 or 221, and SEQ ID NO: 222, respectively; or (vi) heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 225, SEQ ID NO: 226, and SEQ ID NO: 227, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 228, SEQ ID NO: 229 or 230, and SEQ ID NO: 231, respectively; or (vii) heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 234, SEQ ID NO: 235, and SEQ ID NO: 236, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 237, SEQ ID NO: 211 or 238, and SEQ ID NO: 239, respectively; or (viii) heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 258, SEQ ID NO: 259 and SEQ ID NO: 260, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 219, SEQ ID NO: 220 or 221, and SEQ ID NO: 261, respectively.

In some embodiments, the antibody, or the antigen-binding fragment thereof, as described herein, does not bind to the receptor binding domain (RBD) of the coronavirus spike protein. In particular, the antibody, or the antigen-binding fragment thereof, as described above, binds to the fusion peptide of the coronavirus spike (S) protein.

In some embodiments, the antibody, or the antigen-binding fragment thereof, also binds to the spike (S) protein of SARS-like coronavirus WIV-1. As shown in the appended examples, at least the exemplified antibodies of the present invention CSC3_H1 and E2418_G12 also bind to the spike protein of WIV-1. Accordingly, the antibody, or the antigen-binding fragment thereof, also binds to the spike (S) protein of SARS-like coronavirus WIV-1 may comprise (i) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 216, SEQ ID NO: 217, and SEQ ID NO: 218, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 219, SEQ ID NO: 220 or 221, and SEQ ID NO: 222, respectively; or (ii) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 234, SEQ ID NO: 235, and SEQ ID NO: 236, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 237, SEQ ID NO: 211 or 238, and SEQ ID NO: 239, respectively. More

preferably, Preferably, the antibody, or the antigen-binding fragment thereof, also binds to the spike (S) protein of SARS-like coronavirus WIV-1 may comprise (i) heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 216, SEQ ID NO: 217, and SEQ ID NO: 218, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 219, SEQ ID NO: 220 or 221, and SEQ ID NO: 222, respectively; or (ii) heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 234, SEQ ID NO: 235, and SEQ ID NO: 236, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 237, SEQ ID NO: 211 or 238, and SEQ ID NO: 239, respectively.

In some embodiments, the antibody, or the antigen-binding fragment thereof, binds to the spike (S) protein of coronaviruses of all four genera. In other words, the antibody, or the antigen-binding fragment thereof, may bind to the spike (S) protein of an alphacoronavirus, to the spike (S) protein of a betacoronavirus, to the spike (S) protein of a gammacoronavirus, and to the spike (S) protein of a deltacoronavirus. For example, the antibody, or the antigen-binding fragment thereof, as described above, may additionally bind to the spike (S) protein of infectious bronchitis virus (IBV) and porcine deltacoronavirus (PdCV). Accordingly, the antibody, or the antigen-binding fragment thereof, may bind to the spike (S) protein of 229E coronavirus, NL63 coronavirus, HKU1 coronavirus, OC43 coronavirus, MERS coronavirus, SARS-CoV-1, SARS-CoV-2, infectious bronchitis virus (IBV) and porcine deltacoronavirus (PdCV). This is shown in the appended examples for the exemplified antibody CSC3_H1. Accordingly, the antibody, or the antigen-binding fragment thereof, binding to the spike (S) protein of an alphacoronavirus, to the spike (S) protein of a betacoronavirus, to the spike (S) protein of a gammacoronavirus, and to the spike (S) protein of a deltacoronavirus, in particular binding to the spike (S) protein of 229E coronavirus, NL63 coronavirus, HKU1 coronavirus, OC43 coronavirus, MERS coronavirus, SARS-CoV-1, SARS-CoV-2, infectious bronchitis virus (IBV) and porcine deltacoronavirus (PdCV), may comprise heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 216, SEQ ID NO: 217, and SEQ ID NO: 218, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 219, SEQ ID NO: 220 or 221, and SEQ ID NO: 222, respectively. Preferably, the antibody, or the antigen-binding fragment thereof, binding to the spike (S) protein of an alphacoronavirus, to the spike (S) protein of a betacoronavirus, to the spike (S)

protein of a gammacoronavirus, and to the spike (S) protein of a deltacoronavirus, in particular binding to the spike (S) protein of 229E coronavirus, NL63 coronavirus, HKU1 coronavirus, OC43 coronavirus, MERS coronavirus, SARS-CoV-1, SARS-CoV-2, infectious bronchitis virus (IBV) and porcine deltacoronavirus (PdCV), may comprise heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 216, SEQ ID NO: 217, and SEQ ID NO: 218, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 219, SEQ ID NO: 220 or 221, and SEQ ID NO: 222, respectively.

In some embodiments, the antibody, or the antigen-binding fragment thereof, binds to an amino acid sequence according to any one of SEQ ID NOs 1 – 8 and 264 – 269. SEQ ID NOs 1 – 8 and 264 – 269 show exemplified sequences of (fusion peptide) epitopes of different coronaviruses. However, it is understood that for each coronavirus (species), there are usually different isolates (variants). For example, for HKU1 includes isolates N1, N2 and N5, while SARS-CoV-2 includes alpha, delta, gamma, and omicron variants. Although the fusion peptide of the spike protein is highly conserved, such isolates/variants may exhibit minor changes in the fusion peptide sequence (even within the same species). Therefore, in some embodiments, the antibody, or the antigen-binding fragment thereof, binds to an amino acid sequence having at least 73%, preferably at least 80%, more preferably at least 86% and even more preferably at least 93% sequence identity to any one of SEQ ID NOs 1 – 7 and 268 – 269. In some embodiments, the antibody, or the antigen-binding fragment thereof, binds to an amino acid sequence having at least 70%, preferably at least 80%, more preferably at least 90% sequence identity to SEQ ID NO: 8. In some embodiments, the antibody, or the antigen-binding fragment thereof, binds to an amino acid sequence having at least 62%, preferably at least 75%, more preferably at least 87% sequence identity to SEQ ID NO: 264. In some embodiments, the antibody, or the antigen-binding fragment thereof, binds to an amino acid sequence having at least 72%, preferably at least 81%, more preferably at least 90% sequence identity to SEQ ID NO: 265. In some embodiments, the antibody, or the antigen-binding fragment thereof, binds to an amino acid sequence having at least 75%, preferably at least 83%, more preferably at least 91% sequence identity to SEQ ID NO: 267. Preferably, the antibody, or the antigen-binding fragment thereof, binds to an amino acid sequence having at least 75%, preferably at least 80%, more preferably at least 85%, even more preferably at least 90%, still more preferably at least 95% sequence identity to SEQ ID NO: 266. For such

sequence variants, the changes (mutations) occur preferably at positions X_1, X_2 and/or X_3 of general formulae I, Ia or II, as described below. Preferred mutations for each of those positions are also described below.

Preferably, the antibody, or the antigen-binding fragment thereof, binds to an amino acid sequence according to each of SEQ ID NOs 1 – 7; and, optionally, additionally to an amino acid sequence according to SEQ ID NO: 268 and to an amino acid sequence according to SEQ ID NO: 269. SEQ ID NOs 1 – 8 and 264 – 269 relate to amino acid sequences of (fragments/epitopes of) the fusion peptide of the spike protein of different coronaviruses. For example, SEQ ID NO: 266 is the amino acid sequence of the fusion peptide of SARS-CoV-2. Accordingly, antibodies, or antigen-binding fragments, as described herein to bind to the (fusion peptide of the) spike protein of SARS-CoV-2 may bind to an amino acid sequence according to SEQ ID NO: 266. For example, SEQ ID NO: 1 is a fragment of the spike protein (fusion peptide) of SARS-CoV-2. Accordingly, antibodies, or antigen-binding fragments, as described herein to bind to the (fusion peptide of the) spike protein of SARS-CoV-2 may bind to an amino acid sequence according to SEQ ID NO: 1. For example, SEQ ID NO: 2 is a fragment of the spike protein (fusion peptide) of SARS-CoV-1. Accordingly, antibodies, or antigen-binding fragments, as described herein to bind to the (fusion peptide of the) spike protein of SARS-CoV-1 may bind to an amino acid sequence according to SEQ ID NO: 2. For example, SEQ ID NO: 3 is a fragment of the spike protein (fusion peptide) of MERS-CoV. Accordingly, antibodies, or antigen-binding fragments, as described herein to bind to the (fusion peptide of the) spike protein of MERS-CoV may bind to an amino acid sequence according to SEQ ID NO: 3. For example, SEQ ID NO: 4 is a fragment of the spike protein (fusion peptide) of OC43 coronavirus. Accordingly, antibodies, or antigen-binding fragments, as described herein to bind to the (fusion peptide of the) spike protein of OC43 coronavirus may bind to an amino acid sequence according to SEQ ID NO: 4. For example, SEQ ID NO: 5 is a fragment of the spike protein (fusion peptide) of HKU1 coronavirus. Accordingly, antibodies, or antigen-binding fragments, as described herein to bind to the (fusion peptide of the) spike protein of HKU1 coronavirus may bind to an amino acid sequence according to SEQ ID NO: 5. For example, SEQ ID NO: 6 is a fragment of the spike protein (fusion peptide) of NL63 coronavirus. Accordingly, antibodies, or antigen-binding fragments, as described herein to bind to the (fusion peptide of the) spike protein of NL63 coronavirus may bind to

an amino acid sequence according to SEQ ID NO: 6. For example, SEQ ID NO: 7 is a fragment of the spike protein (fusion peptide) of 229E coronavirus. Accordingly, antibodies, or antigen-binding fragments, as described herein to bind to the (fusion peptide of the) spike protein of 229E coronavirus may bind to an amino acid sequence according to SEQ ID NO: 7. For example, SEQ ID NO: 268 is a fragment of the spike protein (fusion peptide) of IBV. Accordingly, antibodies, or antigen-binding fragments, as described herein to bind to the (fusion peptide of the) spike protein of IBV may bind to an amino acid sequence according to SEQ ID NO: 268. For example, SEQ ID NO: 269 is a fragment of the spike protein (fusion peptide) of PdCV. Accordingly, antibodies, or antigen-binding fragments, as described herein to bind to the (fusion peptide of the) spike protein of PdCV may bind to an amino acid sequence according to SEQ ID NO: 269. For example, SEQ ID NO: 8, SEQ ID NO: 264 and SEQ ID NO: 265 are fragments of the spike protein (fusion peptide) shared by SARS-CoV-1, SARS-CoV-2 and HKU1 coronavirus. Accordingly, antibodies, or antigen-binding fragments, as described herein to bind to the (fusion peptide of the) spike protein of SARS-CoV-1, SARS-CoV-2 and HKU1 coronavirus may bind to an amino acid sequence according to SEQ ID NO: 8, SEQ ID NO: 264 and SEQ ID NO: 265. For example, SEQ ID NO: 267 is a fragment of the spike protein (fusion peptide) shared by SARS-CoV-1 and SARS-CoV-2. Accordingly, antibodies, or antigen-binding fragments, as described herein to bind to the (fusion peptide of the) spike protein of SARS-CoV-1 and SARS-CoV-2 may bind to an amino acid sequence according to SEQ ID NO: 267.

As described above, the present invention provides an (isolated) antibody, or an antigen-binding fragment thereof, which (specifically) binds to the fusion peptide (FP) of the coronavirus spike (S) protein. In particular, the antibody, or the antigen-binding fragment thereof, may bind to the fusion peptide of the spike protein of different coronaviruses as described above.

Coronaviruses typically enter host cells with their spike (S) glycoprotein. The coronavirus S protein (schematically shown in Figure 2) contains two functional subunits, the N-terminal S1 subunit and the C-terminal S2 subunit. The fusion peptide (FP) is located in the S2 subunit of the S protein. The fusion peptide is usually involved in the fusion of the virus and the host cell (Madu I.G., Roth S.L., Belouzard S., Whittaker G.R. Characterization of a highly

conserved domain within the severe acute respiratory syndrome coronavirus spike protein S2 domain with characteristics of a viral fusion peptide. J. Virol. 2009;83:7411–7421. doi: 10.1128/JVI.00079-09).

The present inventors identified antibodies broadly targeting the spike protein of different coronaviruses, in particular targeting the spike protein of various alpha- and betacoronaviruses. Epitope mapping revealed that these antibodies bind to the fusion peptide (FP) of the spike protein. Accordingly, antibodies binding to the fusion peptide of the coronavirus S protein can target various distinct coronaviruses. Therefore, antibodies targeting the fusion peptide of the coronavirus S protein represent a group of broadly targeting anti-coronavirus antibodies.

Preferably, the antibody, or the antigen-binding fragment thereof, binds to an amino acid sequence according to general formula I or Ia:

$$SX_1X_2EDLLFX_3K \quad (I)$$

$$X_2EDLLFX_3K \quad (Ia)$$

wherein X_1, X_2 and X_3 may be any amino acid.

More preferably, the antibody, or the antigen-binding fragment thereof, binds to an amino acid sequence according to general formula II:

$$RSX_1X_2EDLLFX_3K \quad (II)$$

wherein X_1, X_2 and X_3 may be any amino acid.

In general formula I and II, X_1 may be a non-polar and/or neutral amino acid, such as an amino acid selected from A, C, G, I, L, M, F, P, W and V; preferably X_1 is selected from A, C, G, I, L, M, F, P, W and V; more preferably X_1 is A, L or F; even more preferably X_1 is Y, V, L, I or E. In some embodiments, X_1 is not P. Preferably, X_1 is F.

In general formula I, Ia and II, X_2 is preferably an aliphatic, non-polar and/or neutral amino acid, such as an amino acid selected from A, G, I, L, and V. In some embodiments, X_2 is I, L, F, S or V. More preferably X_2 is I or L. Even more preferably X_2 is I.

In general formula I, Ia and II, X_3 is preferably a polar amino acid, such as an amino acid selected from R, N, D, Q, E, H, K, S, T or Y; more preferably X_3 is N, H, K, S, T or D; even more preferably X_3 is N, S, T or D; still more preferably X_3 is N, S or D. In some embodiments, X_3 is N or D.

In some embodiments, the antibody, or the antigen-binding fragment thereof, binds to an amino acid sequence according to general formula I or II, wherein X_1 is A, L or F; X_2 is I or L; and X_3 is N, S, T or D, preferably wherein X_1 is A, L or F; X_2 is I or L; and X_3 is N, S or D.

In some embodiments, the antibody, or the antigen-binding fragment thereof, binds to an epitope in the fusion peptide of the coronavirus spike (S) protein (in particular of SARS-CoV-2 S protein), which is exposed in an intermediate (transient) conformation of the S protein, in particular following receptor (in particular ACE2) binding, and/or which is more/better accessible upon receptor (in particular ACE2) binding (as compared to without receptor binding). In some embodiments, the antibody, or the antigen-binding fragment thereof, binds to a (cryptic) epitope in the fusion peptide (region) of the spike protein (e.g., sarbecovirus, such as SARS-CoV-2, spike protein) that becomes exposed (accessible for antibodies) in the prefusion conformation upon ACE2 binding.

In some embodiments, the antibody, or the antigen-binding fragment thereof, binds to an amino acid sequence according to SEQ ID NO: 264 or to a sequence variant thereof which includes 1, 2, 3 or 4 mutations in comparison to SEQ ID NO: 264. In some embodiments, the sequence variant includes three or four mutations in comparison to SEQ ID NO: 264. Preferred positions of these mutations are positions I1, L4, N7 and/or K8 in SEQ ID NO: 264. Preferably, the sequence variant has at least 75% sequence identity, preferably at least 87% sequence identity to SEQ ID NO: 264. Accordingly, it is preferred that SEQ ID NO: 264 includes no more than one or two mutation(s). Also these mutations may preferably occur at

any one of positions I1, L4, N7 and/or K8 in SEQ ID NO: 264. More preferred positions of these mutations are those of X_2 and X_3 in general formula Ia above (corresponding to positions I1 and N7 in SEQ ID NO: 264, respectively). Accordingly, an amino acid sequence with at least 75% sequence identity to SEQ ID NO: 264 is preferably mutated at positions X_2 and X_3 of general formula Ia. An amino acid sequence with at least 87% sequence identity to SEQ ID NO: 264 is preferably mutated either at position X_2 or at position X_3 (but not at both) of general formula Ia. Even more preferably, the antibody, or the antigen-binding fragment thereof, binds to an amino acid sequence according to SEQ ID NO: 264.

In some embodiments, the antibody, or the antigen-binding fragment thereof, binds to an amino acid sequence according to SEQ ID NO: 8 or to a sequence variant thereof having at least 70% sequence identity, preferably at least 80% sequence identity and more preferably at least 90% sequence identity. In some embodiments, SEQ ID NO: 8 may include one or more (e.g., 1, 2, 3, 4 or 5) mutations, preferably at any one of positions F2, I3, L6, N9 and/or K10 of SEQ ID NO: 8. Preferably, SEQ ID NO: 8 may include up to three (1, 2 or 3) mutations. Preferred positions of these mutations are those of X_1, X_2 and X_3 in general formula I above (corresponding to F2, I3 and N9, respectively, in SEQ ID NO: 8). The above-mentioned preferred mutations for each of those positions in general formula I likewise apply to SEQ ID NO: 8. Accordingly, an amino acid sequence with at least 70% sequence identity to SEQ ID NO: 8 is preferably mutated at positions X_1, X_2 and X_3 of general formula I. An amino acid sequence with at least 80% sequence identity to SEQ ID NO: 8 is preferably mutated at positions X_1 and X_3 of general formula I or at positions X_2 and X_3 of general formula I. An amino acid sequence with at least 90% sequence identity to SEQ ID NO: 8 is preferably mutated at position X_1, X_2 or X_3 of general formula I. Even more preferably, the antibody, or the antigen-binding fragment thereof, binds to an amino acid sequence according to SEQ ID NO: 8.

In some embodiments, the antibody, or the antigen-binding fragment thereof, binds to an amino acid sequence according to SEQ ID NO: 265 or a sequence variant thereof having at least 70% sequence identity, preferably at least 80% sequence identity and more preferably at least 90% sequence identity. In some embodiments, SEQ ID NO: 265 may include one or more (e.g., 1, 2, 3, 4 or 5) mutations, preferably at any one of positions F3, I4, L7, N10 and/or

K11 of SEQ ID NO: 265. Preferably, SEQ ID NO: 265 may include up to three (1, 2 or 3) mutations. Preferred positions of these mutations are those of X_1, X_2 and X_3 in general formula II above (corresponding to F3, I4 and N10, respectively, in SEQ ID NO: 265). The above-mentioned preferred mutations for each of those positions in general formula II likewise apply to SEQ ID NO: 265. Accordingly, an amino acid sequence with at least 70% sequence identity to SEQ ID NO: 265 is preferably mutated at positions X_1, X_2 and X_3 of general formula II. An amino acid sequence with at least 80% sequence identity to SEQ ID NO: 265 is preferably mutated at positions X_1 and X_3 of general formula II or at positions X_2 and X_3 of general formula II. An amino acid sequence with at least 90% sequence identity to SEQ ID NO: 265 is preferably mutated at position X_1, X_2 or X_3 of general formula II. Even more preferably, the antibody, or the antigen-binding fragment thereof, binds to an amino acid sequence according to SEQ ID NO: 265.

In some embodiments, the antibody, or the antigen-binding fragment thereof, binds to an amino acid sequence according to SEQ ID NO: 265 or a sequence variant thereof, wherein R_1, E_5 and F_9 of SEQ ID NO: 265 are maintained. In some embodiments, the antibody, or the antigen-binding fragment thereof, binds to an amino acid sequence according to SEQ ID NO: 265 or a sequence variant thereof, wherein R_1, E_5 and F_9 of SEQ ID NO: 265 may be maintained and wherein

S_2 is substituted with V, R, M, G, E or A, preferably with G;

F_3 is substituted with Y, V, T, S, R, M, L, K, I, E, D or A, preferably with Y, V, L, I, or E;

I_4 is substituted with Y, V or L, preferably with L;

D_6 is substituted with Y, W, V, T, S, M, L, I, F, C or A, preferably with Y, T, S or F;

L_7 is substituted with Y, V, T, M, I, or F, preferably with Y, V, I or F;

L_8 is substituted with I;

N_{10} is substituted with any amino acid except P, preferably with Y, W, V, T, S, R, Q, M, L, K, I, G, F, E, D, C or A; and/or

K_{11} is substituted with V, T, S, M, I, G, F, E or A, preferably with T, S, M, G, E or A.

In some embodiments, the antibody, or the antigen-binding fragment thereof, binds to an amino acid sequence according to SEQ ID NO: 265 or a sequence variant thereof, wherein R_1, E_5, L_8 and F_9 of SEQ ID NO: 265 may be maintained and wherein

S_2 is substituted with V, T, R, Q, P, M, K, G, E, D or A, preferably with E, D or A;

F_3 is substituted with any amino acid, preferably with V, I, M, E, D or A;

I_4 is substituted with Y, V, L or F;

D_6 is substituted with E;

L_7 is substituted with Y, V, T, S, M, I, F or A, preferably with V, I or F;

N_{10} is substituted with any amino acid except P, preferably with Y, W, V, T, S, R, Q, M, L, K, I, G, F, E, D, C or A; and/or

K_{11} with V, T, S, M, G, E or A, preferably with T, S, G, E or A.

In some embodiments, the antibody, or the antigen-binding fragment thereof, binds to an amino acid sequence according to SEQ ID NO: 267 or a sequence variant thereof having at least 70% sequence identity, preferably at least 80% sequence identity and more preferably at least 90% sequence identity. In some embodiments, SEQ ID NO: 267 may include one or more (e.g., 1, 2, 3, 4 or 5) mutations, preferably at any one of positions F4, I5, L8, N11 and/or K12 of SEQ ID NO: 267. Even more preferably, the antibody, or the antigen-binding fragment thereof, binds to an amino acid sequence according to SEQ ID NO: 267.

In some embodiments, the antibody, or the antigen-binding fragment thereof, binds to an amino acid sequence according to SEQ ID NO: 266 or a sequence variant thereof having at least 70% or 75% sequence identity, preferably at least 80% or 85% sequence identity and more preferably at least 90% or 95% sequence identity. In some embodiments, SEQ ID NO: 266 may include one or more (e.g., 1, 2, 3, 4 or 5) mutations, preferably at any one of positions F7, I8, L11, N14 and/or K15 of SEQ ID NO: 266.

In some embodiments, the antibody, or the antigen-binding fragment thereof, binds to an amino acid sequence according to one or more of SEQ ID NOs 1 – 7, 268 and 269; or to a sequence variant thereof, as described herein, having at least 66%, preferably at least 73%, more preferably at least 80%, even more preferably at least 86% and still more preferably at least 93% sequence identity. In some embodiments, the sequence variant of SEQ ID NOs 1 – 7, 268 and 269 may include one or more (e.g., 1, 2, 3, 4 or 5) mutations, preferably at any one of positions corresponding to F7, I8, L11, N14 and/or K15 of SEQ ID NO: 1.

Preferably, the antibody, or the antigen-binding fragment thereof, binds to an amino acid sequence according to any one of SEQ ID NOs 1 – 7. An alignment of SEQ ID NOs 1 – 7 is shown in Fig. 3. In particular, the antibody, or the antigen-binding fragment thereof, may bind to an amino acid sequence according to SEQ ID NO: 1 or to a sequence variant thereof having at least 70% sequence identity, preferably at least 80% sequence identity and more preferably at least 90% sequence identity. More preferably, the antibody, or the antigen-binding fragment thereof, binds to an amino acid sequence according to SEQ ID NO: 1.

In some embodiments, the antibody, or the antigen-binding fragment thereof, binds to an amino acid sequence according to SEQ ID NO: 1 and to an amino acid sequence according to SEQ ID NO: 2. Preferably, the antibody, or the antigen-binding fragment thereof, binds to amino acid sequences according to SEQ ID NOs 1, 2, 4 and 5. More preferably, the antibody, or the antigen-binding fragment thereof, binds to amino acid sequences according to according to SEQ ID NOs 1, 2, 3, 4 and 5. Even more preferably, the antibody, or the antigen-binding fragment thereof, binds to each of the amino acid sequences according to SEQ ID NOs 1 – 7. In some embodiments, the antibody, or the antigen-binding fragment thereof, (additionally) binds to an amino acid sequence according to SEQ ID NO: 268 and/or to an amino acid sequence according to SEQ ID NO: 269.

In general, the antibody, or an antigen-binding fragment thereof, according to the present invention, may comprise (at least) three complementarity determining regions (CDRs) on a heavy chain and (at least) three CDRs on a light chain. In general, complementarity determining regions (CDRs) are the hypervariable regions present in heavy chain variable domains and light chain variable domains. Typically, the CDRs of a heavy chain and the connected light chain of an antibody together form the antigen receptor. Usually, the three CDRs (CDR1, CDR2, and CDR3) are arranged non-consecutively in the variable domain. Since antigen receptors are typically composed of two variable domains (on two different polypeptide chains, i.e. heavy and light chain: heavy chain variable region (VH) and light chain variable region (VL)), there are typically six CDRs for each antigen receptor (heavy chain: CDRH1, CDRH2, and CDRH3; light chain: CDRL1, CDRL2, and CDRL3). For example, a classical IgG antibody molecule usually has two antigen receptors and therefore contains twelve CDRs. The CDRs on the heavy and/or light chain may be separated by

framework regions, whereby a framework region (FR) is a region in the variable domain which is less "variable" than the CDR. For example, a variable region (or each variable region, respectively) may be composed of four framework regions, separated by three CDR's.

The sequences of the heavy chains and light chains of exemplary antibodies of the invention, comprising three different CDRs on the heavy chain and three different CDRs on the light chain were determined. The position of the CDR amino acids are defined according to the IMGT numbering system (IMGT: http://www.imgt.org/; cf. Lefranc, M.-P. et al. (2009) Nucleic Acids Res. 37, D1006-D1012).

In some embodiments, the antibody or the antigen-binding fragment thereof comprises (i) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% or 75% sequence identity with the amino acid sequences of SEQ ID NO: 9, SEQ ID NO: 10, and SEQ ID NO: 11, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% or 75% sequence identity with the amino acid sequences of SEQ ID NO: 12, SEQ ID NO: 13 (or 14), and SEQ ID NO: 15, respectively; or (ii) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% or 75% sequence identity with the amino acid sequences of SEQ ID NO: 20, SEQ ID NO: 21, and SEQ ID NO: 22, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% or 75% sequence identity with the amino acid sequences of SEQ ID NO: 12, SEQ ID NO: 23 (or 24), and SEQ ID NO: 25, respectively; or (iii) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% or 75% sequence identity with the amino acid sequences of SEQ ID NO: 207, SEQ ID NO: 208, and SEQ ID NO: 209, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% or 75% sequence identity with the amino acid sequences of SEQ ID NO: 210, SEQ ID NO: 211 (or 212), and SEQ ID NO: 213, respectively; or (iv) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% or 75% sequence identity with the amino acid sequences of SEQ ID NO: 216, SEQ ID NO: 217, and SEQ ID NO: 218, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% or 75% sequence identity with the amino acid sequences of SEQ ID NO: 219, SEQ ID NO: 220 (or 221), and SEQ ID NO: 222, respectively; or (v) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% or 75% sequence identity with the amino acid sequences of SEQ ID NO: 225, SEQ ID NO: 226, and SEQ ID NO: 227, respectively, and light chain CDR1, CDR2, and CDR3

sequences having at least 70% or 75% sequence identity with the amino acid sequences of SEQ ID NO: 228, SEQ ID NO: 229 (or 230), and SEQ ID NO: 231, respectively; or (vi) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% or 75% sequence identity with the amino acid sequences of SEQ ID NO: 234, SEQ ID NO: 235, and SEQ ID NO: 236, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% or 75% sequence identity with the amino acid sequences of SEQ ID NO: 237, SEQ ID NO: 211 (or 238), and SEQ ID NO: 239, respectively; or (vii) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% or 75% sequence identity with the amino acid sequences of SEQ ID NO: 242, SEQ ID NO: 243, and SEQ ID NO: 244, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% or 75% sequence identity with the amino acid sequences of SEQ ID NO: 245, SEQ ID NO: 31 (or 32), and SEQ ID NO: 246, respectively; or (viii) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% or 75% sequence identity with the amino acid sequences of SEQ ID NO: 249, SEQ ID NO: 250, and SEQ ID NO: 251, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% or 75% sequence identity with the amino acid sequences of SEQ ID NO: 252, SEQ ID NO: 253 (or 254), and SEQ ID NO: 255, respectively.

The present invention also provides an antibody, or an antigen-binding fragment thereof, which binds to the coronavirus spike (S) protein, wherein the antibody or the antigen-binding fragment thereof comprises (i) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% or 75% sequence identity with the amino acid sequences of SEQ ID NO: 9, SEQ ID NO: 10, and SEQ ID NO: 11, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% or 75% sequence identity with the amino acid sequences of SEQ ID NO: 12, SEQ ID NO: 13 (or 14), and SEQ ID NO: 15, respectively; or (ii) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% or 75% sequence identity with the amino acid sequences of SEQ ID NO: 20, SEQ ID NO: 21, and SEQ ID NO: 22, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% or 75% sequence identity with the amino acid sequences of SEQ ID NO: 12, SEQ ID NO: 23 (or 24), and SEQ ID NO: 25, respectively; or (iii) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% or 75% sequence identity with the amino acid sequences of SEQ ID NO: 28, SEQ ID NO: 29, and SEQ ID NO: 30, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% or 75% sequence identity with the amino acid sequences of

SEQ ID NO: 12, SEQ ID NO: 31 (or 32), and SEQ ID NO: 33, respectively; or (iv) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% or 75% sequence identity with the amino acid sequences of SEQ ID NO: 36, SEQ ID NO: 37, and SEQ ID NO: 38, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% or 75% sequence identity with the amino acid sequences of SEQ ID NO: 39, SEQ ID NO: 40 (or 41), and SEQ ID NO: 42, respectively; or (v) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% or 75% sequence identity with the amino acid sequences of SEQ ID NO: 45, SEQ ID NO: 46, and SEQ ID NO: 47, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% or 75% sequence identity with the amino acid sequences of SEQ ID NO: 48, SEQ ID NO: 40 (or 49), and SEQ ID NO: 42, respectively; or (vi) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% or 75% sequence identity with the amino acid sequences of SEQ ID NO: 52, SEQ ID NO: 37, and SEQ ID NO: 38, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% or 75% sequence identity with the amino acid sequences of SEQ ID NO: 53, SEQ ID NO: 40 (or 41), and SEQ ID NO: 42, respectively; or (vii) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% or 75% sequence identity with the amino acid sequences of SEQ ID NO: 56, SEQ ID NO: 57, and SEQ ID NO: 58, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% or 75% sequence identity with the amino acid sequences of SEQ ID NO: 59, SEQ ID NO: 60 (or 61), and SEQ ID NO: 62, respectively; or (viii) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% or 75% sequence identity with the amino acid sequences of SEQ ID NO: 65, SEQ ID NO: 66, and SEQ ID NO: 67, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% or 75% sequence identity with the amino acid sequences of SEQ ID NO: 68, SEQ ID NO: 40 (or 69), and SEQ ID NO: 70, respectively; or (ix) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% or 75% sequence identity with the amino acid sequences of SEQ ID NO: 207, SEQ ID NO: 208, and SEQ ID NO: 209, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% or 75% sequence identity with the amino acid sequences of SEQ ID NO: 210, SEQ ID NO: 211 (or 212), and SEQ ID NO: 213, respectively; or (x) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% or 75% sequence identity with the amino acid sequences of SEQ ID NO: 216, SEQ ID NO: 217, and SEQ ID NO: 218, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% or 75% sequence identity with the amino acid sequences of SEQ ID NO: 219, SEQ ID

NO: 220 (or 221), and SEQ ID NO: 222, respectively; or (xi) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% or 75% sequence identity with the amino acid sequences of SEQ ID NO: 225, SEQ ID NO: 226, and SEQ ID NO: 227, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% or 75% sequence identity with the amino acid sequences of SEQ ID NO: 228, SEQ ID NO: 229 (or 230), and SEQ ID NO: 231, respectively; or (xii) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% or 75% sequence identity with the amino acid sequences of SEQ ID NO: 234, SEQ ID NO: 235, and SEQ ID NO: 236, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% or 75% sequence identity with the amino acid sequences of SEQ ID NO: 237, SEQ ID NO: 211 (or 238), and SEQ ID NO: 239, respectively; or (xiii) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% or 75% sequence identity with the amino acid sequences of SEQ ID NO: 242, SEQ ID NO: 243, and SEQ ID NO: 244, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% or 75% sequence identity with the amino acid sequences of SEQ ID NO: 245, SEQ ID NO: 31 (or 32), and SEQ ID NO: 246, respectively; or (xiv) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% or 75% sequence identity with the amino acid sequences of SEQ ID NO: 249, SEQ ID NO: 250, and SEQ ID NO: 251, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% or 75% sequence identity with the amino acid sequences of SEQ ID NO: 252, SEQ ID NO: 253 (or 254), and SEQ ID NO: 255, respectively; or (xv) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% or 75% sequence identity with the amino acid sequences of SEQ ID NO: 258, SEQ ID NO: 259 and SEQ ID NO: 260, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% or 75% sequence identity with the amino acid sequences of SEQ ID NO: 219, SEQ ID NO: 220 (or 221), and SEQ ID NO: 261, respectively.

In some embodiments, the antibody or the antigen-binding fragment thereof comprises (i) heavy chain CDR1, CDR2, and CDR3 sequences having at least 80% or 85% sequence identity with the amino acid sequences of SEQ ID NO: 9, SEQ ID NO: 10, and SEQ ID NO: 11, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 80% or 85% sequence identity with the amino acid sequences of SEQ ID NO: 12, SEQ ID NO: 13 (or 14), and SEQ ID NO: 15, respectively; or (ii) heavy chain CDR1, CDR2, and CDR3 sequences having at least 80% or 85% sequence identity with the amino acid sequences of

SEQ ID NO: 20, SEQ ID NO: 21, and SEQ ID NO: 22, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 80% or 85% sequence identity with the amino acid sequences of SEQ ID NO: 12, SEQ ID NO: 23 (or 24), and SEQ ID NO: 25, respectively; or (iii) heavy chain CDR1, CDR2, and CDR3 sequences having at least 80% or 85% sequence identity with the amino acid sequences of SEQ ID NO: 28, SEQ ID NO: 29, and SEQ ID NO: 30, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 80% or 85% sequence identity with the amino acid sequences of SEQ ID NO: 12, SEQ ID NO: 31 (or 32), and SEQ ID NO: 33, respectively; or (iv) heavy chain CDR1, CDR2, and CDR3 sequences having at least 80% or 85% sequence identity with the amino acid sequences of SEQ ID NO: 36, SEQ ID NO: 37, and SEQ ID NO: 38, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 80% or 85% sequence identity with the amino acid sequences of SEQ ID NO: 39, SEQ ID NO: 40 (or 41), and SEQ ID NO: 42, respectively; or (v) heavy chain CDR1, CDR2, and CDR3 sequences having at least 80% or 85% sequence identity with the amino acid sequences of SEQ ID NO: 45, SEQ ID NO: 46, and SEQ ID NO: 47, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 80% or 85% sequence identity with the amino acid sequences of SEQ ID NO: 48, SEQ ID NO: 40 (or 49), and SEQ ID NO: 42, respectively; or (vi) heavy chain CDR1, CDR2, and CDR3 sequences having at least 80% or 85% sequence identity with the amino acid sequences of SEQ ID NO: 52, SEQ ID NO: 37, and SEQ ID NO: 38, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 80% or 85% sequence identity with the amino acid sequences of SEQ ID NO: 53, SEQ ID NO: 40 (or 41), and SEQ ID NO: 42, respectively; or (vii) heavy chain CDR1, CDR2, and CDR3 sequences having at least 80% or 85% sequence identity with the amino acid sequences of SEQ ID NO: 56, SEQ ID NO: 57, and SEQ ID NO: 58, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 80% or 85% sequence identity with the amino acid sequences of SEQ ID NO: 59, SEQ ID NO: 60 (or 61), and SEQ ID NO: 62, respectively; or (viii) heavy chain CDR1, CDR2, and CDR3 sequences having at least 80% or 85% sequence identity with the amino acid sequences of SEQ ID NO: 65, SEQ ID NO: 66, and SEQ ID NO: 67, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 80% or 85% sequence identity with the amino acid sequences of SEQ ID NO: 68, SEQ ID NO: 40 (or 69), and SEQ ID NO: 70, respectively; or (ix) heavy chain CDR1, CDR2, and CDR3 sequences having at least 80% or 85% sequence identity with the amino acid sequences of SEQ ID NO: 207, SEQ ID NO: 208, and SEQ ID

NO: 209, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 80% or 85% sequence identity with the amino acid sequences of SEQ ID NO: 210, SEQ ID NO: 211 (or 212), and SEQ ID NO: 213, respectively; or (x) heavy chain CDR1, CDR2, and CDR3 sequences having at least 80% or 85% sequence identity with the amino acid sequences of SEQ ID NO: 216, SEQ ID NO: 217, and SEQ ID NO: 218, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 80% or 85% sequence identity with the amino acid sequences of SEQ ID NO: 219, SEQ ID NO: 220 (or 221), and SEQ ID NO: 222, respectively; or (xi) heavy chain CDR1, CDR2, and CDR3 sequences having at least 80% or 85% sequence identity with the amino acid sequences of SEQ ID NO: 225, SEQ ID NO: 226, and SEQ ID NO: 227, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 80% or 85% sequence identity with the amino acid sequences of SEQ ID NO: 228, SEQ ID NO: 229 (or 230), and SEQ ID NO: 231, respectively; or (xii) heavy chain CDR1, CDR2, and CDR3 sequences having at least 80% or 85% sequence identity with the amino acid sequences of SEQ ID NO: 234, SEQ ID NO: 235, and SEQ ID NO: 236, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 80% or 85% sequence identity with the amino acid sequences of SEQ ID NO: 237, SEQ ID NO: 211 (or 238), and SEQ ID NO: 239, respectively; or (xiii) heavy chain CDR1, CDR2, and CDR3 sequences having at least 80% or 85% sequence identity with the amino acid sequences of SEQ ID NO: 242, SEQ ID NO: 243, and SEQ ID NO: 244, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 80% or 85% sequence identity with the amino acid sequences of SEQ ID NO: 245, SEQ ID NO: 31 (or 32), and SEQ ID NO: 246, respectively; or (xiv) heavy chain CDR1, CDR2, and CDR3 sequences having at least 80% or 85% sequence identity with the amino acid sequences of SEQ ID NO: 249, SEQ ID NO: 250, and SEQ ID NO: 251, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 80% or 85% sequence identity with the amino acid sequences of SEQ ID NO: 252, SEQ ID NO: 253 (or 254), and SEQ ID NO: 255, respectively; or (xv) heavy chain CDR1, CDR2, and CDR3 sequences having at least 80% or 85% sequence identity with the amino acid sequences of SEQ ID NO: 258, SEQ ID NO: 259 and SEQ ID NO: 260, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 80% or 85% sequence identity with the amino acid sequences of SEQ ID NO: 219, SEQ ID NO: 220 (or 221), and SEQ ID NO: 261, respectively.

As used throughout the present specification, "sequence identity" is usually calculated with regard to the full length of the reference sequence (i.e. the sequence recited in the application). Percentage identity, as referred to herein, can be determined, for example, by methods known in the art, such as BLAST using the default parameters specified by the NCBI (the National Center for Biotechnology Information; http://www.ncbi.nlm.nih.gov/) [Blosum 62 matrix; gap open penalty=11 and gap extension penalty=1].

A "sequence variant" has an altered sequence in which one or more of the amino acids (or nucleotides) as compared to the respective reference sequence is/are deleted or substituted, and/or one or more amino acids (or nucleotides) is/are inserted into the sequence of the reference amino acid sequence. As a result of the alterations, the amino acid sequence variant has an amino acid sequence which is at least 70% identical to the reference sequence. Variant sequences which are at least 70% identical have no more than 30 alterations, i.e. any combination of deletions, insertions or substitutions, per 100 amino acids of the reference sequence. In general, a (nucleic acid or amino acid) "sequence variant" may have at least 70%, preferably at least 75%, more preferably at least 80%, even more preferably at least 85%, still more preferably at least 90% and particularly preferably at least 95% (such as at least 97% or 98%) sequence identity in comparison to the respective reference sequence (e.g., the sequences according to SEQ ID NOs 1 to 269 as described herein). In general, in a "sequence variant" the functionality of the reference sequence (e.g., in the present case binding to the coronavirus spike protein, for example of various distinct coronaviruses, e.g. alpha- and betacoronaviruses) may be maintained.

In general, while it is possible to have non-conservative amino acid substitutions, the substitutions are usually conservative amino acid substitutions, in which the substituted amino acid has similar structural or chemical properties with the corresponding amino acid in the reference sequence. By way of example, conservative amino acid substitutions involve substitution of one aliphatic or hydrophobic amino acids, e.g. alanine, valine, leucine and isoleucine, with another; substitution of one hydoxyl-containing amino acid, e.g. serine and threonine, with another; substitution of one acidic residue, e.g. glutamic acid or aspartic acid, with another; replacement of one amide-containing residue, e.g. asparagine and glutamine, with another; replacement of one aromatic residue, e.g. phenylalanine and tyrosine, with

another; replacement of one basic residue, e.g. lysine, arginine and histidine, with another; and replacement of one small amino acid, e.g., alanine, serine, threonine, cysteine, and glycine, with another.

Amino acid sequence insertions include amino- and/or carboxyl-terminal fusions ranging in length from one residue to polypeptides containing a hundred or more residues, as well as intrasequence insertions of single or multiple amino acid residues. Examples of terminal insertions include the fusion to the N- or C-terminus of an amino acid sequence to a reporter molecule or an enzyme.

In some embodiments, the antibody, or an antigen-binding fragment thereof, of the present invention may comprise (i) heavy chain CDR1, CDR2, and CDR3 sequences having at least 90% sequence identity (e.g., 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) with the amino acid sequences of SEQ ID NO: 9, SEQ ID NO: 10, and SEQ ID NO: 11, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 90% sequence identity (e.g., 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) with the amino acid sequences of SEQ ID NO: 12, SEQ ID NO: 13 (or 14), and SEQ ID NO: 15, respectively; or (ii) heavy chain CDR1, CDR2, and CDR3 sequences having at least 90% sequence identity (e.g., 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) with the amino acid sequences of SEQ ID NO: 20, SEQ ID NO: 21, and SEQ ID NO: 22, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 90% sequence identity (e.g., 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) with the amino acid sequences of SEQ ID NO: 12, SEQ ID NO: 23 (or 24), and SEQ ID NO: 25, respectively; or (iii) heavy chain CDR1, CDR2, and CDR3 sequences having at least 90% sequence identity (e.g., 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) with the amino acid sequences of SEQ ID NO: 28, SEQ ID NO: 29, and SEQ ID NO: 30, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 90% sequence identity (e.g., 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) with the amino acid sequences of SEQ ID NO: 12, SEQ ID NO: 31 (or 32), and SEQ ID NO: 33, respectively; or (iv) heavy chain CDR1, CDR2, and CDR3 sequences having at least 90% sequence identity (e.g., 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) with the amino acid sequences of SEQ ID NO: 36, SEQ ID NO: 37, and SEQ ID NO: 38,

respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 90% sequence identity (e.g., 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) with the amino acid sequences of SEQ ID NO: 39, SEQ ID NO: 40 (or 41), and SEQ ID NO: 42, respectively; or (v) heavy chain CDR1, CDR2, and CDR3 sequences having at least 90% sequence identity (e.g., 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) with the amino acid sequences of SEQ ID NO: 45, SEQ ID NO: 46, and SEQ ID NO: 47, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 90% sequence identity (e.g., 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) with the amino acid sequences of SEQ ID NO: 48, SEQ ID NO: 40 (or 49), and SEQ ID NO: 42, respectively; or (vi) heavy chain CDR1, CDR2, and CDR3 sequences having at least 90% sequence identity (e.g., 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) with the amino acid sequences of SEQ ID NO: 52, SEQ ID NO: 37, and SEQ ID NO: 38, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 90% sequence identity (e.g., 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) with the amino acid sequences of SEQ ID NO: 53, SEQ ID NO: 40 (or 41), and SEQ ID NO: 42, respectively; or (vii) heavy chain CDR1, CDR2, and CDR3 sequences having at least 90% sequence identity (e.g., 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) with the amino acid sequences of SEQ ID NO: 56, SEQ ID NO: 57, and SEQ ID NO: 58, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 90% sequence identity (e.g., 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) with the amino acid sequences of SEQ ID NO: 59, SEQ ID NO: 60 (or 61), and SEQ ID NO: 62, respectively; or (viii) heavy chain CDR1, CDR2, and CDR3 sequences having at least 90% sequence identity (e.g., 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) with the amino acid sequences of SEQ ID NO: 65, SEQ ID NO: 66, and SEQ ID NO: 67, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 90% sequence identity (e.g., 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) with the amino acid sequences of SEQ ID NO: 68, SEQ ID NO: 40 (or 69), and SEQ ID NO: 70, respectively; or (ix) heavy chain CDR1, CDR2, and CDR3 sequences having at least 90% sequence identity (e.g., 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) with the amino acid sequences of SEQ ID NO: 207, SEQ ID NO: 208, and SEQ ID NO: 209, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 90% sequence identity (e.g., 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) with

the amino acid sequences of SEQ ID NO: 210, SEQ ID NO: 211 (or 212), and SEQ ID NO: 213, respectively; or (x) heavy chain CDR1, CDR2, and CDR3 sequences having at least 90% sequence identity (e.g., 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) with the amino acid sequences of SEQ ID NO: 216, SEQ ID NO: 217, and SEQ ID NO: 218, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 90% sequence identity (e.g., 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) with the amino acid sequences of SEQ ID NO: 219, SEQ ID NO: 220 (or 221), and SEQ ID NO: 222, respectively; or (xi) heavy chain CDR1, CDR2, and CDR3 sequences having at least 90% sequence identity (e.g., 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) with the amino acid sequences of SEQ ID NO: 225, SEQ ID NO: 226, and SEQ ID NO: 227, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 90% sequence identity (e.g., 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) with the amino acid sequences of SEQ ID NO: 228, SEQ ID NO: 229 (or 230), and SEQ ID NO: 231, respectively; or (xii) heavy chain CDR1, CDR2, and CDR3 sequences having at least 90% sequence identity (e.g., 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) with the amino acid sequences of SEQ ID NO: 234, SEQ ID NO: 235, and SEQ ID NO: 236, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 90% sequence identity (e.g., 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) with the amino acid sequences of SEQ ID NO: 237, SEQ ID NO: 211 (or 238), and SEQ ID NO: 239, respectively; or (xiii) heavy chain CDR1, CDR2, and CDR3 sequences having at least 90% sequence identity (e.g., 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) with the amino acid sequences of SEQ ID NO: 242, SEQ ID NO: 243, and SEQ ID NO: 244, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 90% sequence identity (e.g., 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) with the amino acid sequences of SEQ ID NO: 245, SEQ ID NO: 31 (or 32), and SEQ ID NO: 246, respectively; or (xiv) heavy chain CDR1, CDR2, and CDR3 sequences having at least 90% sequence identity (e.g., 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) with the amino acid sequences of SEQ ID NO: 249, SEQ ID NO: 250, and SEQ ID NO: 251, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 90% sequence identity (e.g., 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) with the amino acid sequences of SEQ ID NO: 252, SEQ ID NO: 253 (or 254), and SEQ ID NO: 255, respectively; or (xv) heavy chain CDR1, CDR2, and CDR3 sequences having at least

90% sequence identity (e.g., 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) with the amino acid sequences of SEQ ID NO: 258, SEQ ID NO: 259 and SEQ ID NO: 260, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 90% sequence identity (e.g., 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) with the amino acid sequences of SEQ ID NO: 219, SEQ ID NO: 220 (or 221), and SEQ ID NO: 261, respectively.

Preferably, the antibody or the antigen-binding fragment thereof comprises (i) heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 9, SEQ ID NO: 10, and SEQ ID NO: 11, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 12, SEQ ID NO: 13 (or 14), and SEQ ID NO: 15, respectively; or (ii) heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 20, SEQ ID NO: 21, and SEQ ID NO: 22, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 12, SEQ ID NO: 23 (or 24), and SEQ ID NO: 25, respectively; or (iii) heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 28, SEQ ID NO: 29, and SEQ ID NO: 30, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 12, SEQ ID NO: 31 (or 32), and SEQ ID NO: 33, respectively; or (iv) heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 36, SEQ ID NO: 37, and SEQ ID NO: 38, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 39, SEQ ID NO: 40 (or 41), and SEQ ID NO: 42, respectively; or (v) heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 45, SEQ ID NO: 46, and SEQ ID NO: 47, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 48, SEQ ID NO: 40 (or 49), and SEQ ID NO: 42, respectively; or (vi) heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 52, SEQ ID NO: 37, and SEQ ID NO: 38, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 53, SEQ ID NO: 40 (or 41), and SEQ ID NO: 42, respectively; or (vii) heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 56, SEQ ID NO: 57, and SEQ ID NO: 58, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 59, SEQ ID NO: 60 (or 61), and SEQ ID NO: 62, respectively; or (viii) heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 65, SEQ ID NO: 66, and SEQ ID NO: 67, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 68, SEQ ID NO: 40 (or 69), and SEQ ID NO: 70,

respectively; or (ix) heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 207, SEQ ID NO: 208, and SEQ ID NO: 209, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 210, SEQ ID NO: 211 (or 212), and SEQ ID NO: 213, respectively; or (x) heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 216, SEQ ID NO: 217, and SEQ ID NO: 218, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 219, SEQ ID NO: 220 (or 221), and SEQ ID NO: 222, respectively; or (xi) heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 225, SEQ ID NO: 226, and SEQ ID NO: 227, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 228, SEQ ID NO: 229 (or 230), and SEQ ID NO: 231, respectively; or (xii) heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 234, SEQ ID NO: 235, and SEQ ID NO: 236, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 237, SEQ ID NO: 211 (or 238), and SEQ ID NO: 239, respectively; or (xiii) heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 242, SEQ ID NO: 243, and SEQ ID NO: 244, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 245, SEQ ID NO: 31 (or 32), and SEQ ID NO: 246, respectively; or (xiv) heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 249, SEQ ID NO: 250, and SEQ ID NO: 251, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 252, SEQ ID NO: 253 (or 254), and SEQ ID NO: 255, respectively; or (xv) heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 258, SEQ ID NO: 259 and SEQ ID NO: 260, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 219, SEQ ID NO: 220 (or 221), and SEQ ID NO: 261, respectively.

Preferably, the antibody or the antigen-binding fragment thereof comprises heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 9 (CDRH1), SEQ ID NO: 10 (CDRH2), and SEQ ID NO: 11 (CDRH3), respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 12 (CDRL1), SEQ ID NO: 13 or 14 (CDRL2), and SEQ ID NO: 15 (CDRL3), respectively.

It is also preferred that the antibody or the antigen-binding fragment thereof comprises heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 20 (CDRH1), SEQ ID

NO: 21 (CDRH2), and SEQ ID NO: 22 (CDRH3), respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 12 (CDRL1), SEQ ID NO: 23 or 24 (CDRL2), and SEQ ID NO: 25 (CDRL3), respectively.

In some embodiments, the antibody or the antigen-binding fragment thereof comprises heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 28 (CDRH1), SEQ ID NO: 29 (CDRH2), and SEQ ID NO: 30 (CDRH3), respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 12 (CDRL1), SEQ ID NO: 31 or 32 (CDRL2), and SEQ ID NO: 33 (CDRL3), respectively.

In some embodiments, the antibody or the antigen-binding fragment thereof comprises heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 36 (CDRH1), SEQ ID NO: 37 (CDRH2), and SEQ ID NO: 38 (CDRH3), respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 39 (CDRL1), SEQ ID NO: 40 or 41 (CDRL2), and SEQ ID NO: 42 (CDRL3), respectively.

In some embodiments, the antibody or the antigen-binding fragment thereof comprises heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 45 (CDRH1), SEQ ID NO: 46 (CDRH2), and SEQ ID NO: 47 (CDRH3), respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 48 (CDRL1), SEQ ID NO: 40 or 49 (CDRL2), and SEQ ID NO: 42 (CDRL3), respectively.

In some embodiments, the antibody or the antigen-binding fragment thereof comprises heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 52 (CDRH1), SEQ ID NO: 37 (CDRH2), and SEQ ID NO: 38 (CDRH3), respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 53 (CDRL1), SEQ ID NO: 40 or 41 (CDRL2), and SEQ ID NO: 42 (CDRL3), respectively.

In some embodiments, the antibody or the antigen-binding fragment thereof comprises heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 56 (CDRH1), SEQ ID NO: 57 (CDRH2), and SEQ ID NO: 58 (CDRH3), respectively, and light chain CDR1, CDR2,

and CDR3 sequences according to SEQ ID NO: 59 (CDRL1), SEQ ID NO: 60 or 61 (CDRL2), and SEQ ID NO: 62 (CDRL3), respectively.

In some embodiments, the antibody or the antigen-binding fragment thereof comprises heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 65 (CDRH1), SEQ ID NO: 66 (CDRH2), and SEQ ID NO: 67 (CDRH3), respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 68 (CDRL1), SEQ ID NO: 40 or 69 (CDRL2), and SEQ ID NO: 70 (CDRL3), respectively.

Preferably, the antibody or the antigen-binding fragment thereof comprises heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 207 (CDRH1), SEQ ID NO: 208 (CDRH2), and SEQ ID NO: 209 (CDRH3), respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 210 (CDRL1), SEQ ID NO: 211 or 212 (CDRL2), and SEQ ID NO: 213 (CDRL3), respectively.

It is also preferred that the antibody or the antigen-binding fragment thereof comprises heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 216 (CDRH1), SEQ ID NO: 217 (CDRH2), and SEQ ID NO: 218 (CDRH3), respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 219 (CDRL1), SEQ ID NO: 220 or 221 (CDRL2), and SEQ ID NO: 222 (CDRL3), respectively.

It is also preferred that the antibody or the antigen-binding fragment thereof comprises heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 225 (CDRH1), SEQ ID NO: 226 (CDRH2), and SEQ ID NO: 227 (CDRH3), respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 228 (CDRL1), SEQ ID NO: 229 or 230 (CDRL2), and SEQ ID NO: 231 (CDRL3), respectively.

It is also preferred that the antibody or the antigen-binding fragment thereof comprises heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 234 (CDRH1), SEQ ID NO: 235 (CDRH2), and SEQ ID NO: 236 (CDRH3), respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 237 (CDRL1), SEQ ID NO: 211 or 238 (CDRL2), and SEQ ID NO: 239 (CDRL3), respectively.

It is also preferred that the antibody or the antigen-binding fragment thereof comprises heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 242 (CDRH1), SEQ ID NO: 243 (CDRH2), and SEQ ID NO: 244 (CDRH3), respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 245 (CDRL1), SEQ ID NO: 31 or 32 (CDRL2), and SEQ ID NO: 246 (CDRL3), respectively.

It is also preferred that the antibody or the antigen-binding fragment thereof comprises heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 249 (CDRH1), SEQ ID NO: 250 (CDRH2), and SEQ ID NO: 251 (CDRH3), respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 252 (CDRL1), SEQ ID NO: 253 or 254 (CDRL2), and SEQ ID NO: 255 (CDRL3), respectively.

In some embodiments, the antibody or the antigen-binding fragment thereof comprises heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 258 (CDRH1), SEQ ID NO: 259 (CDRH2) and SEQ ID NO: 260 (CDRH3), respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 219 (CDRL1), SEQ ID NO: 220 or 221 (CDRL2), and SEQ ID NO: 261 (CDRL3), respectively.

The antibody or the antigen-binding fragment thereof may comprise (i) a heavy chain variable region comprising an amino acid sequence having at least 70% or 75% identity to SEQ ID NO: 16 and a light chain variable region comprising an amino acid sequence having at least 70% or 75% identity to SEQ ID NO: 17; or (ii) a heavy chain variable region comprising an amino acid sequence having at least 70% or 75% identity to SEQ ID NO: 18 and a light chain variable region comprising an amino acid sequence having at least 70% or 75% identity to SEQ ID NO: 19; or (iii) a heavy chain variable region comprising an amino acid sequence having at least 70% or 75% identity to SEQ ID NO: 26 and a light chain variable region comprising an amino acid sequence having at least 70% or 75% identity to SEQ ID NO: 27; or (iv) a heavy chain variable region comprising an amino acid sequence having at least 70% or 75% identity to SEQ ID NO: 34 and a light chain variable region comprising an amino acid sequence having at least 70% or 75% identity to SEQ ID NO: 35; or (v) a heavy chain variable region comprising an amino acid sequence having at least 70% or 75% identity to

SEQ ID NO: 43 and a light chain variable region comprising an amino acid sequence having at least 70% or 75% identity to SEQ ID NO: 44; or (vi) a heavy chain variable region comprising an amino acid sequence having at least 70% or 75% identity to SEQ ID NO: 50 and a light chain variable region comprising an amino acid sequence having at least 70% or 75% identity to SEQ ID NO: 51; or (vii) a heavy chain variable region comprising an amino acid sequence having at least 70% or 75% identity to SEQ ID NO: 54 and a light chain variable region comprising an amino acid sequence having at least 70% or 75% identity to SEQ ID NO: 55; or (viii) a heavy chain variable region comprising an amino acid sequence having at least 70% or 75% identity to SEQ ID NO: 63 and a light chain variable region comprising an amino acid sequence having at least 70% or 75% identity to SEQ ID NO: 64; or (ix) a heavy chain variable region comprising an amino acid sequence having at least 70% or 75% identity to SEQ ID NO: 71 and a light chain variable region comprising an amino acid sequence having at least 70% or 75% identity to SEQ ID NO: 72; or (x) a heavy chain variable region comprising an amino acid sequence having at least 70% or 75% identity to SEQ ID NO: 214 and a light chain variable region comprising an amino acid sequence having at least 70% or 75% identity to SEQ ID NO: 215; or (xi) a heavy chain variable region comprising an amino acid sequence having at least 70% or 75% identity to SEQ ID NO: 223 and a light chain variable region comprising an amino acid sequence having at least 70% or 75% identity to SEQ ID NO: 224; or (xii) a heavy chain variable region comprising an amino acid sequence having at least 70% or 75% identity to SEQ ID NO: 232 and a light chain variable region comprising an amino acid sequence having at least 70% or 75% identity to SEQ ID NO: 233; or (xiii) a heavy chain variable region comprising an amino acid sequence having at least 70% or 75% identity to SEQ ID NO: 240 and a light chain variable region comprising an amino acid sequence having at least 70% or 75% identity to SEQ ID NO: 241; or (xiv) a heavy chain variable region comprising an amino acid sequence having at least 70% or 75% identity to SEQ ID NO: 247 and a light chain variable region comprising an amino acid sequence having at least 70% or 75% identity to SEQ ID NO: 248; or (xv) a heavy chain variable region comprising an amino acid sequence having at least 70% or 75% identity to SEQ ID NO: 256 and a light chain variable region comprising an amino acid sequence having at least 70% or 75% identity to SEQ ID NO: 257; or (xvi) a heavy chain variable region comprising an amino acid sequence having at least 70% or 75% identity to

SEQ ID NO: 262 and a light chain variable region comprising an amino acid sequence having at least 70% or 75% identity to SEQ ID NO: 263.

Preferably, the antibody of the invention, or the antigen-binding fragment thereof, comprises (i) a heavy chain variable region (VH) comprising an amino acid sequence having 70% or more (e.g., 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 16 and a light chain variable region (VL) comprising the amino acid sequence having 70% or more (e.g., 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 17. Thereby, the CDR sequences as defined above (heavy chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 9, SEQ ID NO: 10, and SEQ ID NO: 11, respectively; and light chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 12, SEQ ID NO: 13 (or 14), and SEQ ID NO: 15, respectively) may be maintained.

It is also preferred that the antibody of the invention, or the antigen-binding fragment thereof, comprises (i) a heavy chain variable region (VH) comprising an amino acid sequence having 70% or more (e.g., 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 18 and a light chain variable region (VL) comprising the amino acid sequence having 70% or more (e.g., 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 19. Thereby, the CDR sequences as defined above (heavy chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 9, SEQ ID NO: 10, and SEQ ID NO: 11, respectively; and light chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 12, SEQ ID NO: 13 (or 14), and SEQ ID NO: 15, respectively) may be maintained.

In some embodiments, the antibody of the invention, or the antigen-binding fragment thereof, comprises (i) a heavy chain variable region (VH) comprising an amino acid sequence having 70% or more (e.g., 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%,

83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 26 and a light chain variable region (VL) comprising the amino acid sequence having 70% or more (e.g., 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 27. Thereby, the CDR sequences as defined above (heavy chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 20, SEQ ID NO: 21, and SEQ ID NO: 22, respectively; and light chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 12, SEQ ID NO: 23 (or 24), and SEQ ID NO: 25, respectively) may be maintained.

In some embodiments, the antibody of the invention, or the antigen-binding fragment thereof, comprises (i) a heavy chain variable region (VH) comprising an amino acid sequence having 70% or more (e.g., 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 34 and a light chain variable region (VL) comprising the amino acid sequence having 70% or more (e.g., 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 35. Thereby, the CDR sequences as defined above (heavy chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 28, SEQ ID NO: 29, and SEQ ID NO: 30, respectively; and light chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 12, SEQ ID NO: 31 (or 32), and SEQ ID NO: 33, respectively) may be maintained.

In some embodiments, the antibody of the invention, or the antigen-binding fragment thereof, comprises (i) a heavy chain variable region (VH) comprising an amino acid sequence having 70% or more (e.g., 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 43 and a light chain variable region (VL) comprising the amino acid sequence having 70% or more (e.g., 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 44. Thereby, the CDR sequences as defined above (heavy chain CDR1, CDR2, and CDR3

sequences as set forth in SEQ ID NO: 36, SEQ ID NO: 37, and SEQ ID NO: 38, respectively; and light chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 39, SEQ ID NO: 40 (or 41), and SEQ ID NO: 42, respectively) may be maintained.

In some embodiments, the antibody of the invention, or the antigen-binding fragment thereof, comprises (i) a heavy chain variable region (VH) comprising an amino acid sequence having 70% or more (e.g., 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 50 and a light chain variable region (VL) comprising the amino acid sequence having 70% or more (e.g., 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 51. Thereby, the CDR sequences as defined above (heavy chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 45, SEQ ID NO: 46, and SEQ ID NO: 47, respectively; and light chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 48, SEQ ID NO: 40 (or 49), and SEQ ID NO: 42, respectively) may be maintained.

In some embodiments, the antibody of the invention, or the antigen-binding fragment thereof, comprises (i) a heavy chain variable region (VH) comprising an amino acid sequence having 70% or more (e.g., 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 54 and a light chain variable region (VL) comprising the amino acid sequence having 70% or more (e.g., 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 55. Thereby, the CDR sequences as defined above (heavy chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 52, SEQ ID NO: 37, and SEQ ID NO: 38, respectively; and light chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 53, SEQ ID NO: 40 (or 41), and SEQ ID NO: 42, respectively) may be maintained.

In some embodiments, the antibody of the invention, or the antigen-binding fragment thereof, comprises (i) a heavy chain variable region (VH) comprising an amino acid sequence having

70% or more (e.g., 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 63 and a light chain variable region (VL) comprising the amino acid sequence having 70% or more (e.g., 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 64. Thereby, the CDR sequences as defined above (heavy chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 56, SEQ ID NO: 57, and SEQ ID NO: 58, respectively; and light chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 59, SEQ ID NO: 60 (or 61), and SEQ ID NO: 62, respectively) may be maintained.

In some embodiments, the antibody of the invention, or the antigen-binding fragment thereof, comprises (i) a heavy chain variable region (VH) comprising an amino acid sequence having 70% or more (e.g., 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 71 and a light chain variable region (VL) comprising the amino acid sequence having 70% or more (e.g., 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 72. Thereby, the CDR sequences as defined above (heavy chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 65, SEQ ID NO: 66, and SEQ ID NO: 67, respectively; and light chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 68, SEQ ID NO: 40 (or 69), and SEQ ID NO: 70, respectively) may be maintained.

Preferably, the antibody of the invention, or the antigen-binding fragment thereof, comprises (i) a heavy chain variable region (VH) comprising an amino acid sequence having 70% or more (e.g., 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 214 and a light chain variable region (VL) comprising the amino acid sequence having 70% or more (e.g., 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 215. Thereby, the CDR

sequences as defined above (heavy chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 207, SEQ ID NO: 208, and SEQ ID NO: 209, respectively; and light chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 210, SEQ ID NO: 211 (or 212), and SEQ ID NO: 213, respectively) may be maintained.

It is also preferred that the antibody of the invention, or the antigen-binding fragment thereof, comprises (i) a heavy chain variable region (VH) comprising an amino acid sequence having 70% or more (e.g., 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 223 and a light chain variable region (VL) comprising the amino acid sequence having 70% or more (e.g., 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 224. Thereby, the CDR sequences as defined above (heavy chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 216, SEQ ID NO: 217, and SEQ ID NO: 218, respectively; and light chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 219, SEQ ID NO: 220 (or 221), and SEQ ID NO: 222, respectively) may be maintained.

It is also preferred that the antibody of the invention, or the antigen-binding fragment thereof, comprises (i) a heavy chain variable region (VH) comprising an amino acid sequence having 70% or more (e.g., 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 232 and a light chain variable region (VL) comprising the amino acid sequence having 70% or more (e.g., 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 233. Thereby, the CDR sequences as defined above (heavy chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 225, SEQ ID NO: 226, and SEQ ID NO: 227, respectively; and light chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 228, SEQ ID NO: 229 (or 230), and SEQ ID NO: 231, respectively) may be maintained.

It is also preferred that the antibody of the invention, or the antigen-binding fragment thereof, comprises (i) a heavy chain variable region (VH) comprising an amino acid sequence having 70% or more (e.g., 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 240 and a light chain variable region (VL) comprising the amino acid sequence having 70% or more (e.g., 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 241. Thereby, the CDR sequences as defined above (heavy chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 234, SEQ ID NO: 235, and SEQ ID NO: 236, respectively; and light chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 237, SEQ ID NO: 211 (or 238), and SEQ ID NO: 239, respectively) may be maintained.

It is also preferred that the antibody of the invention, or the antigen-binding fragment thereof, comprises (i) a heavy chain variable region (VH) comprising an amino acid sequence having 70% or more (e.g., 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 247 and a light chain variable region (VL) comprising the amino acid sequence having 70% or more (e.g., 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 248. Thereby, the CDR sequences as defined above (heavy chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 242, SEQ ID NO: 243, and SEQ ID NO: 244, respectively; and light chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 245, SEQ ID NO: 31 (or 32), and SEQ ID NO: 246, respectively) may be maintained.

It is also preferred that the antibody of the invention, or the antigen-binding fragment thereof, comprises (i) a heavy chain variable region (VH) comprising an amino acid sequence having 70% or more (e.g., 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 256 and a light chain variable region (VL) comprising the amino acid sequence having 70% or more (e.g., 71%, 72%, 73%, 74%, 75%,

76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 257. Thereby, the CDR sequences as defined above (heavy chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 249, SEQ ID NO: 250, and SEQ ID NO: 251, respectively; and light chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 252, SEQ ID NO: 253 (or 254), and SEQ ID NO: 255, respectively) may be maintained.

In some embodiments, the antibody of the invention, or the antigen-binding fragment thereof, comprises (i) a heavy chain variable region (VH) comprising an amino acid sequence having 70% or more (e.g., 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 262 and a light chain variable region (VL) comprising the amino acid sequence having 70% or more (e.g., 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 263. Thereby, the CDR sequences as defined above (heavy chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 258, SEQ ID NO: 259, and SEQ ID NO: 260, respectively; and light chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 219, SEQ ID NO: 220 (or 221), and SEQ ID NO: 261, respectively) may be maintained.

Preferably, the antibody of the invention, or the antigen-binding fragment thereof, comprises (i) a heavy chain variable region (VH) comprising an amino acid sequence having 75% or more (e.g., 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 16 and a light chain variable region (VL) comprising the amino acid sequence having 75% or more (e.g., 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 17. Thereby, the CDR sequences as defined above (heavy chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 9, SEQ ID NO: 10, and SEQ ID NO: 11, respectively; and light chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 12, SEQ ID NO: 13 (or 14), and SEQ ID NO: 15, respectively) may be maintained.

It is also preferred that the antibody of the invention, or the antigen-binding fragment thereof, comprises (i) a heavy chain variable region (VH) comprising an amino acid sequence having 75% or more (e.g., 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 18 and a light chain variable region (VL) comprising the amino acid sequence having 75% or more (e.g., 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 19. Thereby, the CDR sequences as defined above (heavy chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 9, SEQ ID NO: 10, and SEQ ID NO: 11, respectively; and light chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 12, SEQ ID NO: 13 (or 14), and SEQ ID NO: 15, respectively) may be maintained.

In some embodiments, the antibody of the invention, or the antigen-binding fragment thereof, comprises (i) a heavy chain variable region (VH) comprising an amino acid sequence having 75% or more (e.g., 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 26 and a light chain variable region (VL) comprising the amino acid sequence having 75% or more (e.g., 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 27. Thereby, the CDR sequences as defined above (heavy chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 20, SEQ ID NO: 21, and SEQ ID NO: 22, respectively; and light chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 12, SEQ ID NO: 23 (or 24), and SEQ ID NO: 25, respectively) may be maintained.

In some embodiments, the antibody of the invention, or the antigen-binding fragment thereof, comprises (i) a heavy chain variable region (VH) comprising an amino acid sequence having 75% or more (e.g., 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 34 and a light chain variable region (VL) comprising the amino acid sequence having 75% or more (e.g., 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 35. Thereby, the CDR sequences as defined above (heavy chain CDR1, CDR2,

and CDR3 sequences as set forth in SEQ ID NO: 28, SEQ ID NO: 29, and SEQ ID NO: 30, respectively; and light chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 12, SEQ ID NO: 31 (or 32), and SEQ ID NO: 33, respectively) may be maintained.

In some embodiments, the antibody of the invention, or the antigen-binding fragment thereof, comprises (i) a heavy chain variable region (VH) comprising an amino acid sequence having 75% or more (e.g., 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 43 and a light chain variable region (VL) comprising the amino acid sequence having 75% or more (e.g., 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 44. Thereby, the CDR sequences as defined above (heavy chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 36, SEQ ID NO: 37, and SEQ ID NO: 38, respectively; and light chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 39, SEQ ID NO: 40 (or 41), and SEQ ID NO: 42, respectively) may be maintained.

In some embodiments, the antibody of the invention, or the antigen-binding fragment thereof, comprises (i) a heavy chain variable region (VH) comprising an amino acid sequence having 75% or more (e.g., 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 50 and a light chain variable region (VL) comprising the amino acid sequence having 75% or more (e.g., 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 51. Thereby, the CDR sequences as defined above (heavy chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 45, SEQ ID NO: 46, and SEQ ID NO: 47, respectively; and light chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 48, SEQ ID NO: 40 (or 49), and SEQ ID NO: 42, respectively) may be maintained.

In some embodiments, the antibody of the invention, or the antigen-binding fragment thereof, comprises (i) a heavy chain variable region (VH) comprising an amino acid sequence having 75% or more (e.g., 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to

SEQ ID NO: 54 and a light chain variable region (VL) comprising the amino acid sequence having 75% or more (e.g., 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 55. Thereby, the CDR sequences as defined above (heavy chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 52, SEQ ID NO: 37, and SEQ ID NO: 38, respectively; and light chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 53, SEQ ID NO: 40 (or 41), and SEQ ID NO: 42, respectively) may be maintained.

In some embodiments, the antibody of the invention, or the antigen-binding fragment thereof, comprises (i) a heavy chain variable region (VH) comprising an amino acid sequence having 75% or more (e.g., 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 63 and a light chain variable region (VL) comprising the amino acid sequence having 75% or more (e.g., 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 64. Thereby, the CDR sequences as defined above (heavy chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 56, SEQ ID NO: 57, and SEQ ID NO: 58, respectively; and light chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 59, SEQ ID NO: 60 (or 61), and SEQ ID NO: 62, respectively) may be maintained.

In some embodiments, the antibody of the invention, or the antigen-binding fragment thereof, comprises (i) a heavy chain variable region (VH) comprising an amino acid sequence having 75% or more (e.g., 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 71 and a light chain variable region (VL) comprising the amino acid sequence having 75% or more (e.g., 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 72. Thereby, the CDR sequences as defined above (heavy chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 65, SEQ ID NO: 66, and SEQ ID NO: 67, respectively; and light chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 68, SEQ ID NO: 40 (or 69), and SEQ ID NO: 70, respectively) may be maintained.

Preferably, the antibody of the invention, or the antigen-binding fragment thereof, comprises (i) a heavy chain variable region (VH) comprising an amino acid sequence having 75% or more (e.g., 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 214 and a light chain variable region (VL) comprising the amino acid sequence having 75% or more (e.g., 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 215. Thereby, the CDR sequences as defined above (heavy chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 207, SEQ ID NO: 208, and SEQ ID NO: 209, respectively; and light chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 210, SEQ ID NO: 211 (or 212), and SEQ ID NO: 213, respectively) may be maintained.

It is also preferred that the antibody of the invention, or the antigen-binding fragment thereof, comprises (i) a heavy chain variable region (VH) comprising an amino acid sequence having 75% or more (e.g., 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 223 and a light chain variable region (VL) comprising the amino acid sequence having 75% or more (e.g., 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 224. Thereby, the CDR sequences as defined above (heavy chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 216, SEQ ID NO: 217, and SEQ ID NO: 218, respectively; and light chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 219, SEQ ID NO: 220 (or 221), and SEQ ID NO: 222, respectively) may be maintained.

It is also preferred that the antibody of the invention, or the antigen-binding fragment thereof, comprises (i) a heavy chain variable region (VH) comprising an amino acid sequence having 75% or more (e.g., 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 232 and a light chain variable region (VL) comprising the amino acid sequence having 75% or more (e.g., 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity

to SEQ ID NO: 233. Thereby, the CDR sequences as defined above (heavy chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 225, SEQ ID NO: 226, and SEQ ID NO: 227, respectively; and light chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 228, SEQ ID NO: 229 (or 230), and SEQ ID NO: 231, respectively) may be maintained.

It is also preferred that the antibody of the invention, or the antigen-binding fragment thereof, comprises (i) a heavy chain variable region (VH) comprising an amino acid sequence having 75% or more (e.g., 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 240 and a light chain variable region (VL) comprising the amino acid sequence having 75% or more (e.g., 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 241. Thereby, the CDR sequences as defined above (heavy chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 234, SEQ ID NO: 235, and SEQ ID NO: 236, respectively; and light chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 237, SEQ ID NO: 211 (or 238), and SEQ ID NO: 239, respectively) may be maintained.

It is also preferred that the antibody of the invention, or the antigen-binding fragment thereof, comprises (i) a heavy chain variable region (VH) comprising an amino acid sequence having 75% or more (e.g., 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 247 and a light chain variable region (VL) comprising the amino acid sequence having 75% or more (e.g., 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 248. Thereby, the CDR sequences as defined above (heavy chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 242, SEQ ID NO: 243, and SEQ ID NO: 244, respectively; and light chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 245, SEQ ID NO: 31 (or 32), and SEQ ID NO: 246, respectively) may be maintained.

It is also preferred that the antibody of the invention, or the antigen-binding fragment thereof, comprises (i) a heavy chain variable region (VH) comprising an amino acid sequence having 75% or more (e.g., 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 256 and a light chain variable region (VL) comprising the amino acid sequence having 75% or more (e.g., 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 257. Thereby, the CDR sequences as defined above (heavy chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 249, SEQ ID NO: 250, and SEQ ID NO: 251, respectively; and light chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 252, SEQ ID NO: 253 (or 254), and SEQ ID NO: 255, respectively) may be maintained.

In some embodiments, the antibody of the invention, or the antigen-binding fragment thereof, comprises (i) a heavy chain variable region (VH) comprising an amino acid sequence having 75% or more (e.g., 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 262 and a light chain variable region (VL) comprising the amino acid sequence having 75% or more (e.g., 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 263. Thereby, the CDR sequences as defined above (heavy chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 258, SEQ ID NO: 259, and SEQ ID NO: 260, respectively; and light chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 219, SEQ ID NO: 220 (or 221), and SEQ ID NO: 261, respectively) may be maintained.

Preferably, the antibody of the invention, or the antigen-binding fragment thereof, comprises (i) a heavy chain variable region (VH) comprising an amino acid sequence having 80% or more (e.g., 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 16 and a light chain variable region (VL) comprising the amino acid sequence having 80% or more (e.g., 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%

or more) identity to SEQ ID NO: 17. Thereby, the CDR sequences as defined above (heavy chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 9, SEQ ID NO: 10, and SEQ ID NO: 11, respectively; and light chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 12, SEQ ID NO: 13 (or 14), and SEQ ID NO: 15, respectively) may be maintained.

It is also preferred that the antibody of the invention, or the antigen-binding fragment thereof, comprises (i) a heavy chain variable region (VH) comprising an amino acid sequence having 80% or more (e.g., 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 18 and a light chain variable region (VL) comprising the amino acid sequence having 80% or more (e.g., 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 19. Thereby, the CDR sequences as defined above (heavy chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 9, SEQ ID NO: 10, and SEQ ID NO: 11, respectively; and light chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 12, SEQ ID NO: 13 (or 14), and SEQ ID NO: 15, respectively) may be maintained.

In some embodiments, the antibody of the invention, or the antigen-binding fragment thereof, comprises (i) a heavy chain variable region (VH) comprising an amino acid sequence having 80% or more (e.g., 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 26 and a light chain variable region (VL) comprising the amino acid sequence having 80% or more (e.g., 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 27. Thereby, the CDR sequences as defined above (heavy chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 20, SEQ ID NO: 21, and SEQ ID NO: 22, respectively; and light chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 12, SEQ ID NO: 23 (or 24), and SEQ ID NO: 25, respectively) may be maintained.

In some embodiments, the antibody of the invention, or the antigen-binding fragment thereof, comprises (i) a heavy chain variable region (VH) comprising an amino acid sequence having

80% or more (e.g., 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 34 and a light chain variable region (VL) comprising the amino acid sequence having 80% or more (e.g., 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 35. Thereby, the CDR sequences as defined above (heavy chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 28, SEQ ID NO: 29, and SEQ ID NO: 30, respectively; and light chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 12, SEQ ID NO: 31 (or 32), and SEQ ID NO: 33, respectively) may be maintained.

In some embodiments, the antibody of the invention, or the antigen-binding fragment thereof, comprises (i) a heavy chain variable region (VH) comprising an amino acid sequence having 80% or more (e.g., 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 43 and a light chain variable region (VL) comprising the amino acid sequence having 80% or more (e.g., 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 44. Thereby, the CDR sequences as defined above (heavy chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 36, SEQ ID NO: 37, and SEQ ID NO: 38, respectively; and light chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 39, SEQ ID NO: 40 (or 41), and SEQ ID NO: 42, respectively) may be maintained.

In some embodiments, the antibody of the invention, or the antigen-binding fragment thereof, comprises (i) a heavy chain variable region (VH) comprising an amino acid sequence having 80% or more (e.g., 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 50 and a light chain variable region (VL) comprising the amino acid sequence having 80% or more (e.g., 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 51. Thereby, the CDR sequences as defined above (heavy chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 45, SEQ ID NO: 46, and SEQ ID NO: 47, respectively; and light chain CDR1, CDR2, and

CDR3 sequences as set forth in SEQ ID NO: 48, SEQ ID NO: 40 (or 49), and SEQ ID NO: 42, respectively) may be maintained.

In some embodiments, the antibody of the invention, or the antigen-binding fragment thereof, comprises (i) a heavy chain variable region (VH) comprising an amino acid sequence having 80% or more (e.g., 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 54 and a light chain variable region (VL) comprising the amino acid sequence having 80% or more (e.g., 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 55. Thereby, the CDR sequences as defined above (heavy chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 52, SEQ ID NO: 37, and SEQ ID NO: 38, respectively; and light chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 53, SEQ ID NO: 40 (or 41), and SEQ ID NO: 42, respectively) may be maintained.

In some embodiments, the antibody of the invention, or the antigen-binding fragment thereof, comprises (i) a heavy chain variable region (VH) comprising an amino acid sequence having 80% or more (e.g., 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 63 and a light chain variable region (VL) comprising the amino acid sequence having 80% or more (e.g., 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 64. Thereby, the CDR sequences as defined above (heavy chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 56, SEQ ID NO: 57, and SEQ ID NO: 58, respectively; and light chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 59, SEQ ID NO: 60 (or 61), and SEQ ID NO: 62, respectively) may be maintained.

In some embodiments, the antibody of the invention, or the antigen-binding fragment thereof, comprises (i) a heavy chain variable region (VH) comprising an amino acid sequence having 80% or more (e.g., 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 71 and a light chain variable region (VL) comprising the amino acid sequence having 80% or more (e.g.,

81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 72. Thereby, the CDR sequences as defined above (heavy chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 65, SEQ ID NO: 66, and SEQ ID NO: 67, respectively; and light chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 68, SEQ ID NO: 40 (or 69), and SEQ ID NO: 70, respectively) may be maintained.

Preferably, the antibody of the invention, or the antigen-binding fragment thereof, comprises (i) a heavy chain variable region (VH) comprising an amino acid sequence having 80% or more (e.g., 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 214 and a light chain variable region (VL) comprising the amino acid sequence having 80% or more (e.g., 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 215. Thereby, the CDR sequences as defined above (heavy chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 207, SEQ ID NO: 208, and SEQ ID NO: 209, respectively; and light chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 210, SEQ ID NO: 211 (or 212), and SEQ ID NO: 213, respectively) may be maintained.

It is also preferred that the antibody of the invention, or the antigen-binding fragment thereof, comprises (i) a heavy chain variable region (VH) comprising an amino acid sequence having 80% or more (e.g., 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 223 and a light chain variable region (VL) comprising the amino acid sequence having 80% or more (e.g., 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 224. Thereby, the CDR sequences as defined above (heavy chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 216, SEQ ID NO: 217, and SEQ ID NO: 218, respectively; and light chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 219, SEQ ID NO: 220 (or 221), and SEQ ID NO: 222, respectively) may be maintained.

It is also preferred that the antibody of the invention, or the antigen-binding fragment thereof, comprises (i) a heavy chain variable region (VH) comprising an amino acid sequence having 80% or more (e.g., 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 232 and a light chain variable region (VL) comprising the amino acid sequence having 80% or more (e.g., 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 233. Thereby, the CDR sequences as defined above (heavy chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 225, SEQ ID NO: 226, and SEQ ID NO: 227, respectively; and light chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 228, SEQ ID NO: 229 (or 230), and SEQ ID NO: 231, respectively) may be maintained.

It is also preferred that the antibody of the invention, or the antigen-binding fragment thereof, comprises (i) a heavy chain variable region (VH) comprising an amino acid sequence having 80% or more (e.g., 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 240 and a light chain variable region (VL) comprising the amino acid sequence having 80% or more (e.g., 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 241. Thereby, the CDR sequences as defined above (heavy chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 234, SEQ ID NO: 235, and SEQ ID NO: 236, respectively; and light chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 237, SEQ ID NO: 211 (or 238), and SEQ ID NO: 239, respectively) may be maintained.

It is also preferred that the antibody of the invention, or the antigen-binding fragment thereof, comprises (i) a heavy chain variable region (VH) comprising an amino acid sequence having 80% or more (e.g., 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 247 and a light chain variable region (VL) comprising the amino acid sequence having 80% or more (e.g., 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 248. Thereby, the CDR sequences as defined above (heavy chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO:

242, SEQ ID NO: 243, and SEQ ID NO: 244, respectively; and light chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 245, SEQ ID NO: 31 (or 32), and SEQ ID NO: 246, respectively) may be maintained.

It is also preferred that the antibody of the invention, or the antigen-binding fragment thereof, comprises (i) a heavy chain variable region (VH) comprising an amino acid sequence having 80% or more (e.g., 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 256 and a light chain variable region (VL) comprising the amino acid sequence having 80% or more (e.g., 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 257. Thereby, the CDR sequences as defined above (heavy chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 249, SEQ ID NO: 250, and SEQ ID NO: 251, respectively; and light chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 252, SEQ ID NO: 253 (or 254), and SEQ ID NO: 255, respectively) may be maintained.

In some embodiments, the antibody of the invention, or the antigen-binding fragment thereof, comprises (i) a heavy chain variable region (VH) comprising an amino acid sequence having 80% or more (e.g., 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 262 and a light chain variable region (VL) comprising the amino acid sequence having 80% or more (e.g., 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 263. Thereby, the CDR sequences as defined above (heavy chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 258, SEQ ID NO: 259, and SEQ ID NO: 260, respectively; and light chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 219, SEQ ID NO: 220 (or 221), and SEQ ID NO: 261, respectively) may be maintained.

Preferably, the antibody of the invention, or the antigen-binding fragment thereof, comprises (i) a heavy chain variable region (VH) comprising an amino acid sequence having 85% or more (e.g., 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 16 and a light chain variable region (VL) comprising the

amino acid sequence having 85% or more (e.g., 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 17. Thereby, the CDR sequences as defined above (heavy chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 9, SEQ ID NO: 10, and SEQ ID NO: 11, respectively; and light chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 12, SEQ ID NO: 13 (or 14), and SEQ ID NO: 15, respectively) may be maintained.

It is also preferred that the antibody of the invention, or the antigen-binding fragment thereof, comprises (i) a heavy chain variable region (VH) comprising an amino acid sequence having 85% or more (e.g., 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 18 and a light chain variable region (VL) comprising the amino acid sequence having 85% or more (e.g., 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 19. Thereby, the CDR sequences as defined above (heavy chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 9, SEQ ID NO: 10, and SEQ ID NO: 11, respectively; and light chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 12, SEQ ID NO: 13 (or 14), and SEQ ID NO: 15, respectively) may be maintained.

In some embodiments, the antibody of the invention, or the antigen-binding fragment thereof, comprises (i) a heavy chain variable region (VH) comprising an amino acid sequence having 85% or more (e.g., 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 26 and a light chain variable region (VL) comprising the amino acid sequence having 85% or more (e.g., 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 27. Thereby, the CDR sequences as defined above (heavy chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 20, SEQ ID NO: 21, and SEQ ID NO: 22, respectively; and light chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 12, SEQ ID NO: 23 (or 24), and SEQ ID NO: 25, respectively) may be maintained.

In some embodiments, the antibody of the invention, or the antigen-binding fragment thereof, comprises (i) a heavy chain variable region (VH) comprising an amino acid sequence having 85% or more (e.g., 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%,

98%, 99% or more) identity to SEQ ID NO: 34 and a light chain variable region (VL) comprising the amino acid sequence having 85% or more (e.g., 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 35. Thereby, the CDR sequences as defined above (heavy chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 28, SEQ ID NO: 29, and SEQ ID NO: 30, respectively; and light chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 12, SEQ ID NO: 31 (or 32), and SEQ ID NO: 33, respectively) may be maintained.

In some embodiments, the antibody of the invention, or the antigen-binding fragment thereof, comprises (i) a heavy chain variable region (VH) comprising an amino acid sequence having 85% or more (e.g., 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 43 and a light chain variable region (VL) comprising the amino acid sequence having 85% or more (e.g., 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 44. Thereby, the CDR sequences as defined above (heavy chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 36, SEQ ID NO: 37, and SEQ ID NO: 38, respectively; and light chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 39, SEQ ID NO: 40 (or 41), and SEQ ID NO: 42, respectively) may be maintained.

In some embodiments, the antibody of the invention, or the antigen-binding fragment thereof, comprises (i) a heavy chain variable region (VH) comprising an amino acid sequence having 85% or more (e.g., 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 50 and a light chain variable region (VL) comprising the amino acid sequence having 85% or more (e.g., 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 51. Thereby, the CDR sequences as defined above (heavy chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 45, SEQ ID NO: 46, and SEQ ID NO: 47, respectively; and light chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 48, SEQ ID NO: 40 (or 49), and SEQ ID NO: 42, respectively) may be maintained.

In some embodiments, the antibody of the invention, or the antigen-binding fragment thereof, comprises (i) a heavy chain variable region (VH) comprising an amino acid sequence having

85% or more (e.g., 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 54 and a light chain variable region (VL) comprising the amino acid sequence having 85% or more (e.g., 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 55. Thereby, the CDR sequences as defined above (heavy chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 52, SEQ ID NO: 37, and SEQ ID NO: 38, respectively; and light chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 53, SEQ ID NO: 40 (or 41), and SEQ ID NO: 42, respectively) may be maintained.

In some embodiments, the antibody of the invention, or the antigen-binding fragment thereof, comprises (i) a heavy chain variable region (VH) comprising an amino acid sequence having 85% or more (e.g., 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 63 and a light chain variable region (VL) comprising the amino acid sequence having 85% or more (e.g., 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 64. Thereby, the CDR sequences as defined above (heavy chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 56, SEQ ID NO: 57, and SEQ ID NO: 58, respectively; and light chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 59, SEQ ID NO: 60 (or 61), and SEQ ID NO: 62, respectively) may be maintained.

In some embodiments, the antibody of the invention, or the antigen-binding fragment thereof, comprises (i) a heavy chain variable region (VH) comprising an amino acid sequence having 85% or more (e.g., 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 71 and a light chain variable region (VL) comprising the amino acid sequence having 85% or more (e.g., 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 72. Thereby, the CDR sequences as defined above (heavy chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 65, SEQ ID NO: 66, and SEQ ID NO: 67, respectively; and light chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 68, SEQ ID NO: 40 (or 69), and SEQ ID NO: 70, respectively) may be maintained.

Preferably, the antibody of the invention, or the antigen-binding fragment thereof, comprises (i) a heavy chain variable region (VH) comprising an amino acid sequence having 85% or more (e.g., 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 214 and a light chain variable region (VL) comprising the amino acid sequence having 85% or more (e.g., 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 215. Thereby, the CDR sequences as defined above (heavy chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 207, SEQ ID NO: 208, and SEQ ID NO: 209, respectively; and light chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 210, SEQ ID NO: 211 (or 212), and SEQ ID NO: 213, respectively) may be maintained.

It is also preferred that the antibody of the invention, or the antigen-binding fragment thereof, comprises (i) a heavy chain variable region (VH) comprising an amino acid sequence having 85% or more (e.g., 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 223 and a light chain variable region (VL) comprising the amino acid sequence having 85% or more (e.g., 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 224. Thereby, the CDR sequences as defined above (heavy chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 216, SEQ ID NO: 217, and SEQ ID NO: 218, respectively; and light chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 219, SEQ ID NO: 220 (or 221), and SEQ ID NO: 222, respectively) may be maintained.

It is also preferred that the antibody of the invention, or the antigen-binding fragment thereof, comprises (i) a heavy chain variable region (VH) comprising an amino acid sequence having 85% or more (e.g., 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 232 and a light chain variable region (VL) comprising the amino acid sequence having 85% or more (e.g., 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 233. Thereby, the CDR sequences as defined above (heavy chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 225, SEQ ID NO: 226, and SEQ ID NO: 227, respectively; and light chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 228, SEQ ID NO: 229 (or 230), and SEQ ID NO: 231, respectively) may be maintained.

It is also preferred that the antibody of the invention, or the antigen-binding fragment thereof, comprises (i) a heavy chain variable region (VH) comprising an amino acid sequence having 85% or more (e.g., 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 240 and a light chain variable region (VL) comprising the amino acid sequence having 85% or more (e.g., 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 241. Thereby, the CDR sequences as defined above (heavy chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 234, SEQ ID NO: 235, and SEQ ID NO: 236, respectively; and light chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 237, SEQ ID NO: 211 (or 238), and SEQ ID NO: 239, respectively) may be maintained.

It is also preferred that the antibody of the invention, or the antigen-binding fragment thereof, comprises (i) a heavy chain variable region (VH) comprising an amino acid sequence having 85% or more (e.g., 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 247 and a light chain variable region (VL) comprising the amino acid sequence having 85% or more (e.g., 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 248. Thereby, the CDR sequences as defined above (heavy chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 242, SEQ ID NO: 243, and SEQ ID NO: 244, respectively; and light chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 245, SEQ ID NO: 31 (or 32), and SEQ ID NO: 246, respectively) may be maintained.

It is also preferred that the antibody of the invention, or the antigen-binding fragment thereof, comprises (i) a heavy chain variable region (VH) comprising an amino acid sequence having 85% or more (e.g., 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 256 and a light chain variable region (VL) comprising the amino acid sequence having 85% or more (e.g., 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 257. Thereby, the CDR sequences as defined above (heavy chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 249, SEQ ID NO: 250, and SEQ ID NO: 251,

respectively; and light chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 252, SEQ ID NO: 253 (or 254), and SEQ ID NO: 255, respectively) may be maintained.

In some embodiments, the antibody of the invention, or the antigen-binding fragment thereof, comprises (i) a heavy chain variable region (VH) comprising an amino acid sequence having 85% or more (e.g., 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 262 and a light chain variable region (VL) comprising the amino acid sequence having 85% or more (e.g., 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 263. Thereby, the CDR sequences as defined above (heavy chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 258, SEQ ID NO: 259, and SEQ ID NO: 260, respectively; and light chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 219, SEQ ID NO: 220 (or 221), and SEQ ID NO: 261, respectively) may be maintained.

Preferably, the antibody of the invention, or the antigen-binding fragment thereof, comprises (i) a heavy chain variable region (VH) comprising an amino acid sequence having 90% or more (e.g., 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 16 and a light chain variable region (VL) comprising the amino acid sequence having 90% or more (e.g., 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 17. Thereby, the CDR sequences as defined above (heavy chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 9, SEQ ID NO: 10, and SEQ ID NO: 11, respectively; and light chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 12, SEQ ID NO: 13 (or 14), and SEQ ID NO: 15, respectively) may be maintained.

It is also preferred that the antibody of the invention, or the antigen-binding fragment thereof, comprises (i) a heavy chain variable region (VH) comprising an amino acid sequence having 90% or more (e.g., 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 18 and a light chain variable region (VL) comprising the amino acid sequence having 90% or more (e.g., 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 19. Thereby, the CDR sequences as defined above (heavy chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 9, SEQ ID NO: 10, and SEQ ID NO: 11, respectively; and light chain CDR1, CDR2, and CDR3 sequences as set forth in

SEQ ID NO: 12, SEQ ID NO: 13 (or 14), and SEQ ID NO: 15, respectively) may be maintained.

In some embodiments, the antibody of the invention, or the antigen-binding fragment thereof, comprises (i) a heavy chain variable region (VH) comprising an amino acid sequence having 90% or more (e.g., 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 26 and a light chain variable region (VL) comprising the amino acid sequence having 90% or more (e.g., 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 27. Thereby, the CDR sequences as defined above (heavy chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 20, SEQ ID NO: 21, and SEQ ID NO: 22, respectively; and light chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 12, SEQ ID NO: 23 (or 24), and SEQ ID NO: 25, respectively) may be maintained.

In some embodiments, the antibody of the invention, or the antigen-binding fragment thereof, comprises (i) a heavy chain variable region (VH) comprising an amino acid sequence having 90% or more (e.g., 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 34 and a light chain variable region (VL) comprising the amino acid sequence having 90% or more (e.g., 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 35. Thereby, the CDR sequences as defined above (heavy chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 28, SEQ ID NO: 29, and SEQ ID NO: 30, respectively; and light chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 12, SEQ ID NO: 31 (or 32), and SEQ ID NO: 33, respectively) may be maintained.

In some embodiments, the antibody of the invention, or the antigen-binding fragment thereof, comprises (i) a heavy chain variable region (VH) comprising an amino acid sequence having 90% or more (e.g., 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 43 and a light chain variable region (VL) comprising the amino acid sequence having 90% or more (e.g., 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 44. Thereby, the CDR sequences as defined above (heavy chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 36, SEQ ID NO: 37, and SEQ

ID NO: 38, respectively; and light chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 39, SEQ ID NO: 40 (or 41), and SEQ ID NO: 42, respectively) may be maintained.

In some embodiments, the antibody of the invention, or the antigen-binding fragment thereof, comprises (i) a heavy chain variable region (VH) comprising an amino acid sequence having 90% or more (e.g., 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 50 and a light chain variable region (VL) comprising the amino acid sequence having 90% or more (e.g., 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 51. Thereby, the CDR sequences as defined above (heavy chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 45, SEQ ID NO: 46, and SEQ ID NO: 47, respectively; and light chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 48, SEQ ID NO: 40 (or 49), and SEQ ID NO: 42, respectively) may be maintained.

In some embodiments, the antibody of the invention, or the antigen-binding fragment thereof, comprises (i) a heavy chain variable region (VH) comprising an amino acid sequence having 90% or more (e.g., 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 54 and a light chain variable region (VL) comprising the amino acid sequence having 90% or more (e.g., 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 55. Thereby, the CDR sequences as defined above (heavy chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 52, SEQ ID NO: 37, and SEQ ID NO: 38, respectively; and light chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 53, SEQ ID NO: 40 (or 41), and SEQ ID NO: 42, respectively) may be maintained.

In some embodiments, the antibody of the invention, or the antigen-binding fragment thereof, comprises (i) a heavy chain variable region (VH) comprising an amino acid sequence having 90% or more (e.g., 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 63 and a light chain variable region (VL) comprising the amino acid sequence having 90% or more (e.g., 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 64. Thereby, the CDR sequences as defined above (heavy chain

CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 56, SEQ ID NO: 57, and SEQ ID NO: 58, respectively; and light chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 59, SEQ ID NO: 60 (or 61), and SEQ ID NO: 62, respectively) may be maintained.

In some embodiments, the antibody of the invention, or the antigen-binding fragment thereof, comprises (i) a heavy chain variable region (VH) comprising an amino acid sequence having 90% or more (e.g., 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 71 and a light chain variable region (VL) comprising the amino acid sequence having 90% or more (e.g., 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 72. Thereby, the CDR sequences as defined above (heavy chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 65, SEQ ID NO: 66, and SEQ ID NO: 67, respectively; and light chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 68, SEQ ID NO: 40 (or 69), and SEQ ID NO: 70, respectively) may be maintained.

Preferably, the antibody of the invention, or the antigen-binding fragment thereof, comprises (i) a heavy chain variable region (VH) comprising an amino acid sequence having 90% or more (e.g., 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 214 and a light chain variable region (VL) comprising the amino acid sequence having 90% or more (e.g., 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 215. Thereby, the CDR sequences as defined above (heavy chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 207, SEQ ID NO: 208, and SEQ ID NO: 209, respectively; and light chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 210, SEQ ID NO: 211 (or 212), and SEQ ID NO: 213, respectively) may be maintained.

It is also preferred that the antibody of the invention, or the antigen-binding fragment thereof, comprises (i) a heavy chain variable region (VH) comprising an amino acid sequence having 90% or more (e.g., 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 223 and a light chain variable region (VL) comprising the amino acid sequence having 90% or more (e.g., 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 224. Thereby, the CDR sequences as defined above (heavy chain

CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 216, SEQ ID NO: 217, and SEQ ID NO: 218, respectively; and light chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 219, SEQ ID NO: 220 (or 221), and SEQ ID NO: 222, respectively) may be maintained.

It is also preferred that the antibody of the invention, or the antigen-binding fragment thereof, comprises (i) a heavy chain variable region (VH) comprising an amino acid sequence having 90% or more (e.g., 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 232 and a light chain variable region (VL) comprising the amino acid sequence having 90% or more (e.g., 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 233. Thereby, the CDR sequences as defined above (heavy chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 225, SEQ ID NO: 226, and SEQ ID NO: 227, respectively; and light chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 228, SEQ ID NO: 229 (or 230), and SEQ ID NO: 231, respectively) may be maintained.

It is also preferred that the antibody of the invention, or the antigen-binding fragment thereof, comprises (i) a heavy chain variable region (VH) comprising an amino acid sequence having 90% or more (e.g., 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 240 and a light chain variable region (VL) comprising the amino acid sequence having 90% or more (e.g., 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 241. Thereby, the CDR sequences as defined above (heavy chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 234, SEQ ID NO: 235, and SEQ ID NO: 236, respectively; and light chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 237, SEQ ID NO: 211 (or 238), and SEQ ID NO: 239, respectively) may be maintained.

It is also preferred that the antibody of the invention, or the antigen-binding fragment thereof, comprises (i) a heavy chain variable region (VH) comprising an amino acid sequence having 90% or more (e.g., 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 247 and a light chain variable region (VL) comprising the amino acid sequence having 90% or more (e.g., 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more)

identity to SEQ ID NO: 248. Thereby, the CDR sequences as defined above (heavy chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 242, SEQ ID NO: 243, and SEQ ID NO: 244, respectively; and light chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 245, SEQ ID NO: 31 (or 32), and SEQ ID NO: 246, respectively) may be maintained.

It is also preferred that the antibody of the invention, or the antigen-binding fragment thereof, comprises (i) a heavy chain variable region (VH) comprising an amino acid sequence having 90% or more (e.g., 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 256 and a light chain variable region (VL) comprising the amino acid sequence having 90% or more (e.g., 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 257. Thereby, the CDR sequences as defined above (heavy chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 249, SEQ ID NO: 250, and SEQ ID NO: 251, respectively; and light chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 252, SEQ ID NO: 253 (or 254), and SEQ ID NO: 255, respectively) may be maintained.

In some embodiments, the antibody of the invention, or the antigen-binding fragment thereof, comprises (i) a heavy chain variable region (VH) comprising an amino acid sequence having 90% or more (e.g., 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 262 and a light chain variable region (VL) comprising the amino acid sequence having 90% or more (e.g., 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 263. Thereby, the CDR sequences as defined above (heavy chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 258, SEQ ID NO: 259, and SEQ ID NO: 260, respectively; and light chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 219, SEQ ID NO: 220 (or 221), and SEQ ID NO: 261, respectively) may be maintained.

Preferably, the antibody of the invention, or the antigen-binding fragment thereof, comprises (i) a heavy chain variable region (VH) comprising an amino acid sequence having 95% or more (e.g., 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 16 and a light chain variable region (VL) comprising the amino acid sequence having 95% or more (e.g., 96%,

97%, 98%, 99% or more) identity to SEQ ID NO: 17. Thereby, the CDR sequences as defined above (heavy chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 9, SEQ ID NO: 10, and SEQ ID NO: 11, respectively; and light chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 12, SEQ ID NO: 13 (or 14), and SEQ ID NO: 15, respectively) may be maintained.

It is also preferred that the antibody of the invention, or the antigen-binding fragment thereof, comprises (i) a heavy chain variable region (VH) comprising an amino acid sequence having 95% or more (e.g., 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 18 and a light chain variable region (VL) comprising the amino acid sequence having 95% or more (e.g., 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 19. Thereby, the CDR sequences as defined above (heavy chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 9, SEQ ID NO: 10, and SEQ ID NO: 11, respectively; and light chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 12, SEQ ID NO: 13 (or 14), and SEQ ID NO: 15, respectively) may be maintained.

In some embodiments, the antibody of the invention, or the antigen-binding fragment thereof, comprises (i) a heavy chain variable region (VH) comprising an amino acid sequence having 95% or more (e.g., 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 26 and a light chain variable region (VL) comprising the amino acid sequence having 95% or more (e.g., 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 27. Thereby, the CDR sequences as defined above (heavy chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 20, SEQ ID NO: 21, and SEQ ID NO: 22, respectively; and light chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 12, SEQ ID NO: 23 (or 24), and SEQ ID NO: 25, respectively) may be maintained.

In some embodiments, the antibody of the invention, or the antigen-binding fragment thereof, comprises (i) a heavy chain variable region (VH) comprising an amino acid sequence having 95% or more (e.g., 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 34 and a light chain variable region (VL) comprising the amino acid sequence having 95% or more (e.g., 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 35. Thereby, the CDR sequences as defined above (heavy chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO:

28, SEQ ID NO: 29, and SEQ ID NO: 30, respectively; and light chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 12, SEQ ID NO: 31 (or 32), and SEQ ID NO: 33, respectively) may be maintained.

In some embodiments, the antibody of the invention, or the antigen-binding fragment thereof, comprises (i) a heavy chain variable region (VH) comprising an amino acid sequence having 95% or more (e.g., 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 43 and a light chain variable region (VL) comprising the amino acid sequence having 95% or more (e.g., 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 44. Thereby, the CDR sequences as defined above (heavy chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 36, SEQ ID NO: 37, and SEQ ID NO: 38, respectively; and light chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 39, SEQ ID NO: 40 (or 41), and SEQ ID NO: 42, respectively) may be maintained.

In some embodiments, the antibody of the invention, or the antigen-binding fragment thereof, comprises (i) a heavy chain variable region (VH) comprising an amino acid sequence having 95% or more (e.g., 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 50 and a light chain variable region (VL) comprising the amino acid sequence having 95% or more (e.g., 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 51. Thereby, the CDR sequences as defined above (heavy chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 45, SEQ ID NO: 46, and SEQ ID NO: 47, respectively; and light chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 48, SEQ ID NO: 40 (or 49), and SEQ ID NO: 42, respectively) may be maintained.

In some embodiments, the antibody of the invention, or the antigen-binding fragment thereof, comprises (i) a heavy chain variable region (VH) comprising an amino acid sequence having 95% or more (e.g., 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 54 and a light chain variable region (VL) comprising the amino acid sequence having 95% or more (e.g., 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 55. Thereby, the CDR sequences as defined above (heavy chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 52, SEQ ID NO: 37, and SEQ ID NO: 38, respectively; and light chain CDR1, CDR2, and

CDR3 sequences as set forth in SEQ ID NO: 53, SEQ ID NO: 40 (or 41), and SEQ ID NO: 42, respectively) may be maintained.

In some embodiments, the antibody of the invention, or the antigen-binding fragment thereof, comprises (i) a heavy chain variable region (VH) comprising an amino acid sequence having 95% or more (e.g., 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 63 and a light chain variable region (VL) comprising the amino acid sequence having 95% or more (e.g., 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 64. Thereby, the CDR sequences as defined above (heavy chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 56, SEQ ID NO: 57, and SEQ ID NO: 58, respectively; and light chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 59, SEQ ID NO: 60 (or 61), and SEQ ID NO: 62, respectively) may be maintained.

In some embodiments, the antibody of the invention, or the antigen-binding fragment thereof, comprises (i) a heavy chain variable region (VH) comprising an amino acid sequence having 95% or more (e.g., 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 71 and a light chain variable region (VL) comprising the amino acid sequence having 95% or more (e.g., 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 72. Thereby, the CDR sequences as defined above (heavy chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 65, SEQ ID NO: 66, and SEQ ID NO: 67, respectively; and light chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 68, SEQ ID NO: 40 (or 69), and SEQ ID NO: 70, respectively) may be maintained.

Preferably, the antibody of the invention, or the antigen-binding fragment thereof, comprises (i) a heavy chain variable region (VH) comprising an amino acid sequence having 95% or more (e.g., 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 214 and a light chain variable region (VL) comprising the amino acid sequence having 95% or more (e.g., 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 215. Thereby, the CDR sequences as defined above (heavy chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 207, SEQ ID NO: 208, and SEQ ID NO: 209, respectively; and light chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 210, SEQ ID NO: 211 (or 212), and SEQ ID NO: 213, respectively) may be maintained.

It is also preferred that the antibody of the invention, or the antigen-binding fragment thereof, comprises (i) a heavy chain variable region (VH) comprising an amino acid sequence having 95% or more (e.g., 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 223 and a light chain variable region (VL) comprising the amino acid sequence having 95% or more (e.g., 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 224. Thereby, the CDR sequences as defined above (heavy chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 216, SEQ ID NO: 217, and SEQ ID NO: 218, respectively; and light chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 219, SEQ ID NO: 220 (or 221), and SEQ ID NO: 222, respectively) may be maintained.

It is also preferred that the antibody of the invention, or the antigen-binding fragment thereof, comprises (i) a heavy chain variable region (VH) comprising an amino acid sequence having 95% or more (e.g., 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 232 and a light chain variable region (VL) comprising the amino acid sequence having 95% or more (e.g., 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 233. Thereby, the CDR sequences as defined above (heavy chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 225, SEQ ID NO: 226, and SEQ ID NO: 227, respectively; and light chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 228, SEQ ID NO: 229 (or 230), and SEQ ID NO: 231, respectively) may be maintained.

It is also preferred that the antibody of the invention, or the antigen-binding fragment thereof, comprises (i) a heavy chain variable region (VH) comprising an amino acid sequence having 95% or more (e.g., 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 240 and a light chain variable region (VL) comprising the amino acid sequence having 95% or more (e.g., 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 241. Thereby, the CDR sequences as defined above (heavy chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 234, SEQ ID NO: 235, and SEQ ID NO: 236, respectively; and light chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 237, SEQ ID NO: 211 (or 238), and SEQ ID NO: 239, respectively) may be maintained.

It is also preferred that the antibody of the invention, or the antigen-binding fragment thereof, comprises (i) a heavy chain variable region (VH) comprising an amino acid sequence having 95% or more (e.g., 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 247 and a light chain variable region (VL) comprising the amino acid sequence having 95% or more (e.g., 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 248. Thereby, the CDR sequences as defined above (heavy chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 242, SEQ ID NO: 243, and SEQ ID NO: 244, respectively; and light chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 245, SEQ ID NO: 31 (or 32), and SEQ ID NO: 246, respectively) may be maintained.

It is also preferred that the antibody of the invention, or the antigen-binding fragment thereof, comprises (i) a heavy chain variable region (VH) comprising an amino acid sequence having 95% or more (e.g., 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 256 and a light chain variable region (VL) comprising the amino acid sequence having 95% or more (e.g., 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 257. Thereby, the CDR sequences as defined above (heavy chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 249, SEQ ID NO: 250, and SEQ ID NO: 251, respectively; and light chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 252, SEQ ID NO: 253 (or 254), and SEQ ID NO: 255, respectively) may be maintained.

In some embodiments, the antibody of the invention, or the antigen-binding fragment thereof, comprises (i) a heavy chain variable region (VH) comprising an amino acid sequence having 95% or more (e.g., 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 262 and a light chain variable region (VL) comprising the amino acid sequence having 95% or more (e.g., 96%, 97%, 98%, 99% or more) identity to SEQ ID NO: 263. Thereby, the CDR sequences as defined above (heavy chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 258, SEQ ID NO: 259, and SEQ ID NO: 260, respectively; and light chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NO: 219, SEQ ID NO: 220 (or 221), and SEQ ID NO: 261, respectively) may be maintained.

The antibody, or an antigen-binding fragment thereof, according to the present invention may comprise (i) a heavy chain variable region comprising an amino acid sequence according to

SEQ ID NO: 16 and a light chain variable region comprising an amino acid sequence according to SEQ ID NO: 17; or (ii) a heavy chain variable region comprising an amino acid sequence according to SEQ ID NO: 18 and a light chain variable region comprising an amino acid sequence according to SEQ ID NO: 19; or (iii) a heavy chain variable region comprising an amino acid sequence according to SEQ ID NO: 26 and a light chain variable region comprising an amino acid sequence according to SEQ ID NO: 27; or (iv) a heavy chain variable region comprising an amino acid sequence according to SEQ ID NO: 34 and a light chain variable region comprising an amino acid sequence according to SEQ ID NO: 35; or (v) a heavy chain variable region comprising an amino acid sequence according to SEQ ID NO: 43 and a light chain variable region comprising an amino acid sequence according to SEQ ID NO: 44; or (vi) a heavy chain variable region comprising an amino acid sequence according to SEQ ID NO: 50 and a light chain variable region comprising an amino acid sequence according to SEQ ID NO: 51; or (vii) a heavy chain variable region comprising an amino acid sequence according to SEQ ID NO: 54 and a light chain variable region comprising an amino acid sequence according to SEQ ID NO: 55; or (viii) a heavy chain variable region comprising an amino acid sequence according to SEQ ID NO: 63 and a light chain variable region comprising an amino acid sequence according to SEQ ID NO: 64; or (ix) a heavy chain variable region comprising an amino acid sequence according to SEQ ID NO: 71 and a light chain variable region comprising an amino acid sequence according to SEQ ID NO: 72; or (x) a heavy chain variable region comprising an amino acid sequence according to SEQ ID NO: 214 and a light chain variable region comprising an amino acid sequence according to SEQ ID NO: 215; or (xi) a heavy chain variable region comprising an amino acid sequence according to SEQ ID NO: 223 and a light chain variable region comprising an amino acid sequence according to SEQ ID NO: 224; or (xii) a heavy chain variable region comprising an amino acid sequence according to SEQ ID NO: 232 and a light chain variable region comprising an amino acid sequence according to SEQ ID NO: 233; (xiii) a heavy chain variable region comprising an amino acid sequence according to SEQ ID NO: 240 and a light chain variable region comprising an amino acid sequence according to SEQ ID NO: 241; or (xiv) a heavy chain variable region comprising an amino acid sequence according to SEQ ID NO: 247 and a light chain variable region comprising an amino acid sequence according to SEQ ID NO: 248; or (xv) a heavy chain variable region comprising an amino acid sequence according to SEQ ID NO: 256 and a light chain variable region

comprising an amino acid sequence according to SEQ ID NO: 257; or (xvi) a heavy chain variable region comprising an amino acid sequence according to SEQ ID NO: 262 and a light chain variable region comprising an amino acid sequence according to SEQ ID NO: 263.

Preferably, the antibody, or an antigen-binding fragment thereof, according to the present invention may comprise a heavy chain variable region comprising an amino acid sequence according to SEQ ID NO: 16 and a light chain variable region comprising the amino acid sequence according to SEQ ID NO: 17.

It is also preferred that the antibody, or an antigen-binding fragment thereof, according to the present invention may comprise a heavy chain variable region comprising an amino acid sequence according to SEQ ID NO: 18 and a light chain variable region comprising the amino acid sequence according to SEQ ID NO: 19.

In some embodiments, the antibody, or an antigen-binding fragment thereof, according to the present invention may comprise a heavy chain variable region comprising an amino acid sequence according to SEQ ID NO: 26 and a light chain variable region comprising the amino acid sequence according to SEQ ID NO: 27.

In some embodiments, the antibody, or an antigen-binding fragment thereof, according to the present invention may comprise a heavy chain variable region comprising an amino acid sequence according to SEQ ID NO: 34 and a light chain variable region comprising the amino acid sequence according to SEQ ID NO: 35.

In some embodiments, the antibody, or an antigen-binding fragment thereof, according to the present invention may comprise a heavy chain variable region comprising an amino acid sequence according to SEQ ID NO: 43 and a light chain variable region comprising the amino acid sequence according to SEQ ID NO: 44.

In some embodiments, the antibody, or an antigen-binding fragment thereof, according to the present invention may comprise a heavy chain variable region comprising an amino acid

sequence according to SEQ ID NO: 50 and a light chain variable region comprising the amino acid sequence according to SEQ ID NO: 51.

In some embodiments, the antibody, or an antigen-binding fragment thereof, according to the present invention may comprise a heavy chain variable region comprising an amino acid sequence according to SEQ ID NO: 54 and a light chain variable region comprising the amino acid sequence according to SEQ ID NO: 55.

In some embodiments, the antibody, or an antigen-binding fragment thereof, according to the present invention may comprise a heavy chain variable region comprising an amino acid sequence according to SEQ ID NO: 63 and a light chain variable region comprising the amino acid sequence according to SEQ ID NO: 64.

In some embodiments, the antibody, or an antigen-binding fragment thereof, according to the present invention may comprise a heavy chain variable region comprising an amino acid sequence according to SEQ ID NO: 71 and a light chain variable region comprising the amino acid sequence according to SEQ ID NO: 72.

Preferably, the antibody, or an antigen-binding fragment thereof, according to the present invention may comprise a heavy chain variable region comprising an amino acid sequence according to SEQ ID NO: 214 and a light chain variable region comprising an amino acid sequence according to SEQ ID NO: 215.

It is also preferred that the antibody, or an antigen-binding fragment thereof, according to the present invention may comprise a heavy chain variable region comprising an amino acid sequence according to SEQ ID NO: 223 and a light chain variable region comprising an amino acid sequence according to SEQ ID NO: 224.

It is also preferred that the antibody, or an antigen-binding fragment thereof, according to the present invention may comprise a heavy chain variable region comprising an amino acid sequence according to SEQ ID NO: 232 and a light chain variable region comprising an amino acid sequence according to SEQ ID NO: 233.

It is also preferred that the antibody, or an antigen-binding fragment thereof, according to the present invention may comprise a heavy chain variable region comprising an amino acid sequence according to SEQ ID NO: 240 and a light chain variable region comprising an amino acid sequence according to SEQ ID NO: 241.

It is also preferred that the antibody, or an antigen-binding fragment thereof, according to the present invention may comprise a heavy chain variable region comprising an amino acid sequence according to SEQ ID NO: 247 and a light chain variable region comprising an amino acid sequence according to SEQ ID NO: 248.

It is also preferred that the antibody, or an antigen-binding fragment thereof, according to the present invention may comprise a heavy chain variable region comprising an amino acid sequence according to SEQ ID NO: 256 and a light chain variable region comprising an amino acid sequence according to SEQ ID NO: 257.

In some embodiments, the antibody, or an antigen-binding fragment thereof, according to the present invention may comprise a heavy chain variable region comprising an amino acid sequence according to SEQ ID NO: 262 and a light chain variable region comprising an amino acid sequence according to SEQ ID NO: 263.

The CDR and VH/VL sequences of exemplified antibodies of the invention, namely antibodies CLM20_A7, CLM20_B8, CLM20_C9, CLM20_B8_UCA, CLM99_G12, CLM99_D10, CLM99_E3, CLM13_G9, CLM20_Bis_B3, ISR42_E7, CSC3_H1, E371_F8, E2418_G12, E2121_B7, E1373_G3 and CSC3_H1_UCA are shown in Table 1 below.

Antibody name	Heavy chain				Light chain			
	CDR1	CDR2	CDR3	VH	CDR1	CDR2	CDR3	VL
CLM20_A7	9	10	11	18	12	13/14	15	19
CLM20_B8	9	10	11	16	12	13/14	15	17
CLM20_C9	20	21	22	26	12	23/24	25	27

CLM20_B8_UCA	28	29	30	34	12	31/32	33	35
CLM99_G12	36	37	38	43	39	40/41	42	44
CLM99_D10	45	46	47	50	48	40/49	42	51
CLM99_E3	52	37	38	54	53	40/41	42	55
CLM13_G9	56	57	58	63	59	60/61	62	64
CLM20_Bis_B3	65	66	67	71	68	40/69	70	72
ISR42_E7	207	208	209	214	210	211/212	213	215
CSC3_H1	216	217	218	223	219	220/221	222	224
E371_F8	225	226	227	232	228	229/230	231	233
E2418_G12	234	235	236	240	237	211/238	239	241
E2121_B7	242	243	244	247	245	31/32	246	248
E1373_G3	249	250	251	256	252	253/254	255	257
CSC3_H1_UCA	258	259	260	262	219	220/221	261	263

Table 1: CDR and VH/VL sequences (SEQ ID NOs) of exemplified antibodies of the invention.

The exemplified antibodies bind to the spike (S) protein of different coronaviruses, e.g. to the spike (S) protein of various alphacoronaviruses and betacoronaviruses. Accordingly, the antibody, or the antigen-binding fragment thereof, of the present invention may bind to the spike (S) protein of alphacoronaviruses, e.g. human coronavirus 229E (HCoV-229E) and/or human coronavirus NL63 (HCoV-NL63), and betacoronaviruses, e.g. human coronavirus OC43 (HCoV-OC43), human coronavirus HKU1 (HCoV-HKU1), Middle East respiratory syndrome-related coronavirus (MERS-CoV), Severe acute respiratory syndrome coronavirus (SARS-CoV; also referred to herein as SARS-CoV-1) and/or Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

In some embodiments, the antibody, or the antigen-binding fragment thereof, of the present invention binds to the spike (S) protein of human coronavirus 229E (HCoV-229E), human coronavirus NL63 (HCoV-NL63), human coronavirus OC43 (HCoV-OC43), human coronavirus HKU1 (HCoV-HKU1), Severe acute respiratory syndrome coronavirus (SARS-CoV) and Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). In some embodiments, the antibody, or the antigen-binding fragment thereof, of the present invention

binds to the spike (S) protein of human coronavirus 229E (HCoV-229E), human coronavirus NL63 (HCoV-NL63), human coronavirus OC43 (HCoV-OC43), human coronavirus HKU1 (HCoV-HKU1), Middle East respiratory syndrome coronavirus (MERS-CoV), Severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1) and Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). In some embodiments, the antibody, or the antigen-binding fragment thereof, of the present invention binds to the spike (S) protein of human coronavirus 229E (HCoV-229E), human coronavirus NL63 (HCoV-NL63), human coronavirus OC43 (HCoV-OC43), human coronavirus HKU1 (HCoV-HKU1), Middle East respiratory syndrome coronavirus (MERS-CoV), Severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1), Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), avian infectious bronchitis virus (IBV) and porcine deltacoronavirus (PdCV).

Standard methods to assess binding of the antibody according to the present invention, or the antigen-binding fragment thereof, are known to those skilled in the art and include, for example, ELISA (enzyme-linked immunosorbent assay). Thereby, the relative affinities of antibody binding may be determined by measuring the concentration of the antibody (EC_{50}) required to achieve 50% maximal binding at saturation.

An exemplary standard ELISA may be performed as follows: ELISA plates may be coated with a sufficient amount (e.g., 1 µg/ml) of the protein/complex/particle to which binding of the antibody is to be tested (e.g., tetanus toxin). Plates may then be incubated with the antibody to be tested. After washing, antibody binding can be revealed, e.g. using a labelled antibody recognizing the test antibody, such as goat anti-human IgG coupled to alkaline phosphatase. Plates may then be washed, the required substrate (e.g., p-NPP) may be added and plates may be read, e.g. at 405 nm. The relative affinities of antibody binding may be determined by measuring the concentration of mAb (EC_{50}) required to achieve 50% maximal binding at saturation. The EC_{50} values may be calculated by interpolation of binding curves fitted with a four-parameter nonlinear regression with a variable slope.

In some embodiments, the antibody, or the antigen-binding fragment thereof, neutralizes infection of a coronavirus, in particular of a human coronavirus, preferably selected from the group consisting of 229E, NL63, OC43, HKU1, MERS, SARS-CoV and/or SARS-CoV-2, more

preferably selected from the group consisting of SARS-CoV, SARS-CoV-2, MERS and/or 229E. In some embodiments, the antibody, or the antigen-binding fragment thereof, neutralizes infection with a human coronavirus selected from the group consisting of 229E, NL63, OC43, HKU1, WIV-1, MERS, SARS-CoV and/or SARS-CoV-2. Preferably, the antibody, or the antigen-binding fragment thereof, neutralizes infection of at least two distinct coronaviruses, in particular of at least two distinct human coronaviruses, which are preferably selected from the group consisting of 229E, NL63, OC43, HKU1, MERS, SARS-CoV and/or SARS-CoV-2, more preferably selected from the group consisting of SARS-CoV, SARS-CoV-2, MERS and/or 229E. In some embodiments, the antibody, or the antigen-binding fragment thereof, neutralizes MERS-CoV and 229E. In some embodiments, the antibody, or the antigen-binding fragment thereof, neutralizes SARS-CoV and SARS-CoV-2. Preferably, the antibody, or the antigen-binding fragment thereof, neutralizes (i) MERS, SARS-CoV and SARS-CoV-2; or (ii) MERS, SARS-CoV-2 and 229E. More preferably, the antibody, or the antigen-binding fragment thereof, neutralizes MERS, SARS-CoV, SARS-CoV-2 and 229E. In some embodiments, the antibody, or the antigen-binding fragment thereof, additionally neutralizes WIV-1.

The antibody and antigen binding fragment of the invention may have high neutralizing potency. In general, neutralization can be measured using standard assays as known to one of skill in the art. For example, to study and quantitate neutralization in the laboratory the person skilled in the art knows various standard neutralization assays, in particular "spike-pseudotyped neutralization assays". For a neutralization assay, the viruses (to be neutralized) are typically propagated in cells and/or cell lines. In particular, for a spike-pseudotyped neutralization assay, the pseudoparticles (to be neutralized) are typically produced in cell lines in the form of lentiviruses. For example, in a neutralization assay cultured cells may be incubated with a fixed amount of a spike-pseudotyped lentiviral particles in the presence (or absence) of the antibody to be tested. As a readout for example flow cytometry may be used. Alternatively, also other readouts are conceivable. A specific example for a suitable coronavirus neutralization assay is described in Crawford, K.H.D., Eguia R., Dingens A.S., Loes A.N., Malone K.D., Wolf C.R., Chu H. Y., Tortorici M.A., Veesler D., Murphy M., Pettie D., King N.P., Balazs A.B., Bloom J.D. (2020) Protocol and Reagents for Pseudotyping Lentiviral Particles with SARS-CoV-2 Spike Protein for Neutralization Assays, doi: 10.3390/v12050513.

In some embodiments, the antibody, or the antigen-binding fragment thereof, inhibits or reduces the fusion of the coronavirus (SARS-CoV-2) spike protein with human ACE2. In some embodiments, the antibody, or the antigen-binding fragment thereof, inhibits or reduces the fusion of coronavirus (SARS-CoV-2) spike-expressing cells with human ACE2-expressing cells. To assess the ability of the antibody, or the antigen-binding fragment thereof, to inhibit or reduce fusion, A549-spike and A549-ACE2-TMPRSS2 cells may be used. A549-spike cells may be co-cultured with titrating doses of the antibodies to be tested. Thereafter, (stained) A549-ACE2-TMPRSS2 cells may be added. After incubation, fusion events may be assessed.

In some embodiments, the antibody, or the antigen-binding fragment thereof, can be tested for its ability to bind to membrane-bound spike using standard flow cytometry assay. To assess the ability of the antibody, or the antigen-binding fragment thereof, to bind to membrane-bound spike, spike-expressing cell lines such as but not limited to, A549-spike, 293T-spike may be used. A549-spike or 293T-spike may be co-incubated with titrating doses of of antibodies to be tested. Thereafter, (stained) A549-spike or 293T-spike may be analyzed by flow cytometry.

In some embodiments, the antibody of the invention is a human antibody. In some embodiments, the antibody of the invention is a monoclonal antibody. For example, the antibody of the invention may be a human monoclonal antibody.

Antibodies of the invention can be of any isotype (*e.g.*, IgA, IgG, IgM i.e. an α, γ or μ heavy chain). For example, the antibody may be of the IgG type. Within the IgG isotype, antibodies may be IgG1, IgG2, IgG3 or IgG4 subclass, for example IgG1. Antibodies of the invention may have a κ or a λ light chain. In some embodiments, the antibody is of IgG1 type and has a lambda or kappa light chain.

In some embodiments, the antibody is of the human IgG1 type. The antibody may be of any allotype. The term "allotype" refers to the allelic variation found among the IgG subclasses. For example, the antibody may be of the G1m1 (or G1m(a)) allotype, of the G1m2 (or G1m(x)) allotype, of the G1m3 (or G1m(f)) allotype, and/or of the G1m17 (or Gm(z)) allotype. The

G1m3 and G1m17 allotypes are located at the same position in the CH1 domain (position 214 according to EU numbering). G1m3 corresponds to R214 (EU), while G1m17 corresponds to K214 (EU). The G1m1 allotype is located in the CH3 domain (at positions 356 and 358 (EU)) and refers to the replacements E356D and M358L. The G1m2 allotype refers to a replacement of the alanine in position 431 (EU) by a glycine. The G1m1 allotype may be combined, for example, with the G1m3 or the G1m17 allotype. In some embodiments, the antibody is of the allotype G1m3 with no G1m1 (G1m3,-1). In some embodiments, the antibody is of the G1m17,1 allotype. In some embodiments, the antibody is of the G1m3,1 allotype. In some embodiments, the antibody is of the allotype G1m17 with no G1m1 (G1m17,-1). Optionally, these allotypes may be combined (or not combined) with the G1m2, G1m27 or G1m28 allotype. For example, the antibody may be of the G1m17,1,2 allotype.

In some embodiments, the antibody according to the present invention, or an antigen binding fragment thereof, comprises an Fc moiety. In some embodiments, the Fc moiety, or the Fc region, comprises or consists of an amino acid sequence derived from a human immunoglobulin sequence (e.g., from an Fc region or Fc moiety from a human IgG molecule). However, polypeptides may comprise one or more amino acids from another mammalian species. For example, a primate Fc moiety or a primate binding site may be included in the subject polypeptides. Alternatively, one or more murine amino acids may be present in the Fc moiety or in the Fc region. Preferably, the Fc moiety is derived from human origin, e.g. from human IgG1, IgG2, IgG3, and/or IgG4, such as human IgG1.

As used herein, the term "Fc moiety" refers to a sequence derived from the portion of an immunoglobulin heavy chain beginning in the hinge region just upstream of the papain cleavage site (e.g., residue 216 in native IgG, taking the first residue of heavy chain constant region to be 114) and ending at the C-terminus of the immunoglobulin heavy chain. Accordingly, an Fc moiety may be a complete Fc moiety or a portion (e.g., a domain) thereof. A complete Fc moiety comprises at least a hinge domain, a CH2 domain, and a CH3 domain (e.g., EU amino acid positions 216-446). An additional lysine residue (K) is sometimes present at the extreme C-terminus of the Fc moiety, but is often cleaved from a mature antibody.

Each of the amino acid positions within an Fc moiety have been numbered herein according to the art-recognized EU numbering system of Kabat, see e.g., by Kabat et al., in "Sequences of Proteins of Immunological Interest", U.S. Dept. Health and Human Services, 1983 and 1987. The EU index or EU index as in Kabat or EU numbering refers to the numbering of the EU antibody (Edelman GM, Cunningham BA, Gall WE, Gottlieb PD, Rutishauser U, Waxdal MJ. The covalent structure of an entire gammaG immunoglobulin molecule. *Proc Natl Acad Sci U S A.* 1969;63(1):78-85; Kabat E.A., National Institutes of Health (U.S.) Office of the Director, "Sequences of Proteins of Immunological Interest", 5th edition, Bethesda, MD : U.S. Dept. of Health and Human Services, Public Health Service, National Institutes of Health, 1991, hereby entirely incorporated by reference).

In some embodiments, in the context of the present invention an Fc moiety comprises at least one of: a hinge (e.g., upper, middle, and/or lower hinge region) domain, a CH2 domain, a CH3 domain, or a variant, portion, or fragment thereof. An Fc moiety may comprise at least a hinge domain, a CH2 domain or a CH3 domain. The Fc moiety may be a complete Fc moiety. The Fc moiety may also comprises one or more amino acid insertions, deletions, or substitutions relative to a naturally-occurring Fc moiety. For example, at least one of a hinge domain, CH2 domain or CH3 domain (or portion thereof) may be deleted. For example, an Fc moiety may comprise or consist of: (i) hinge domain (or portion thereof) fused to a CH2 domain (or portion thereof), (ii) a hinge domain (or portion thereof) fused to a CH3 domain (or portion thereof), (iii) a CH2 domain (or portion thereof) fused to a CH3 domain (or portion thereof), (iv) a hinge domain (or portion thereof), (v) a CH2 domain (or portion thereof), or (vi) a CH3 domain or portion thereof.

In some embodiments, the antibody according to the present invention comprises, in particular in addition to an Fc moiety as described above, other parts derived from a constant region, in particular from a constant region of IgG, such as a constant region of (human) IgG1. The antibody according to the present invention may comprise, in particular in addition to an Fc moiety as described above, all other parts of the constant regions, in particular all other parts of the constant regions of IgG (such as (human) IgG1).

In some embodiments, the antibody, or antigen binding fragment thereof, according to the present invention comprises an Fc region. As used herein, the term "Fc region" refers to the portion of an immunoglobulin formed by two or more Fc moieties of antibody heavy chains. For example, the Fc region may be monomeric or "single-chain" Fc region (i.e., a scFc region). Single chain Fc regions are comprised of Fc moieties linked within a single polypeptide chain (e.g., encoded in a single contiguous nucleic acid sequence). Exemplary scFc regions are disclosed in WO 2008/143954 A2. The Fc region may be dimeric. A "dimeric Fc region" or "dcFc" refers to the dimer formed by the Fc moieties of two separate immunoglobulin heavy chains. The dimeric Fc region may be a homodimer of two identical Fc moieties (e.g., an Fc region of a naturally occurring immunoglobulin) or a heterodimer of two non-identical Fc moieties.

In some embodiments, the antibody according to the present invention comprises a (complete) Fc moiety/Fc region, wherein the interaction/binding with FcR is not compromised. In general, binding of the antibody to an Fc receptor may be assessed by various methods known to the skilled person, such as ELISA (Hessell AJ, Hangartner L, Hunter M, Havenith CEG, Beurskens FJ, Bakker JM, Lanigan CMS, Landucci G, Forthal DN, Parren PWHI, et al.: Fc receptor but not complement binding is important in antibody protection against HIV. Nature 2007, 449:101–104; Grevys A, Bern M, Foss S, Bratlie DB, Moen A, Gunnarsen KS, Aase A, Michaelsen TE, Sandlie I, Andersen JT: Fc Engineering of Human IgG1 for Altered Binding to the Neonatal Fc Receptor Affects Fc Effector Functions. 2015, 194:5497–5508) or flow-cytometry (Perez LG, Costa MR, Todd CA, Haynes BF, Montefiori DC: Utilization of immunoglobulin G Fc receptors by human immunodeficiency virus type 1: a specific role for antibodies against the membrane-proximal external region of gp41. J Virol 2009, 83:7397–7410; Piccoli L, Campo I, Fregni CS, Rodriguez BMF, Minola A, Sallusto F, Luisetti M, Corti D, Lanzavecchia A: Neutralization and clearance of GM-CSF by autoantibodies in pulmonary alveolar proteinosis. Nat Commun 2015, 6:1–9).

It will be understood by one of ordinary skill in the art that the Fc moiety may be modified such that it varies in amino acid sequence from the complete Fc moiety of a naturally occurring immunoglobulin molecule, while retaining at least one desirable function conferred by the naturally-occurring Fc moiety. Such functions include Fc receptor (FcR)

binding, antibody half-life modulation, ADCC function, protein A binding, protein G binding, and complement binding. The portions of naturally occurring Fc moieties, which are responsible and/or essential for such functions are well known by those skilled in the art.

For example, to activate the complement cascade C1q binds to at least two molecules of IgG1 or one molecule of IgM, attached to the antigenic target (Ward, E. S., and Ghetie, V., *Ther. Immunol.* 2 (1995) 77-94). Burton, D. R., described (*Mol. Immunol.* 22 (1985) 161-206) that the heavy chain region comprising amino acid residues 318 to 337 is involved in complement fixation. Duncan, A. R., and Winter, G. (*Nature* 332 (1988) 738-740), using site directed mutagenesis, reported that Glu318, Lys320 and Lys322 form the binding site to C1q. The role of Glu318, Lys320 and Lys 322 residues in the binding of C1q was confirmed by the ability of a short synthetic peptide containing these residues to inhibit complement mediated lysis.

For example, FcR binding can be mediated by the interaction of the Fc moiety (of an antibody) with Fc receptors (FcRs), which are specialized cell surface receptors on hematopoietic cells. Fc receptors belong to the immunoglobulin superfamily, and were shown to mediate both the removal of antibody-coated pathogens by phagocytosis of immune complexes, and the lysis of erythrocytes and various other cellular targets (e.g. tumor cells) coated with the corresponding antibody, via antibody dependent cell mediated cytotoxicity (ADCC; Van de Winkel, J. G., and Anderson, C. L., *J. Leukoc. Biol.* 49 (1991) 511-524). FcRs are defined by their specificity for immunoglobulin classes; Fc receptors for IgG antibodies are referred to as FcγR, for IgE as FcεR, for IgA as FcαR and so on and neonatal Fc receptors are referred to as FcRn. Fc receptor binding is described for example in Ravetch, J. V., and Kinet, J. P., *Annu. Rev. Immunol.* 9 (1991) 457-492; Capel, P. J., et al., *Immunomethods* 4 (1994) 25-34; de Haas, M., et al., *J Lab. Clin. Med.* 126 (1995) 330-341; and Gessner, J. E., et al., *Ann. Hematol.* 76 (1998) 231-248.

Regarding FcγRI binding, modification in native IgG of at least one of E233-G236, P238, D265, N297, A327 and P329 reduces binding to FcγRI. IgG2 residues at positions 233-236, substituted into IgG1 and IgG4, reduces binding to FcγRI by 10^3-fold and eliminated the human monocyte response to antibody-sensitized red blood cells (Armour, K. L., et al. *Eur. J. Immunol.* 29 (1999) 2613-2624). Regarding FcγRII binding, reduced binding for FcγRIIA is

found e.g. for IgG mutation of at least one of E233-G236, P238, D265, N297, A327, P329, D270, Q295, A327, R292 and K414. Regarding FcγRIII binding, reduced binding to FcγRIIIA is found e.g. for mutation of at least one of E233-G236, P238, D265, N297, A327, P329, D270, Q295, A327, S239, E269, E293, Y296, V303, A327, K338 and D376. Mapping of the binding sites on human IgG1 for Fc receptors, the above mentioned mutation sites and methods for measuring binding to FcγRI and FcγRIIA are described in Shields, R. L., et al., *J. Biol. Chem.* 276 (2001) 6591-6604. For example, a single (S239D or I332E), double (S239D/I332E), and triple mutations (S239D/I332E/A330L) improved the affinity against human FcγRIIIa. Furthermore, the addition of the mutation G236A to S239D/I332E improved not only FcγRIIa:FcγRIIb ratio, but also enhanced binding to FcγRIIIa. Accordingly, the mutations G236A/S239D/A330L/I332E were described to enhance engagement of FcγRIIa and FcγRIIIa.

Regarding binding to the crucial FcγRII, two regions of native IgG Fc appear to be critical for interactions of FcγRIIs and IgGs, namely (i) the lower hinge site of IgG Fc, in particular amino acid residues L, L, G, G (234 – 237, EU numbering), and (ii) the adjacent region of the CH2 domain of IgG Fc, in particular a loop and strands in the upper CH2 domain adjacent to the lower hinge region, e.g. in a region of P331 (Wines, B.D., et al., J. Immunol. 2000; 164: 5313 – 5318). Moreover, FcγRI appears to bind to the same site on IgG Fc, whereas FcRn and Protein A bind to a different site on IgG Fc, which appears to be at the CH2-CH3 interface (Wines, B.D., et al., J. Immunol. 2000; 164: 5313 – 5318).

For example, the Fc moiety may comprise or consist of at least the portion of an Fc moiety that is known in the art to be required for FcRn binding or extended half-life. Alternatively or additionally, the Fc moiety of the antibody of the invention comprises at least the portion of known in the art to be required for Protein A binding and/or the Fc moiety of the antibody of the invention comprises at least the portion of an Fc molecule known in the art to be required for protein G binding. The Fc moiety may comprise at least the portion known in the art to be required for FcγR binding. As outlined above, an Fc moiety may thus at least comprise (i) the lower hinge site of native IgG Fc, in particular amino acid residues L, L, G, G (234 – 237, EU numbering), and (ii) the adjacent region of the CH2 domain of native IgG Fc, in particular a loop and strands in the upper CH2 domain adjacent to the lower hinge region, e.g. in a

region of P331, for example a region of at least 3, 4, 5, 6, 7, 8, 9, or 10 consecutive amino acids in the upper CH2 domain of native IgG Fc around P331, e.g. between amino acids 320 and 340 (EU numbering) of native IgG Fc.

Furthermore, the antibody according to the present invention can be modified by introducing (random) amino acid mutations into particular region of the CH2 or CH3 domain of the heavy chain in order to alter their binding affinity for FcR and/or their serum half-life in comparison to unmodified antibodies. Examples of such modifications include, but are not limited to, substitutions of at least one amino acid from the heavy chain constant region selected from the group consisting of amino acid residues 250, 314, and 428. Further examples of such Fc modifications are described in Saxena A, Wu D. Advances in Therapeutic Fc Engineering - Modulation of IgG-Associated Effector Functions and Serum Half-life. *Front Immunol.* 2016;7:580, which is incorporated herein by reference. In some embodiments, the antibody may comprise the "YTE" mutations (M252Y/S254T/T256E; EU numbering). In some embodiments, the antibody may comprise the mutations M428L and/or N434S in the heavy chain constant region (EU numbering).

In general, the antibody according to the present invention may be glycosylated. N-linked glycans attached to the CH2 domain of a heavy chain, for instance, can influence C1q and FcR binding, with glycosylated antibodies having lower affinity for these receptors. Accordingly, the CH2 domain of the Fc moiety of the antibody according to the present invention may comprise one or more mutations, in which a glycosylated residue is substituted by a non-glycosylated residue. For example, the antibody's glycans do not lead to a human immunogenic response after administration.

As outlined above, an antibody according to the present invention may comprise a (complete) Fc region derived from human IgG1. In some embodiments, the antibody according to the present invention comprises, in particular in addition to a (complete) Fc region derived from human IgG1 also all other parts of the constant regions of IgG, such as all other parts of the constant regions of (human) IgG1.

Example sequences of constant regions are the amino acid sequences according to SEQ ID NOs: 73 – 75. For example, the amino acid sequence of IgG1 CH1-CH2-CH3 is according to SEQ ID NO: 73 or a sequence variant thereof (including, for example, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more mutations) having at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95% or at least 99% sequence identity.

In some embodiments, the antibody, or the antigen-binding fragment thereof, has an antibody format of a smaller size as compared to (naturally occurring) IgG antibodies. Without being bound to any theory, the present inventors assume, in particular for antibodies binding to the fusion peptide of the coronavirus spike protein, that smaller antibody footprints, such as Fab fragments, scFv or nanobodies, may have more potent neutralization capacity, as demonstrated in the appended examples. Preferred formats therefore include, but are not limited to, single chain antibodies, nanobodies, Fab, Fab', F(ab')2, Fv, scFv, scFv-Fc, diabodies, scFv-CH3 (minibodies), scFab and scFv-zipper. In some embodiments, the antibody, or the antigen-binding fragment thereof, may have a format selected from Fab, Fab', F(ab')2, Fv, nanobodies or scFv. Preferably, the antibody may be a Fab, scFv or a nanobody. In some embodiments, the antibody is a Fab or an scFv.

Antibodies of the invention also include hybrid antibody molecules that comprise the six CDRs from an antibody of the invention as defined above and one or more CDRs from another antibody to an antigen. For example, the antibody may be bispecific. A bispecific (or multispecific) antibody, or antigen-binding fragment thereof, according to the present invention may comprise at least one specificity (antigen-binding site of an antibody) as described herein.

Variant antibodies are also included within the scope of the invention. Thus, variants of the sequences recited in the application are also included within the scope of the invention. Such variants include natural variants generated by somatic mutation *in vivo* during the immune response or *in vitro* upon culture of immortalized B cell clones. Alternatively, variants may arise due to the degeneracy of the genetic code or may be produced due to errors in transcription or translation.

Antibodies of the invention may be provided in purified form. Typically, the antibody will be present in a composition that is substantially free of other polypeptides *e.g.*, where less than 90% (by weight), usually less than 60% and more usually less than 50% of the composition is made up of other polypeptides.

Antibodies of the invention may be immunogenic in non-human (or heterologous) hosts e.g., in mice. In particular, the antibodies may have an idiotope that is immunogenic in non-human hosts, but not in a human host. In particular, antibodies of the invention for human use include those that cannot be easily isolated from hosts such as mice, goats, rabbits, rats, non-primate mammals, etc. and cannot generally be obtained by humanization or from xeno-mice.

Nucleic Acids

In another aspect, the invention also provides a nucleic acid molecule comprising a polynucleotide encoding the antibody according to the present invention, or an antigen-binding fragment thereof, as described above.

In some embodiments, the nucleic acid molecule comprises one or more polynucleotide(s) encoding the exemplified antibodies of the invention (e.g., as described in Table 1 above), or a sequence variant thereof as described herein (e.g., having at least 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more sequence identity as described above).

Exemplified nucleic acid sequences encoding the CDR and VH/VL sequences of exemplified antibodies of the invention are shown in Table 2 below.

Table 2: Exemplified nucleic acid CDR and VH/VL sequences (SEQ ID NOs) of exemplified antibodies of the invention.

Antibody name	Heavy chain				Light chain			
	CDR1	CDR2	CDR3	VH	CDR1	CDR2	CDR3	VL
CLM20_A7	76	77	85	87	79	80/86	82	88
CLM20_B8	76	77	78	83	79	80/81	82	84
CLM20_C9	89	90	91	96	92	93/94	95	97
CLM20_B8_UCA	98	99	100	104	79	101/102	103	105
CLM99_G12	106	107	108	113	109	110/111	112	114
CLM99_D10	115	116	117	121	118	110/119	120	122
CLM99_E3	123	124	108	128	125	110/126	127	129
CLM13_G9	130	131	132	137	133	134/135	136	138
CLM20_Bis_B3	139	140	141	145	142	110/143	144	146
ISR42_E7	147	148	149	154	150	151/152	153	155
CSC3_H1	156	157	158	163	159	160/161	162	164
E371_F8	165	166	167	172	168	169/170	171	173
E2418_G12	174	175	176	180	177	151/178	179	181
E2121_B7	182	183	184	189	185	186/187	188	190
E1373_G3	191	192	193	198	194	195/196	197	199
CSC3_H1_UCA	200	201	202	205	159	160/203	204	206

For example, the nucleic acid molecule may comprise:

(i) a polynucleotide according to any one of SEQ ID NOs 83. 87, 96, 104, 113, 121, 128, 137, 145, 154, 163, 172, 180, 189, 198 or 205, or a sequence variant thereof; and a polynucleotide according to any one of SEQ ID NOs 84, 88, 97, 105, 114, 122, 129, 138, 146, 155, 164, 173, 181, 190, 199 or 206, or a sequence variant thereof; or

(ii) a polynucleotide according to any one of SEQ ID NOs 76, 89, 98, 106, 115, 123, 130, 139, 147, 156, 165, 174, 182, 191 or 200, or a sequence variant thereof; a polynucleotide according to any one of SEQ ID NOs 77, 90, 99, 107, 116, 124, 131, 140, 148, 157, 166, 175, 183, 192 or 201, or a sequence variant thereof; a polynucleotide according to any one of SEQ ID NOs 78, 85, 91, 100, 108, 117, 132,

141, 149, 158, 167, 176, 184, 193 or 202, or a sequence variant thereof; a polynucleotide according to any one of SEQ ID NOs 79, 92, 109, 118, 125, 133, 142, 150, 159, 168, 177, 185 or 194, or a sequence variant thereof; a polynucleotide according to any one of SEQ ID NOs 80, 81, 86, 93, 94, 101, 102, 110, 111, 119, 126, 134, 135, 143, 151, 152, 160, 161, 169, 170, 178, 186, 187, 195, 196 or 203, or a sequence variant thereof; and a polynucleotide according to any one of SEQ ID NOs 82, 95, 103, 112, 120, 127, 136, 144, 153, 162, 171, 179, 188, 197 or 204, or a sequence variant thereof.

Preferred sequence combinations are those of the combined six CDR sequences (or the combined VH/VL sequences) of the exemplified antibodies shown in Table 2.

Examples of nucleic acid molecules and/or polynucleotides include, e.g., a recombinant polynucleotide, a vector, an oligonucleotide, an RNA molecule such as an rRNA, an mRNA, an miRNA, an siRNA, or a tRNA, or a DNA molecule such as a cDNA. Nucleic acids may encode the light chain and/or the heavy chain of an antibody. In other words, the light chain and the heavy chain of the antibody may be encoded by the same nucleic acid molecule (e.g., in bicistronic manner). Alternatively, the light chain and the heavy chain of the antibody may be encoded by distinct nucleic acid molecules.

Due to the redundancy of the genetic code, the present invention also comprises sequence variants of nucleic acid sequences, which encode the same amino acid sequences. The polynucleotide encoding the antibody (or the complete nucleic acid molecule) may be optimized for expression of the antibody. For example, codon optimization of the nucleotide sequence may be used to improve the efficiency of translation in expression systems for the production of the antibody. Moreover, the nucleic acid molecule may comprise heterologous elements (i.e., elements, which in nature do not occur on the same nucleic acid molecule as the coding sequence for the (heavy or light chain of) an antibody. For example, a nucleic acid molecule may comprise a heterologous promotor, a heterologous enhancer, a heterologous UTR (e.g., for optimal translation/expression), a heterologous Poly-A-tail, and the like.

A nucleic acid molecule is a molecule comprising nucleic acid components. The term nucleic acid molecule usually refers to DNA or RNA molecules. It may be used synonymous with the term "polynucleotide", i.e. the nucleic acid molecule may consist of a polynucleotide encoding the antibody. Alternatively, the nucleic acid molecule may also comprise further elements in addition to the polynucleotide encoding the antibody. Typically, a nucleic acid molecule is a polymer comprising or consisting of nucleotide monomers which are covalently linked to each other by phosphodiester-bonds of a sugar/phosphate-backbone. The term "nucleic acid molecule" also encompasses modified nucleic acid molecules, such as base-modified, sugar-modified or backbone-modified etc. DNA or RNA molecules.

In general, the nucleic acid molecule may be manipulated to insert, delete or alter certain nucleic acid sequences. Changes from such manipulation include, but are not limited to, changes to introduce restriction sites, to amend codon usage, to add or optimize transcription and/or translation regulatory sequences, etc. It is also possible to change the nucleic acid to alter the encoded amino acids. For example, it may be useful to introduce one or more (*e.g.*, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, etc.) amino acid substitutions, deletions and/or insertions into the antibody's amino acid sequence. Such point mutations can modify effector functions, antigen-binding affinity, post-translational modifications, immunogenicity, etc., can introduce amino acids for the attachment of covalent groups (e.g., labels) or can introduce tags (e.g., for purification purposes). Alternatively, a mutation in a nucleic acid sequence may be "silent", i.e. not reflected in the amino acid sequence due to the redundancy of the genetic code. In general, mutations can be introduced in specific sites or can be introduced at random, followed by selection (e.g., molecular evolution). For instance, one or more nucleic acids encoding any of the light or heavy chains of an (exemplary) antibody can be randomly or directionally mutated to introduce different properties in the encoded amino acids. Such changes can be the result of an iterative process wherein initial changes are retained and new changes at other nucleotide positions are introduced. Further, changes achieved in independent steps may be combined.

In some embodiments, the polynucleotide encoding the antibody, or an antigen-binding fragment thereof, (or the (complete) nucleic acid molecule) may be codon-optimized. The skilled artisan is aware of various tools for codon optimization, such as those described in: Ju

Xin Chin, Bevan Kai-Sheng Chung, Dong-Yup Lee, Codon Optimization OnLine (COOL): a web-based multi-objective optimization platform for synthetic gene design, *Bioinformatics*, Volume 30, Issue 15, 1 August 2014, Pages 2210–2212; or in: Grote A, Hiller K, Scheer M, Munch R, Nortemann B, Hempel DC, Jahn D, JCat: a novel tool to adapt codon usage of a target gene to its potential expression host. Nucleic Acids Res. 2005 Jul 1;33(Web Server issue):W526-31; or, for example, Genscript's OptimumGene™ algorithm (as described in US 2011/0081708 A1).

For example, the nucleic acid molecule of the invention may comprise a nucleic acid sequence as set forth in any one of SEQ ID NOs 76 - 206; or a sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity.

The present invention also provides a combination of a first and a second nucleic acid molecule, wherein the first nucleic acid molecule comprises a polynucleotide encoding the heavy chain of the antibody, or an antigen-binding fragment thereof, of the present invention; and the second nucleic acid molecule comprises a polynucleotide encoding the corresponding light chain of the same antibody, or the same antigen-binding fragment thereof. The above description regarding the (general) features of the nucleic acid molecule of the invention applies accordingly to the first and second nucleic acid molecule of the combination. Accordingly, one or both of the polynucleotides encoding the heavy and/or light chain(s) of the antibody, or an antigen-binding fragment thereof, may be codon-optimized. For example, the combination may comprise a nucleic acid sequence as set forth in any one of SEQ ID NOs 76 – 206; or a sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity.

The present invention also provides a combination of a first and a second nucleic acid molecule, wherein

— the first nucleic acid molecule comprises a polynucleotide encoding the heavy chain of an antibody, or an antigen-binding fragment thereof, the polynucleotide

comprising: (a) nucleotide sequences according to SEQ ID NOs 76, 77 and 78, or sequence variants thereof; or (b) nucleotide sequences according to SEQ ID NOs 76, 77 and 85, or sequence variants thereof; or (c) nucleotide sequences according to SEQ ID NOs 89, 90 and 91, or sequence variants thereof; or (d) nucleotide sequences according to SEQ ID NOs 98, 99 and 100, or sequence variants thereof; or (e) nucleotide sequences according to SEQ ID NOs 106, 107 and 108, or sequence variants thereof; or (f) nucleotide sequences according to SEQ ID NOs 115, 116 and 117, or sequence variants thereof; or (g) nucleotide sequences according to SEQ ID NOs 123, 124 and 108, or sequence variants thereof; or (h) nucleotide sequences according to SEQ ID NOs 130, 131 and 132, or sequence variants thereof; or (i) nucleotide sequences according to SEQ ID NOs 139, 140 and 141, or sequence variants thereof; or (j) nucleotide sequences according to SEQ ID NOs 147, 148 and 149, or sequence variants thereof; or (k) nucleotide sequences according to SEQ ID NOs 156, 157 and 158, or sequence variants thereof; or (l) nucleotide sequences according to SEQ ID NOs 165, 166 and 167, or sequence variants thereof; or (m) nucleotide sequences according to SEQ ID NOs 174, 175 and 176, or sequence variants thereof; or (n) nucleotide sequences according to SEQ ID NOs 182, 183 and 184, or sequence variants thereof; or (o) nucleotide sequences according to SEQ ID NOs 191, 192 and 193, or sequence variants thereof; or (p) nucleotide sequences according to SEQ ID NOs 200, 201 and 202, or sequence variants thereof; and

— the second nucleic acid molecule comprises a polynucleotide encoding the light chain of an antibody, or an antigen-binding fragment thereof, the polynucleotide comprising: (A) nucleotide sequences according to SEQ ID NOs 79, 80 (or 81), and 82, or sequence variants thereof; or (B) nucleotide sequences according to SEQ ID NOs 79, 80 (or 86), and 82, or sequence variants thereof; or (C) nucleotide sequences according to SEQ ID NOs 92, 93 (or 94), and 95, or sequence variants thereof; or (D) nucleotide sequences according to SEQ ID NOs 79, 101 (or 102), and 103, or sequence variants thereof; or (E) nucleotide sequences according to SEQ ID NOs 109, 110 (or 111), and 112, or sequence variants thereof; or (F) nucleotide sequences according to SEQ ID NOs 118, 110 (or 119), and 120, or sequence variants thereof; or (G) nucleotide sequences according to SEQ ID NOs 125, 110 (or 126), and 127, or sequence variants thereof; or (H) nucleotide sequences according to SEQ ID NOs

133, 134 (or 135), and 136, or sequence variants thereof; or (I) nucleotide sequences according to SEQ ID NOs 142, 110 (or 143), and 144, or sequence variants thereof; or (J) nucleotide sequences according to SEQ ID NOs 150, 151 (or 152), and 153, or sequence variants thereof; or (K) nucleotide sequences according to SEQ ID NOs 159, 160 (or 161), and 162, or sequence variants thereof; or (L) nucleotide sequences according to SEQ ID NOs 168, 169 (or 170), and 171, or sequence variants thereof; or (M) nucleotide sequences according to SEQ ID NOs 177, 151 (or 178), and 179, or sequence variants thereof; or (N) nucleotide sequences according to SEQ ID NOs 185, 186 (or 187), and 188, or sequence variants thereof; or (O) nucleotide sequences according to SEQ ID NOs 194, 195 (or 196), and 197, or sequence variants thereof; or (P) nucleotide sequences according to SEQ ID NOs 159, 160 (or 203), and 204, or sequence variants thereof.

Such a combination usually encodes the antibody, or an antigen-binding fragment thereof, of the present invention as described above. Again, the above description regarding the (general) features of the nucleic acid molecule of the invention applies accordingly to the first and second nucleic acid molecule of the combination. As described above, preferred sequence combinations are those of the combined six CDR sequences (or the combined VH/VL sequences) of the exemplified antibodies shown in Table 2.

Vector

Further included within the scope of the invention are vectors, for example, expression vectors, comprising a nucleic acid molecule according to the present invention. Usually, a vector comprises a nucleic acid molecule as described above.

The present invention also provides a combination of a first and a second vector, wherein the first vector comprises a first nucleic acid molecule as described above (for the combination of nucleic acid molecules) and the second vector comprises a second nucleic acid molecule as described above (for the combination of nucleic acid molecules).

A vector is usually a recombinant nucleic acid molecule, i.e. a nucleic acid molecule which does not occur in nature. Accordingly, the vector may comprise heterologous elements (i.e., sequence elements of different origin in nature). For example, the vector may comprise a multi cloning site, a heterologous promotor, a heterologous enhancer, a heterologous selection marker (to identify cells comprising said vector in comparison to cells not comprising said vector) and the like. A vector in the context of the present invention is suitable for incorporating or harboring a desired nucleic acid sequence. Such vectors may be storage vectors, expression vectors, cloning vectors, transfer vectors etc. A storage vector is a vector which allows the convenient storage of a nucleic acid molecule. Thus, the vector may comprise a sequence corresponding, e.g., to a (heavy and/or light chain of a) desired antibody according to the present invention. An expression vector may be used for production of expression products such as RNA, e.g. mRNA, or peptides, polypeptides or proteins. For example, an expression vector may comprise sequences needed for transcription of a sequence stretch of the vector, such as a (heterologous) promoter sequence. A cloning vector is typically a vector that contains a cloning site, which may be used to incorporate nucleic acid sequences into the vector. A cloning vector may be, e.g., a plasmid vector or a bacteriophage vector. A transfer vector may be a vector which is suitable for transferring nucleic acid molecules into cells or organisms, for example, viral vectors. A vector in the context of the present invention may be, e.g., an RNA vector or a DNA vector. For example, a vector in the sense of the present application comprises a cloning site, a selection marker, such as an antibiotic resistance factor, and a sequence suitable for multiplication of the vector, such as an origin of replication. A vector in the context of the present application may be a plasmid vector.

Cells

In a further aspect, the present invention also provides cell expressing the antibody according to the present invention, or an antigen-binding fragment thereof; and/or comprising the vector (or the combination of vectors) according the present invention.

Examples of such cells include but are not limited to, eukaryotic cells, e.g., yeast cells, animal cells or plant cells. Other examples of such cells include but are not limited, to prokaryotic cells, e.g. *E. coli*. In some embodiments, the cells are mammalian cells, such as a mammalian cell line. Examples include human cells, CHO cells, HEK293T cells, PER.C6 cells, NS0 cells, human liver cells, myeloma cells or hybridoma cells.

The cell may be transfected with a vector according to the present invention, for example with an expression vector. The term "transfection" refers to the introduction of nucleic acid molecules, such as DNA or RNA (e.g. mRNA) molecules, into cells, e.g. into eukaryotic or prokaryotic cells. In the context of the present invention, the term "transfection" encompasses any method known to the skilled person for introducing nucleic acid molecules into cells, such as into mammalian cells. Such methods encompass, for example, electroporation, lipofection, e.g. based on cationic lipids and/or liposomes, calcium phosphate precipitation, nanoparticle based transfection, virus based transfection, or transfection based on cationic polymers, such as DEAE-dextran or polyethylenimine etc. In some embodiments, the introduction is non-viral.

Moreover, the cells of the present invention may be transfected stably or transiently with the vector according to the present invention, e.g. for expressing the antibody according to the present invention. In some embodiments, the cells are stably transfected with the vector according to the present invention encoding the antibody according to the present invention. In other embodiments, the cells are transiently transfected with the vector according to the present invention encoding the antibody according to the present invention.

Accordingly, the present invention also provides a recombinant host cell, which heterologously expresses the antibody of the invention or the antigen-binding fragment thereof. For example, the cell may be of another species than the antibody (e.g., CHO cells expressing human antibodies). In some embodiments, the cell type of the cell does not express (such) antibodies in nature. Moreover, the host cell may impart a post-translational modification (PTM; e.g., glycosylation) on the antibody that is not present in their native state. Such a PTM may result in a functional difference (e.g., reduced immunogenicity). Accordingly, the antibody of the invention, or the antigen-binding fragment thereof, may have

a post-translational modification, which is distinct from the naturally produced antibody (e.g., an antibody of an immune response in a human).

Production of Antibodies

Antibodies according to the invention can be made by any method known in the art. For example, the general methodology for making monoclonal antibodies using hybridoma technology is well known (Kohler, G. and Milstein, C., 1975; Kozbar et al. 1983). In some embodiments, the method as described in WO 2004/076677, which is incorporated herein by reference, is used. In this method B cells producing the antibody of the invention are transformed with EBV and a polyclonal B cell activator. Additional stimulants of cellular growth and differentiation may optionally be added during the transformation step to further enhance the efficiency. These stimulants may be cytokines such as IL-2 and IL-15. In one aspect, IL-2 is added during the immortalization step to further improve the efficiency of immortalization, but its use is not essential. The immortalized B cells produced using these methods can then be cultured using methods known in the art and antibodies can be isolated therefrom.

Another exemplified method is described in WO 2010/046775. In this method, plasma cells are cultured in limited numbers, or as single plasma cells in microwell culture plates. Antibodies can be isolated from the plasma cell cultures.

B cells, e.g. obtained from PBMCs of a donor, may be screened for those producing antibodies of the desired specificity or function. The screening step may be carried out by any immunoassay, *e.g.*, ELISA, by staining of tissues or cells (including transfected cells), by neutralization assay or by one of a number of other methods known in the art for identifying desired specificity or function. The assay may be selected on the basis of simple recognition of one or more antigens, or may select on the additional basis of a desired function *e.g.*, to select neutralizing antibodies rather than just antigen-binding antibodies, to select antibodies that can change characteristics of targeted cells, such as their signaling cascades, their shape,

their growth rate, their capability of influencing other cells, their response to the influence by other cells or by other reagents or by a change in conditions, their differentiation status, etc.

The invention also provides (compositions comprising) B cells, such as immortalized B memory cells, or transfected host cells that produce antibodies according to the present invention. From B cell cultures, such as plasma cell cultures, RNA can be extracted and PCR can be performed using methods known in the art. The VH and VL regions of the antibodies can be amplified by RT-PCR (reverse transcriptase PCR) and sequenced.

Based on the sequences of the antibodies, for example the sequences of the exemplified antibodies of the present invention, CDR sequences or VH/VL sequences can be cloned into an expression vector (e.g. for expression of human antibodies, which may contain the sequences of the constant regions). Such expression vectors are well-known in the art and commercially available. The expression vector may then be transfected into HEK293T cells or other host cells, e.g. as described above. The cloning of nucleic acid in expression vectors, the transfection of host cells, the culture of the transfected host cells and the isolation of the produced antibody can be done using any methods known to one of skill in the art.

The antibodies may be further purified, if desired, using filtration, centrifugation and various chromatographic methods such as HPLC or affinity chromatography. Techniques for purification of antibodies, *e.g.*, monoclonal antibodies, including techniques for producing pharmaceutical-grade antibodies, are well known in the art.

Standard techniques of molecular biology may be used to prepare DNA sequences encoding the antibodies of the present invention. Desired DNA sequences may be synthesized completely or in part using oligonucleotide synthesis techniques. Site-directed mutagenesis and polymerase chain reaction (PCR) techniques may be used as appropriate.

Any suitable host cell/vector system may be used for expression of the DNA sequences encoding the antibody molecules of the present invention. Eukaryotic, *e.g.*, mammalian, host cell expression systems may be used for production of antibody molecules, such as complete antibody molecules. Suitable mammalian host cells include, but are not limited to, CHO,

HEK293T, PER.C6, NS0, myeloma or hybridoma cells. Also, prokaryotic, e.g. bacterial host cell expression systems may be used for the production of antibody molecules, such as complete antibody molecules. Suitable bacterial host cells include, but are not limited to, *E. coli* cells.

The present invention also provides a process for the production of an antibody molecule according to the present invention comprising culturing a (heterologous) host cell comprising a vector encoding a nucleic acid of the present invention, in particular under conditions suitable for expression of protein from DNA encoding the antibody molecule of the present invention, and isolating the antibody molecule.

For production of the antibody comprising both heavy and light chains, a host cell, such as a cell line, may be transfected with two vectors, a first vector encoding a light chain polypeptide and a second vector encoding a heavy chain polypeptide, e.g. as described above. Alternatively, a single vector may be used, the vector including sequences encoding light chain and heavy chain polypeptides (e.g. in a bicistronic manner).

Antibodies according to the invention may be produced by (i) expressing a nucleic acid sequence according to the invention in a host cell, e.g. by use of a vector (or host cell) according to the present invention, and (ii) isolating the expressed antibody product. Additionally, the method may include (iii) purifying the isolated antibody.

Thus the invention also provides a method for preparing a recombinant cell, comprising the steps of: (i) obtaining one or more nucleic acids (*e.g.*, heavy and/or light chain mRNAs from the B cell clone or the cultured plasma cells) that encode(s) the antibody of interest; (ii) inserting the nucleic acid into an expression vector and (iii) transfecting the vector into a (heterologous) host cell in order to permit expression of the antibody of interest in that host cell. The nucleic acid of step (i) may, but need not, be manipulated to introduce restriction sites, to change codon usage, and/or to optimize transcription and/or translation regulatory sequences.

Furthermore, the invention also provides a method of preparing a transfected host cell, comprising the step of transfecting a host cell with one or more nucleic acids that encode an antibody of interest, wherein the nucleic acids are nucleic acids that were derived from an immortalized B cell clone or a cultured plasma cell of the invention. Thus the procedures for first preparing the nucleic acid(s) and then using it to transfect a host cell can be performed at different times by different people in different places (e.g., in different countries).

These recombinant cells of the invention can then be used for expression and culture purposes. They are particularly useful for expression of antibodies for large-scale pharmaceutical production. They can also be used as the active ingredient of a pharmaceutical composition. Any suitable culture technique can be used, including but not limited to static culture, roller bottle culture, ascites fluid, hollow-fiber type bioreactor cartridge, modular minifermenter, stirred tank, microcarrier culture, ceramic core perfusion, etc.

Methods for obtaining and sequencing immunoglobulin genes from B cells or plasma cells are well known in the art (e.g., see Chapter 4 of Kuby Immunology, 4th edition, 2000).

The transfected host cell may be a eukaryotic cell, including yeast and animal cells, particularly mammalian cells (e.g., CHO cells, NS0 cells, human cells such as PER.C6, HEK293T or HKB-11 cells, myeloma cells, or a human liver cell), as well as plant cells. In some embodiments, the transfected host cell is a mammalian cell, such as a human cell. In some embodiments, expression hosts can glycosylate the antibody of the invention, particularly with carbohydrate structures that are not themselves immunogenic in humans. In some embodiments the transfected host cell may be able to grow in serum-free media. In further embodiments the transfected host cell may be able to grow in culture without the presence of animal-derived products. The transfected host cell may also be cultured to give a cell line.

The invention also provides a method for preparing one or more nucleic acid molecules (*e.g.*, heavy and light chain genes) that encode an antibody of interest, comprising the steps of: (i) preparing a B cell clone or culturing plasma cells according to the invention; (ii) obtaining

from the B cell clone or the cultured plasma cells nucleic acid that encodes the antibody of interest. Further, the invention provides a method for obtaining a nucleic acid sequence that encodes an antibody of interest, comprising the steps of: (i) preparing a B cell clone or culturing plasma cells according to the invention; (ii) sequencing nucleic acid from the B cell clone or the cultured plasma cells that encodes the antibody of interest.

The invention further provides a method of preparing nucleic acid molecule(s) that encode an antibody of interest, comprising the step of obtaining the nucleic acid that was obtained from a B cell clone or cultured plasma cells of the invention. Thus, the procedures for first obtaining the B cell clone or the cultured plasma cell, and then obtaining nucleic acid(s) from the B cell clone or the cultured plasma cells can be performed at different times by different people in different places (e.g., in different countries).

The invention also comprises a method for preparing an antibody (e.g., for pharmaceutical use) according to the present invention, comprising the steps of: (i) obtaining and/or sequencing one or more nucleic acids (*e.g.*, heavy and light chain genes from the selected B cell clone or the cultured plasma cells) encoding the antibody of interest; (ii) inserting the nucleic acid(s) into or using the nucleic acid(s) sequence(s) to prepare an expression vector; (iii) transfecting a host cell (for expression of the antibody of interest); (iv) culturing or sub-culturing the transfected host cells, in particular under conditions where the antibody of interest is expressed; and, optionally, (v) purifying the antibody of interest.

The invention also provides a method of preparing the antibody of interest comprising the steps of: culturing or sub-culturing a transfected host cell population, e.g. a stably transfected host cell population, under conditions where the antibody of interest is expressed and, optionally, purifying the antibody of interest. The transfected host cell population may be prepared by (i) providing nucleic acid(s) encoding a selected antibody of interest, e.g. that is produced by a B cell clone or cultured plasma cells prepared as described above, (ii) inserting the nucleic acid(s) into an expression vector, (iii) transfecting the vector in a host cell that can express the antibody of interest, and (iv) culturing or sub-culturing the transfected host cell comprising the inserted nucleic acids to produce the antibody of interest. Thus the procedures for first preparing the recombinant host cell and then culturing it to express antibody can be

performed at very different times by different people in different places (e.g., in different countries).

Pharmaceutical Composition

The present invention also provides a pharmaceutical composition comprising one or more of:

(i) the antibody of the present invention, or an antigen-binding fragment thereof;

(ii) the nucleic acid or the combination of nucleic acids of the present invention;

(iii) the vector or the combination of vectors of the present invention; and/or

(iv) the cell expressing the antibody according to the present invention or comprising the vector according to the present invention

and, optionally, a pharmaceutically acceptable excipient, diluent or carrier.

In other words, the present invention also provides a pharmaceutical composition comprising the antibody according to the present invention, the nucleic acid according to the present invention, the vector according to the present invention and/or the cell according to the present invention.

The pharmaceutical composition may optionally also contain a pharmaceutically acceptable carrier, diluent and/or excipient. Although the carrier or excipient may facilitate administration, it should not itself induce the production of antibodies harmful to the individual receiving the composition. Nor should it be toxic. Suitable carriers may be large, slowly metabolized macromolecules such as proteins, polypeptides, liposomes, polysaccharides, polylactic acids, polyglycolic acids, polymeric amino acids, amino acid copolymers and inactive virus particles. In some embodiments, the pharmaceutically acceptable carrier, diluent and/or excipient in the pharmaceutical composition according to the present invention is not an active component in respect to coronavirus infection.

Pharmaceutically acceptable salts can be used, for example mineral acid salts, such as hydrochlorides, hydrobromides, phosphates and sulphates, or salts of organic acids, such as acetates, propionates, malonates and benzoates.

Pharmaceutically acceptable carriers in a pharmaceutical composition may additionally contain liquids such as water, saline, glycerol and ethanol. Additionally, auxiliary substances, such as wetting or emulsifying agents or pH buffering substances, may be present in such compositions. Such carriers enable the pharmaceutical compositions to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries and suspensions, for ingestion by the subject.

Pharmaceutical compositions of the invention may be prepared in various forms. For example, the compositions may be prepared as injectables, either as liquid solutions or suspensions. Solid forms suitable for solution in, or suspension in, liquid vehicles prior to injection can also be prepared (e.g., a lyophilized composition, similar to Synagis™ and Herceptin®, for reconstitution with sterile water containing a preservative). The composition may be prepared for topical administration e.g., as an ointment, cream or powder. The composition may be prepared for oral administration e.g., as a tablet or capsule, as a spray, or as a syrup (optionally flavored). The composition may be prepared for pulmonary administration e.g., as an inhaler, using a fine powder or a spray. The composition may be prepared as a suppository or pessary. The composition may be prepared for nasal, aural or ocular administration e.g., as drops. The composition may be in kit form, designed such that a combined composition is reconstituted just prior to administration to a subject. For example, a lyophilized antibody may be provided in kit form with sterile water or a sterile buffer.

In some embodiments, the (only) active ingredient in the composition is the antibody according to the present invention. As such, it may be susceptible to degradation in the gastrointestinal tract. Thus, if the composition is to be administered by a route using the gastrointestinal tract, the composition may contain agents which protect the antibody from degradation but which release the antibody once it has been absorbed from the gastrointestinal tract.

A thorough discussion of pharmaceutically acceptable carriers is available in Gennaro (2000) Remington: The Science and Practice of Pharmacy, 20th edition, ISBN: 0683306472.

Pharmaceutical compositions of the invention generally have a pH between 5.5 and 8.5, in some embodiments this may be between 6 and 8, for example about 7. The pH may be maintained by the use of a buffer. The composition may be sterile and/or pyrogen free. The composition may be isotonic with respect to humans. In some embodiments pharmaceutical compositions of the invention are supplied in hermetically-sealed containers.

Within the scope of the invention are compositions present in several forms of administration; the forms include, but are not limited to, those forms suitable for parenteral administration, e.g., by injection or infusion, for example by bolus injection or continuous infusion. Where the product is for injection or infusion, it may take the form of a suspension, solution or emulsion in an oily or aqueous vehicle and it may contain formulatory agents, such as suspending, preservative, stabilizing and/or dispersing agents. Alternatively, the antibody may be in dry form, for reconstitution before use with an appropriate sterile liquid.

A vehicle is typically understood to be a material that is suitable for storing, transporting, and/or administering a compound, such as a pharmaceutically active compound, in particular the antibodies according to the present invention. For example, the vehicle may be a physiologically acceptable liquid, which is suitable for storing, transporting, and/or administering a pharmaceutically active compound, in particular the antibodies according to the present invention. Once formulated, the compositions of the invention can be administered directly to the subject. In some embodiments the compositions are adapted for administration to mammalian, e.g., human subjects.

The pharmaceutical compositions of this invention may be administered by any number of routes including, but not limited to, oral, intravenous, intramuscular, intra-arterial, intramedullary, intraperitoneal, intrathecal, intraventricular, transdermal, transcutaneous, topical, subcutaneous, intranasal, enteral, sublingual, intravaginal or rectal routes. Hyposprays may also be used to administer the pharmaceutical compositions of the invention. Optionally, the pharmaceutical composition may be prepared for oral

administration, e.g. as tablets, capsules and the like, for topical administration, or as injectable, e.g. as liquid solutions or suspensions. In some embodiments, the pharmaceutical composition is an injectable. Solid forms suitable for solution in, or suspension in, liquid vehicles prior to injection are also encompassed, for example the pharmaceutical composition may be in lyophilized form.

For injection, e.g. intravenous, cutaneous or subcutaneous injection, or injection at the site of affliction, the active ingredient may be in the form of a parenterally acceptable aqueous solution which is pyrogen-free and has suitable pH, isotonicity and stability. Those of relevant skill in the art are well able to prepare suitable solutions using, for example, isotonic vehicles such as Sodium Chloride Injection, Ringer's Injection, Lactated Ringer's Injection. Preservatives, stabilizers, buffers, antioxidants and/or other additives may be included, as required. Whether it is an antibody, a peptide, a nucleic acid molecule, or another pharmaceutically useful compound according to the present invention that is to be given to an individual, administration is usually in an "effective amount", e.g. in a "prophylactically effective amount" or a "therapeutically effective amount" (as the case may be), this being sufficient to show benefit to the individual. The actual amount administered, and rate and time-course of administration, will depend on the nature and severity of what is being treated. For injection, the pharmaceutical composition according to the present invention may be provided for example in a pre-filled syringe.

The inventive pharmaceutical composition as defined above may also be administered orally in any orally acceptable dosage form including, but not limited to, capsules, tablets, aqueous suspensions or solutions. In the case of tablets for oral use, carriers commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried cornstarch. When aqueous suspensions are required for oral use, the active ingredient, i.e. the antibody as defined above, is combined with emulsifying and suspending agents. If desired, certain sweetening, flavoring or coloring agents may also be added.

The inventive pharmaceutical composition may also be administered topically, especially when the target of treatment includes areas or organs readily accessible by topical

application, e.g. including accessible epithelial tissue. Suitable topical formulations are readily prepared for each of these areas or organs. For topical applications, the inventive pharmaceutical composition may be formulated in a suitable ointment, containing the inventive pharmaceutical composition, particularly its components as defined above, suspended or dissolved in one or more carriers. Carriers for topical administration include, but are not limited to, mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene, polyoxypropylene compound, emulsifying wax and water. Alternatively, the inventive pharmaceutical composition can be formulated in a suitable lotion or cream. In the context of the present invention, suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water.

Dosage treatment may be a single dose schedule or a multiple dose schedule. In particular, the pharmaceutical composition may be provided as single-dose product. In some embodiments, the amount of the antibody in the pharmaceutical composition – in particular if provided as single-dose product – does not exceed 200 mg, for example it does not exceed 100 mg or 50 mg.

For a single dose, e.g. a daily, weekly or monthly dose, the amount of the antibody in the pharmaceutical composition according to the present invention, may not exceed 1 g or 500 mg. In some embodiments, for a single dose, the amount of the antibody in the pharmaceutical composition according to the present invention, may not exceed 200 mg, or 100 mg. For example, for a single dose, the amount of the antibody in the pharmaceutical composition according to the present invention, may not exceed 50 mg.

Pharmaceutical compositions typically include an "effective" amount of one or more antibodies of the invention, i.e. an amount that is sufficient to treat, ameliorate, attenuate, reduce or prevent a desired disease or condition, or to exhibit a detectable therapeutic effect. Therapeutic effects also include reduction or attenuation in pathogenic potency or physical symptoms. The precise effective amount for any particular subject will depend upon their size, weight, and health, the nature and extent of the condition, and the therapeutics or combination of therapeutics selected for administration. The effective amount for a given

situation is determined by routine experimentation and is within the judgment of a clinician. For purposes of the present invention, an effective dose may generally be from about 0.005 to about 100 mg/kg, for example from about 0.0075 to about 50 mg/kg or from about 0.01 to about 10 mg/kg. In some embodiments, the effective dose will be from about 0.02 to about 5 mg/kg, of the antibody of the present invention (e.g. amount of the antibody in the pharmaceutical composition) in relation to the bodyweight (e.g., in kg) of the individual to which it is administered.

Moreover, the pharmaceutical composition according to the present invention may also comprise an additional active component, which may be a further antibody or a component, which is not an antibody. Accordingly, the pharmaceutical composition according to the present invention may comprise one or more of the additional active components.

The antibody according to the present invention can be present either in the same pharmaceutical composition as the additional active component or, alternatively, the antibody according to the present invention is comprised by a first pharmaceutical composition and the additional active component is comprised by a second pharmaceutical composition different from the first pharmaceutical composition. Accordingly, if more than one additional active component is envisaged, each additional active component and the antibody according to the present invention may be comprised in a different pharmaceutical composition. Such different pharmaceutical compositions may be administered either combined/simultaneously or at separate times or at separate locations (e.g. separate parts of the body).

The antibody according to the present invention and the additional active component may provide an additive therapeutic effect, such as a synergistic therapeutic effect. The term "synergy" is used to describe a combined effect of two or more active agents that is greater than the sum of the individual effects of each respective active agent. Thus, where the combined effect of two or more agents results in "synergistic inhibition" of an activity or process, it is intended that the inhibition of the activity or process is greater than the sum of the inhibitory effects of each respective active agent. The term "synergistic therapeutic effect" refers to a therapeutic effect observed with a combination of two or more therapies wherein

the therapeutic effect (as measured by any of a number of parameters) is greater than the sum of the individual therapeutic effects observed with the respective individual therapies.

In other embodiments, the pharmaceutical composition according to the present invention may not comprise an additional active component (in addition to the antibody of the invention or respective nucleic acids, vectors or cells as described above).

In some embodiments, a composition of the invention may include antibodies of the invention, wherein the antibodies may make up at least 50% by weight (*e.g.*, 60%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or more) of the total protein in the composition. In the composition of the invention, the antibodies may be in purified form.

The present invention also provides a method of preparing a pharmaceutical composition comprising the steps of: (i) preparing an antibody of the invention; and (ii) admixing the purified antibody with one or more pharmaceutically acceptable excipients, diluents or carriers.

In other embodiments, a method of preparing a pharmaceutical composition comprises the step of: admixing an antibody with one or more pharmaceutically-acceptable carriers, wherein the antibody is a monoclonal antibody that was obtained from a transformed B cell or a cultured plasma cell of the invention.

As an alternative to delivering antibodies or B cells for therapeutic purposes, it is possible to deliver nucleic acid (typically DNA) that encodes the monoclonal antibody of interest derived from the B cell or the cultured plasma cells to a subject, such that the nucleic acid can be expressed in the subject *in situ* to provide a desired therapeutic effect. Suitable gene therapy and nucleic acid delivery vectors are known in the art.

Pharmaceutical compositions may include an antimicrobial, particularly if packaged in a multiple dose format. They may comprise detergent e.g., a Tween (polysorbate), such as Tween 80. Detergents are generally present at low levels e.g., less than 0.01%. Compositions

may also include sodium salts (e.g., sodium chloride) to give tonicity. For example, a concentration of 10±2mg/ml NaCl is typical.

Further, pharmaceutical compositions may comprise a sugar alcohol (e.g., mannitol) or a disaccharide (e.g., sucrose or trehalose) e.g., at around 15-30 mg/ml (e.g., 25 mg/ml), particularly if they are to be lyophilized or if they include material which has been reconstituted from lyophilized material. The pH of a composition for lyophilization may be adjusted to between 5 and 8, or between 5.5 and 7, or around 6.1 prior to lyophilization.

The compositions of the invention may also comprise one or more immunoregulatory agents. In some embodiments, one or more of the immunoregulatory agents include(s) an adjuvant.

Medical treatments and other uses

In a further aspect, the present invention provides the use of the antibody according to the present invention, or an antigen-binding fragment thereof, the nucleic acid molecule (or the combination of nucleic acid molecules) according to the present invention, the vector (or the combination of vectors) according to the present invention, the cell according to the present invention or the pharmaceutical composition according to the present invention as a medicament. In particular, the antibody according to the present invention, or an antigen-binding fragment thereof, the nucleic acid molecule (or the combination of nucleic acid molecules) according to the present invention, the vector (or the combination of vectors) according to the present invention, the cell according to the present invention, or the pharmaceutical composition according to the present invention may be used in prophylaxis and/or treatment of coronavirus infection; or in (ii) diagnosis of coronavirus infection.

Accordingly, the present invention also provides a method of ameliorating or reducing coronavirus infection (or symptoms thereof), or lowering the risk of coronavirus infection, comprising: administering to a subject in need thereof, a therapeutically effective amount of the antibody, or an antigen-binding fragment thereof, according to the present invention, the nucleic acid molecule (or the combination of nucleic acid molecules) according to the

present invention, the vector (or the combination of vectors) according to the present invention, the cell according to the present invention or the pharmaceutical composition according to the present invention. Moreover, the present invention also provides the use of the antibody according to the present invention, or an antigen-binding fragment thereof, the nucleic acid molecule (or the combination of nucleic acid molecules) according to the present invention, the vector (or the combination of vectors) according to the present invention, the cell according to the present invention, or the pharmaceutical composition according to the present invention in the manufacture of a medicament for prophylaxis, treatment or attenuation of coronavirus infection.

Prophylaxis of coronavirus infection refers in particular to prophylactic settings, wherein the subject was not diagnosed with a coronavirus (either no diagnosis was performed or diagnosis results were negative) and/or the subject does not show symptoms of coronavirus infection. In therapeutic settings, in contrast, the subject is typically diagnosed with coronavirus infection and/or showing symptoms of coronavirus infection. Of note, the terms "treatment" and "therapy"/"therapeutic" of coronavirus infection include (complete) cure as well as attenuation/reduction of coronavirus infection and/or related symptoms.

In some embodiments the subject may be a human. One way of checking efficacy of therapeutic treatment involves monitoring disease symptoms after administration of the antibody according to the present invention, or an antigen-binding fragment thereof, the nucleic acid molecule (or the combination of nucleic acid molecules) according to the present invention, the vector (or the combination of vectors) according to the present invention, the cell according to the present invention, or the pharmaceutical composition according to the present invention. Treatment can be a single dose schedule or a multiple dose schedule. In some embodiments, an antibody, antibody fragment, nucleic acid, vector, cell or composition according to the invention is administered to a subject in need of such treatment. Such a subject includes, but is not limited to, one who is particularly at risk of or susceptible to coronavirus infection, including, for example, an immunocompromised subject.

As used herein, the term "coronavirus infection" refers to the infection with any coronavirus. Different coronaviruses may cause different diseases (which are all coronavirus infections). Preferably, the antibody according to the present invention, or an antigen-binding fragment thereof, the nucleic acid molecule (or the combination of nucleic acid molecules) according to the present invention, the vector (or the combination of vectors) according to the present invention, the cell according to the present invention, or the pharmaceutical composition according to the present invention may be used for the prophylaxis or treatment of SARS-CoV-2 infection. In some embodiments, the antibody according to the present invention, or an antigen-binding fragment thereof, the nucleic acid molecule (or the combination of nucleic acid molecules) according to the present invention, the vector (or the combination of vectors) according to the present invention, the cell according to the present invention, or the pharmaceutical composition according to the present invention may be used for the prophylaxis or treatment of SARS-CoV infection. In some embodiments, the antibody according to the present invention, or an antigen-binding fragment thereof, the nucleic acid molecule (or the combination of nucleic acid molecules) according to the present invention, the vector (or the combination of vectors) according to the present invention, the cell according to the present invention, or the pharmaceutical composition according to the present invention may be used for the prophylaxis or treatment of MERS-CoV infection. In some embodiments, the antibody according to the present invention, or an antigen-binding fragment thereof, the nucleic acid molecule (or the combination of nucleic acid molecules) according to the present invention, the vector (or the combination of vectors) according to the present invention, the cell according to the present invention, or the pharmaceutical composition according to the present invention may be used for the prophylaxis or treatment of HCoV-OC43 infection. In some embodiments, the antibody according to the present invention, or an antigen-binding fragment thereof, the nucleic acid molecule (or the combination of nucleic acid molecules) according to the present invention, the vector (or the combination of vectors) according to the present invention, the cell according to the present invention, or the pharmaceutical composition according to the present invention may be used for the prophylaxis or treatment of HCoV-HKU1 infection. In some embodiments, the antibody according to the present invention, or an antigen-binding fragment thereof, the nucleic acid molecule (or the combination of nucleic acid molecules) according to the present invention, the vector (or the combination of vectors) according to the present

invention, the cell according to the present invention, or the pharmaceutical composition according to the present invention may be used for the prophylaxis or treatment of HCoV-229E infection. In some embodiments, the antibody according to the present invention, or an antigen-binding fragment thereof, the nucleic acid molecule (or the combination of nucleic acid molecules) according to the present invention, the vector (or the combination of vectors) according to the present invention, the cell according to the present invention, or the pharmaceutical composition according to the present invention may be used for the prophylaxis or treatment of HCoV-NL63 infection.

For example, human coronavirus OC43 (HCoV-OC43), human coronavirus HKU1 (HCoV-HKU1), human coronavirus 229E (HCoV-229E), and human coronavirus NL63 (HCoV-NL63) often cause mild symptoms, such as a common cold. On the other hand, more severe symptoms may be caused by Middle East respiratory syndrome-related coronavirus (MERS-CoV), which causes MERS; Severe acute respiratory syndrome coronavirus (SARS-CoV), which causes SARS; and Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes COVID-19. Accordingly, the antibody according to the present invention, or an antigen-binding fragment thereof, the nucleic acid molecule (or the combination of nucleic acid molecules) according to the present invention, the vector (or the combination of vectors) according to the present invention, the cell according to the present invention, or the pharmaceutical composition according to the present invention may be used for the prophylaxis or treatment of (coronavirus-induced) common cold, MERS, SARS or COVID-19.

In a further aspect, the present invention also provides a method of reducing or inhibiting fusion of the coronavirus (SARS-CoV-2) spike protein with (human) ACE2 using the antibody according to the present invention, or an antigen-binding fragment thereof, the nucleic acid molecule (or the combination of nucleic acid molecules) according to the present invention, the vector (or the combination of vectors) according to the present invention, the cell according to the present invention or the pharmaceutical composition according to the present invention.

Moreover, the antibody, or the antigen-binding fragment of the present invention, may be combined with a molecule that can mimic binding to a spike protein receptor, in particular

binding to ACE2. Without being bound to any theory, it is assumed that the combination with a molecule that can mimic binding to ACE2 can greatly enhance the neutralization potency of an anti-fusion peptide antibody of the invention, since ACE2-engagement induces an intermediate conformation change that exposes the fusion peptide epitope. Accordingly, the present invention also provides a combination therapy, wherein administration of the antibody, or the antigen-binding fragment of the present invention, is combined with administration of a molecule that can mimic binding to a spike protein receptor, in particular binding to ACE2. Accordingly, the present invention also provides a combination (therapy), as well as a kit-of-parts, comprising (i) the antibody according to the present invention, or an antigen-binding fragment thereof, the nucleic acid molecule (or the combination of nucleic acid molecules) according to the present invention, the vector (or the combination of vectors) according to the present invention, the cell according to the present invention or the pharmaceutical composition according to the present invention; and (ii) a molecule that can mimic binding to a spike protein receptor, in particular binding to ACE2.

Examples of such molecules that can mimic binding to a spike protein receptor, in particular binding to ACE2, for combination are known in the art and include, but are not limited to, small molecules and antibodies. In some embodiments, the antibody according to the present invention, or an antigen-binding fragment thereof, the nucleic acid molecule (or the combination of nucleic acid molecules) according to the present invention, the vector (or the combination of vectors) according to the present invention, the cell according to the present invention or the pharmaceutical composition according to the present invention may be combined with recombinant soluble human ACE2 protein, e.g. as described in Zoufaly A, Poglitsch M, Aberle JH, Hoepler W, Seitz T, Traugott M, Grieb A, Pawelka E, Laferl H, Wenisch C, Neuhold S, Haider D, Stiasny K, Bergthaler A, Puchhammer-Stoeckl E, Mirazimi A, Montserrat N, Zhang H, Slutsky AS, Penninger JM. Human recombinant soluble ACE2 in severe COVID-19. Lancet Respir Med. 2020 Nov;8(11):1154-1158. doi: 10.1016/S2213-2600(20)30418-5. In some embodiments, the antibody according to the present invention, or an antigen-binding fragment thereof, the nucleic acid molecule (or the combination of nucleic acid molecules) according to the present invention, the vector (or the combination of vectors) according to the present invention, the cell according to the present invention or the pharmaceutical composition according to the present invention may be combined with

human ACE2 peptides, e.g. as described in Karoyan, P., Vieillard, V., Gómez-Morales, L. et al. Human ACE2 peptide-mimics block SARS-CoV-2 pulmonary cells infection. Commun Biol 4, 197 (2021). https://doi.org/10.1038/s42003-021-01736-8.

Suitable antibodies mimicking ACE2, which may be useful for the combination with the antibody according to the present invention, or an antigen-binding fragment thereof, the nucleic acid molecule (or the combination of nucleic acid molecules) according to the present invention, the vector (or the combination of vectors) according to the present invention, the cell according to the present invention or the pharmaceutical composition according to the present invention are known in the art and described, for example, in Tortorici et al., 2020 (Tortorici MA, Beltramello M, Lempp FA, et al. Ultrapotent human antibodies protect against SARS-CoV-2 challenge via multiple mechanisms. *Science.* 2020;370(6519):950-957. doi:10.1126/science.abe3354) and in Lempp et al., 2021 (Lempp, F.A., Soriaga, L.B., Montiel-Ruiz, M. *et al.* Lectins enhance SARS-CoV-2 infection and influence neutralizing antibodies. *Nature* (2021). https://doi.org/10.1038/s41586-021-03925-1). Examples of ACE2-mimicking antibodies, which may be combined with the antibodies of the invention include, but are not limited to, S2E12 (Vir), S2X58 (Vir), S2X259 (Vir), Ly-CoV016 (Eli Lily), CT-P59 (Celltrion) and REGN10933 (Regeneron).

Antibodies and fragments thereof as described in the present invention may also be used for the (*in-vitro*) diagnosis of coronavirus infection. Methods of diagnosis may include contacting an antibody with a sample. Such samples may be isolated from a subject, for example an isolated tissue sample taken from, for example, nasal passages, sinus cavities, salivary glands, lung, liver, pancreas, kidney, ear, eye, placenta, alimentary tract, heart, ovaries, pituitary, adrenals, thyroid, brain, skin or blood, such as plasma or serum. For example, the antibody, or an antigen-binding fragment thereof, may be contacted with an (isolated) blood sample (e.g., whole blood, plasma or serum). The methods of diagnosis may also include the detection of an antigen/antibody complex, in particular following the contacting of an antibody with a sample. Such a detection step is typically performed at the bench, i.e. without any contact to the human or animal body. Examples of detection methods are well-known to the person skilled in the art and include, e.g., ELISA (enzyme-linked immunosorbent assay). Accordingly, the diagnosis may be performed *in vitro*, for example by using an isolated

sample as described above (and an *in vitro* detection step of an antigen/antibody complex). Accordingly, the antibody, or an antigen-binding fragment thereof, may be used in (*in vitro*) diagnosis of coronavirus infection.

Accordingly, the antibody of the present invention, or an antigen-binding fragment thereof, may be used in an (*in vitro*) method for detecting a coronavirus antigen. For detecting a coronavirus antigen, the antibody may be brought in contact with a (isolated) sample (i.e., a sample to be tested for the presence of the antigen), e.g. as described above. By the specific binding of the antibody to its antigen (coronavirus spike protein), an antibody/antigen complex is formed, which can be easily detected by methods known in the art.

Such a detection method may be used in the context of (*in vitro*) diagnosis (with samples isolated from a human or animal body), but also for testing other (e.g., production/manufacture) samples, such as vaccine samples. Furthermore, the antibody of the present invention, or an antigen-binding fragment thereof, may be used as a tool to detect antibodies (or other molecules) that can mimic ACE2 and/or promote spike conformational changes. Accordingly, antibodies, antibody fragments, or variants thereof, as described in the present invention may also be used in a non-therapeutic/non-diagnostic context, e.g. in a vaccine development or manufacture. The present invention therefore also provides the use of the antibody of the present invention, or an antigen-binding fragment thereof, for testing vaccines, in particular whether the antigen (i.e., the desired antigen contained in the vaccine) is properly generated and/or folded (and/or in the correct conformation). Accordingly, the antibodies may be used for monitoring vaccine manufacture with the desired immunogenicity. To this end, the antibody may be brought in contact with the vaccine, e.g. as described above. Accordingly, the present invention also provides a method for testing anti-coronavirus vaccines, wherein the vaccine is contacted with the antibody, or an antigen-binding fragment thereof, and, optionally, the presence of antibody/antigen complexes is determined. Furthermore, the present invention also encompasses the use of the antibody of the present invention, or an antigen-binding fragment thereof, for monitoring the quality of anti-coronavirus vaccines by checking whether the vaccine contains the desired antigen, e.g. the coronavirus spike protein, or a fragment or variant thereof. More specifically, the antibody may be used to check the conformation of the antigen, or an epitope thereof, in a vaccine.

Furthermore, also modified versions of the antigen can be tested with the antibodies of the invention, such as fragments and variants of the coronavirus S protein, which may be useful in a vaccine. In particular, the antibodies of the present invention may also be useful for the design and development of universal vaccines. Without being bound to any theory, it is assumed that in view of the strict conservation of the fusion peptide epitope, that this region of the spike protein may be functionally conserved, such that escape mutants may come at a cost of viral fitness. Therefore, it provides an attractive target for designing a (universal) coronavirus vaccine.

Vaccines and uses thereof

In a further aspect, the present invention also provides a recombinant peptide, polypeptide or protein comprising (or consisting of) an amino acid sequence according to general formula I or Ia:

$$SX_1X_2EDLLFX_3K \quad (I)$$

$$X_2EDLLFX_3K \quad (Ia)$$

wherein X_1, X_2 and X_3 may be any amino acid.

More preferably, the recombinant peptide, polypeptide or protein comprises (or consists of) an amino acid sequence according to general formula II:

$$RSX_1X_2EDLLFX_3K \quad (II)$$

wherein X_1, X_2 and X_3 may be any amino acid.

In general formula I and II, X_1 is preferably a non-polar and/or neutral amino acid, such as an amino acid selected from A, C, G, I, L, M, F, P, W and V; more preferably X_1 is A, L or F; even more preferably X_1 is Y, V, L, I or E. In some embodiments, X_1 is not P. Preferably, X_1 is F.

In general formula I, Ia and II, X_2 is preferably an aliphatic, non-polar and/or neutral amino acid, such as an amino acid selected from A, G, I, L, and V. In some embodiments, X_2 is I, L, F, S or V. More preferably X_2 is I or L. Even more preferably X_2 is I.

In general formula I, Ia and II, X_3 is preferably a polar amino acid, such as an amino acid selected from R, N, D, Q, E, H, K, S, T or Y; more preferably X_3 is N, H, K, S, T or D; even more preferably X_3 is N, S, T or D; still more preferably X_3 is N, S or D. In some embodiments, X_3 is N or D.

In some embodiments, the recombinant peptide, polypeptide or protein comprises an amino acid sequence according to general formula I or II, wherein X_1 is A, L or F; X_2 is I or L; and X_3 is N, S, T or D, preferably wherein X_1 is A, L or F; X_2 is I or L; and X_3 is N, S or D.

In some embodiments, the recombinant peptide, polypeptide or protein comprises (or consists of) an amino acid sequence according to SEQ ID NO: 264 or a sequence variant thereof which includes 1, 2, 3 or 4 mutations in comparison to SEQ ID NO: 264. In some embodiments, the sequence variant includes three or four mutations in comparison to SEQ ID NO: 264. Preferred positions of these mutations are positions I1, L4, N7 and/or K8 in SEQ ID NO: 264. Preferably, the sequence variant has at least 75% sequence identity, preferably at least 87% sequence identity to SEQ ID NO: 264. Accordingly, it is preferred that SEQ ID NO: 264 includes no more than one or two mutation(s). Also these mutations may preferably occur at any one of positions I1, L4, N7 and/or K8 in SEQ ID NO: 264. More preferred positions of these mutations are those of X_2 and X_3 in general formula Ia above (corresponding to positions I1 and N7 in SEQ ID NO: 264, respectively). Accordingly, an amino acid sequence with at least 75% sequence identity to SEQ ID NO: 264 is preferably mutated at positions X_2 and X_3 of general formula Ia. An amino acid sequence with at least 87% sequence identity to SEQ ID NO: 264 is preferably mutated either at position X_2 or at position X_3 (but not at both) of general formula Ia. Even more preferably, the recombinant peptide, polypeptide or protein comprises (or consists of) an amino acid sequence according to SEQ ID NO: 264.

In some embodiments, the recombinant peptide, polypeptide or protein comprises (or consists of) an amino acid sequence according to SEQ ID NO: 8 or a sequence variant thereof having at least 70% sequence identity, preferably at least 80% sequence identity and more preferably at least 90% sequence identity. In some embodiments, SEQ ID NO: 8 may include one or more (e.g., 1, 2, 3, 4 or 5) mutations, preferably at any one of positions F2, I3, L6, N9 and/or K10 of SEQ ID NO: 8. Preferably, SEQ ID NO: 8 may include up to three (1, 2 or 3) mutations. Preferred positions of these mutations are those of X_1, X_2 and X_3 in general formula I above (corresponding to F2, I3 and N9, respectively, in SEQ ID NO: 8). The above-mentioned preferred mutations for each of those positions in general formula I likewise apply to SEQ ID NO: 8. Accordingly, an amino acid sequence with at least 70% sequence identity to SEQ ID NO: 8 is preferably mutated at positions X_1, X_2 and X_3 of general formula I. An amino acid sequence with at least 80% sequence identity to SEQ ID NO: 8 is preferably mutated at positions X_1 and X_3 of general formula I or at positions X_2 and X_3 of general formula I. An amino acid sequence with at least 90% sequence identity to SEQ ID NO: 8 is preferably mutated at position X_1, X_2 or X_3 of general formula I. Even more preferably, the recombinant peptide, polypeptide or protein comprises (or consists of) an amino acid sequence according to SEQ ID NO: 8.

In some embodiments, the recombinant peptide, polypeptide or protein comprises (or consists of) an amino acid sequence according to SEQ ID NO: 265 or a sequence variant thereof having at least 70% sequence identity, preferably at least 80% sequence identity and more preferably at least 90% sequence identity. In some embodiments, SEQ ID NO: 265 may include one or more (e.g., 1, 2, 3, 4 or 5) mutations, preferably at any one of positions F3, I4, L7, N10 and/or K11 of SEQ ID NO: 265. Preferably, SEQ ID NO: 265 may include up to three (1, 2 or 3) mutations. Preferred positions of these mutations are those of X_1, X_2 and X_3 in general formula II above (corresponding to F3, I4 and N10, respectively, in SEQ ID NO: 265). The above-mentioned preferred mutations for each of those positions in general formula II likewise apply to SEQ ID NO: 265. Accordingly, an amino acid sequence with at least 70% sequence identity to SEQ ID NO: 265 is preferably mutated at positions X_1, X_2 and X_3 of general formula II. An amino acid sequence with at least 80% sequence identity to SEQ ID NO: 265 is preferably mutated at positions X_1 and X_3 of general formula II or at positions X_2 and X_3 of general formula II. An amino acid sequence with at least 90% sequence identity to

SEQ ID NO: 265 is preferably mutated at position X_1, X_2 or X_3 of general formula II. Even more preferably, the recombinant peptide, polypeptide or protein comprises (or consists of) an amino acid sequence according to SEQ ID NO: 265.

In some embodiments, the recombinant peptide, polypeptide or protein comprises (or consists of) an amino acid sequence according to SEQ ID NO: 265 or a sequence variant thereof, wherein R_1, E_5 and F_9 of SEQ ID NO: 265 are maintained. In some embodiments, the recombinant peptide, polypeptide or protein comprises (or consists of) an amino acid sequence according to SEQ ID NO: 265 or a sequence variant thereof, wherein R_1, E_5 and F_9 of SEQ ID NO: 265 may be maintained and wherein

S_2 is substituted with V, R, M, G, E or A, preferably with G;

F_3 is substituted with Y, V, T, S, R, M, L, K, I, E, D or A, preferably with Y, V, L, I, or E;

I_4 is substituted with Y, V or L, preferably with L;

D_6 is substituted with Y, W, V, T, S, M, L, I, F, C or A, preferably with Y, T, S or F;

L_7 is substituted with Y, V, T, M, I, or F, preferably with Y, V, I or F;

L_8 is substituted with I;

N_{10} is substituted with any amino acid except P, preferably with Y, W, V, T, S, R, Q, M, L, K, I, G, F, E, D, C or A; and/or

K_{11} is substituted with V, T, S, M, I, G, F, E or A, preferably with T, S, M, G, E or A.

In some embodiments, the recombinant peptide, polypeptide or protein comprises (or consists of) an amino acid sequence according to SEQ ID NO: 265 or a sequence variant thereof, wherein R_1, E_5, L_8 and F_9 of SEQ ID NO: 265 may be maintained and wherein

S_2 is substituted with V, T, R, Q, P, M, K, G, E, D or A, preferably with E, D or A;

F_3 is substituted with any amino acid, preferably with V, I, M, E, D or A;

I_4 is substituted with Y, V, L or F;

D_6 is substituted with E;

L_7 is substituted with Y, V, T, S, M, I, F or A, preferably with V, I or F;

N_{10} is substituted with any amino acid except P, preferably with Y, W, V, T, S, R, Q, M, L, K, I, G, F, E, D, C or A; and/or

K_{11} with V, T, S, M, G, E or A, preferably with T, S, G, E or A.

In some embodiments, the recombinant peptide, polypeptide or protein comprises (or consists of) an amino acid sequence according to SEQ ID NO: 267 or a sequence variant thereof having at least 70% sequence identity, preferably at least 80% sequence identity and more preferably at least 90% sequence identity. In some embodiments, SEQ ID NO: 267 may include one or more (e.g., 1, 2, 3, 4 or 5) mutations, preferably at any one of positions F4, I5, L8, N11 and/or K12 of SEQ ID NO: 267. Preferably, SEQ ID NO: 267 may include up to three (1, 2 or 3) mutations. Preferred positions of these mutations are F4, I5 and/or N11 of SEQ ID NO: 267. The above-mentioned preferred mutations for each of those positions in general formula II likewise apply to SEQ ID NO: 267. Even more preferably, the recombinant peptide, polypeptide or protein comprises (or consists of) an amino acid sequence according to SEQ ID NO: 267.

More preferably, the recombinant peptide, polypeptide or protein comprises (or consists of) an amino acid sequence according to any one of SEQ ID NOs 1 – 7. An alignment of SEQ ID NOs 1 – 7 is shown in Fig. 3. In particular, the recombinant peptide, polypeptide or protein may comprise or consist of an amino acid sequence according to SEQ ID NO: 1 or a sequence variant thereof having at least 70% sequence identity, preferably at least 80% or 85% sequence identity and more preferably at least 90% or 95% sequence identity. Even more preferably, the recombinant peptide, polypeptide or protein comprises (or consists of) the amino acid sequence according to SEQ ID NO: 1. In some embodiments, the recombinant peptide, polypeptide or protein may comprise or consist of an amino acid sequence according to SEQ ID NO: 268 and/or an amino acid sequence according to SEQ ID NO: 269; or a sequence variant thereof having at least 70% sequence identity, preferably at least 80% or 85% sequence identity and more preferably at least 90% or 95% sequence identity.

This sequence of the fusion peptide of the coronavirus spike protein is recognized by the antibodies of the invention, which bind to various alpha- and betacoronaviruses. Accordingly, a peptide, polypeptide or protein comprising said sequence can elicit an immune response with broadly coronavirus targeting antibodies, while antibodies eliciting viral escape mutants, such as antibodies targeting the RBD, can be avoided.

The recombinant peptide, polypeptide or protein does usually not occur in nature. Accordingly, it differs from naturally occurring spike proteins of coronaviruses.

In some embodiments, the recombinant peptide, polypeptide or protein may comprise or consist of a fragment of a (naturally occurring) coronavirus spike protein or a sequence variant thereof, for example a fragment comprising at least the sequence of general formulae I, Ia or II (or the sequence of SEQ ID NOs 1, 264, 265, 267 or 8 including the above-mentioned variants). Preferably, the fragment is a fragment of the coronavirus spike S2 protein (i.e., not the entire spike S2 protein). In some embodiments, the fragment is (consists of) the peptide of general formula I, Ia or II. In some embodiments, the fragment is the peptide of SEQ ID NO: 1 or 8, or a sequence variant thereof as described above. In some embodiments, the fragment is the peptide of SEQ ID NO: 264, 265 or 267, or a sequence variant thereof as described above. Preferably, the fragment contains as few as possible (e.g., none or no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20) additional amino acids (of the coronavirus spike sequence) outside the above-mentioned sequence motifs. In some embodiments, the recombinant peptide, polypeptide or protein contains additional amino acids, in particular sequences of non-coronavirus origin, for example, a linker or a tag. Accordingly, the recombinant peptide, polypeptide or protein may contain (i) a fragment of a (naturally occurring) coronavirus spike protein or a sequence variant thereof, in particular a fragment comprising at least the sequence of general formulae I, Ia or II (or the sequence of SEQ ID NOs 1, 264, 265, 267 or 8 including the above-mentioned sequence variants); and (ii) an additional amino acid sequence, which is preferably not present in coronavirus spike proteins (e.g., sequences of non-coronavirus origin).

In some embodiments, the recombinant peptide, polypeptide or protein comprises or consists of a larger fragment of the coronavirus spike protein (in particular a fragment of the S2 protein), wherein the fragment of the spike protein contains 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35, 40, 45, 50 or more amino acids. For example, the fragment may be restricted to the fusion peptide of the spike protein or to a (N-terminal) portion of said fusion peptide.

In some embodiments, the recombinant peptide, polypeptide or protein (or the fragment of the spike protein contained therein) contains conserved epitopes (among coronaviruses) only. In some embodiments, the recombinant peptide, polypeptide or protein (or the fragment of the spike protein contained therein) does not contain non-conserved epitopes. In some embodiments, the recombinant peptide, polypeptide or protein does not contain an RBD sequence of a coronavirus spike protein. In some embodiments, the recombinant peptide, polypeptide or protein contains a fragment of the coronavirus spike S2 protein, which does not contain a transmembrane domain. In some embodiments, the recombinant peptide, polypeptide or protein contains a fragment of the coronavirus spike S2 protein, which does not contain a heptad repeat (of the coronavirus spike protein). In some embodiments, the recombinant peptide, polypeptide or protein contains a fragment of the coronavirus spike S2 protein, which does not contain a central helix (of the coronavirus spike protein). Fragments of the spike protein, in particular fragments restricted to the above-mentioned sequence motifs of the fusion peptide, may be advantageous to specifically elicit an immune response with broadly coronavirus targeting antibodies, while antibodies eliciting viral escape mutants, such as antibodies targeting the RBD, can be avoided.

In some embodiments, the recombinant peptide, polypeptide or protein contains a mutation (e.g., at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more amino acid positions) in comparison to a (naturally occurring) coronavirus spike protein. The term "mutation" includes addition, deletion or substitution of an amino acid (one or more amino acids as outlined above).

In some embodiments, the length of the recombinant peptide, polypeptide or protein does not exceed 100 amino acids (e.g., it does not exceed 100, 90, 80, 70, 60 or 50 amino acids). Preferably, the length of the recombinant peptide does not exceed 45 amino acids (e.g., it does not exceed 45, 40, 35 or 30 amino acids). More preferably, the length of the recombinant peptide does not exceed 25 amino acids (e.g., it does not exceed 25, 24, 23, 22, 21, 20, 19, 18, 17 or 16 amino acids). Even more preferably, the length of the recombinant peptide does not exceed 15 amino acids (e.g., it does not exceed 15, 14, 13 or 12 amino acids). Particularly preferably, the length of the recombinant peptide does not exceed 10 or 11 amino acids.

In some embodiments, the recombinant peptide, polypeptide or protein is immunogenic. In other words, the recombinant peptide, polypeptide or protein may induce or enhance an immune response, in particular a specific immune response directed to the coronavirus spike protein (in particular to the spike protein sequence of the recombinant peptide, polypeptide or protein). The recombinant peptide, polypeptide or protein may contain amino acid sequences (not present in naturally occurring spike proteins) to increase immunogenicity.

Accordingly, the recombinant peptide, polypeptide or protein may consist of the amino acid sequence as described above; or it may comprise (i) the amino acid sequence as described above and (ii) an additional amino acid sequence, preferably providing a synergistic functionality and/or an additional functionality to the protein. In other words, such an additional amino acid sequence may preferably provide a functionality, in addition to the peptide's functionality (as immunogen/antigen), which is preferably synergistic with to the peptide's functionality (as immunogen/antigen). Non-limiting examples of such functionalities include (i) targeting and (ii) immunogenicity.

To this end, the protein according to the present invention is preferably a fusion protein. Fusion proteins typically comprise two or more distinct functionalities. Accordingly, fusion proteins typically comprise "parts" from different sources, for example a fusion protein comprises distinct proteins/peptides encoded by at least two distinct genes or parts of (distinct) genes. Accordingly, fusion proteins may be also referred to as "chimeric proteins".

In some embodiments, the protein according to the present invention further comprises targeting moiety, such as a targeting peptide. In general, a targeting peptide is peptide chain that directs the transport of a protein to a specific location, for example to a specific cell type, into cells or to a specific region in the cell, including the nucleus, mitochondria, endoplasmic reticulum (ER), chloroplast, apoplast, peroxisome and plasma membrane. Targeting peptides may optionally be cleaved from the protein, e.g. by signal peptidases, after the proteins are transported to the specific location. Preferred targeting peptides include antibodies and fragments thereof, such as scFV. For example, such antibodies or antibody fragments may be directed to surface molecules of specific cell types.

For example, the targeting peptide may have a length of no more than 1000 amino acids, preferably of no more than 500 amino acids, more preferably of no more than 200 amino acids, even more preferably of no more than 100 amino acids, still more preferably of no more than 80 amino acids, particularly preferably of no more than 70 amino acids and most preferably of no more than 50 amino acids. For example, the targeting peptide may have a length from 3 to 70 amino acids.

Preferably the targeting moiety, in particular the targeting peptide, targets the protein according to the present invention to a specific cell type. More preferably, the targeting moiety, in particular the targeting peptide, targets the protein according to the present invention to antigen-presenting cells, such as to dendritic cells. An antigen-presenting cell (APC) typically displays an antigen complexed with major histocompatibility complexes (MHCs) on their surfaces; a process known as "antigen presentation". T cells may recognize these complexes using their T cell receptors (TCRs). Accordingly, APCs process antigens and present them to T-cells. Antigen-presenting cells are vital for effective adaptive immune response, as the functioning of both cytotoxic and helper T cells is dependent on APCs. Antigen presentation allows for specificity of adaptive immunity and can contribute to immune responses against both intracellular and extracellular pathogens.

Preferably, the targeted APC is a professional APC. Professional antigen-presenting cells specialize in presenting antigen to T cells and are very efficient at internalizing antigens, for example by phagocytosis (macrophages and dendritic cells) or by receptor-mediated endocytosis (B cells), processing the antigen into peptide fragments and then displaying those peptides, bound to a class II MHC molecule, on their membrane. Preferred examples of APCs to be targeted include macrophages, B cells and dendritic cells.

Most preferably, the targeted APC is a dendritic cell (DC). Dendritic cells have the broadest range of antigen presentation and are necessary for activation of naive T cells. DCs present antigen to both helper and cytotoxic T cells. They can also perform cross-presentation, a process by which they present an exogenous antigen on MHC class I molecules to cytotoxic T cells. Cross-presentation allows for the activation of these T cells. Dendritic cells may be recognized by a targeting moiety, such as a targeting peptide, by their specific receptors

including DEC-205, Clec9A and Clec12A. Thereby, the protein is typically directed to dendritic cells, which may then process the protein and present the antigen/immunogen, such as the peptide according to the present invention, in order to trigger an immune response.

The recombinant peptide, polypeptide or protein according to the present invention may further comprise an immunogenic (poly)peptide. In general, an immunogenic (poly)peptide increases the immunogenicity of the peptide according to the present invention. To this end, an immunogenic peptide is, by itself, immunogenic, i.e. able to elicit an immune response. For example, an immunogenic peptide may comprise an antigen/immunogen distinct from the peptide according to the present invention. Many immunogenic peptides are known in the art. Moreover, it is well known to the skilled person how immunogenic peptides can be designed, for example as described in Flower D.R., 2013, Nature Chemical Biology 9(12): 749–753: Designing immunogenic peptides.

The recombinant peptide, polypeptide or protein according to the present invention may further comprise linker sequences, as known in the art, for example "GS-linkers".

In a further aspect, the present invention also provides a peptide conjugate, wherein the recombinant peptide, polypeptide or protein according to the present invention is conjugated to an immunogenic carrier, e.g. as described above. Preferably, the peptide conjugate is a peptide-protein conjugate, in particular wherein the recombinant peptide of the invention is conjugated to a carrier protein (which is usually unrelated to the coronavirus spike protein). In some embodiments, the peptide conjugate comprises a linker (for linking the recombinant peptide of the invention to the carrier, e.g., the carrier protein. Preferably, the carrier protein is immunogenic, i.e. capable of initiating or enhancing an immune response. In particular, the immune response elicited with the peptide-protein conjugate is typically greater than the immune response elicited with the recombinant peptide alone. In some embodiments, the carrier protein contains one or more epitopes for stimulation of T-helper cells, which may in turn facilitate the induction of a B cell response. Many suitable carrier proteins are known in the art, which include, for example, KLH (keyhole limpet hemocyanin), BSA (bovine serum albumin), OVA (ovalbumin) and RSA (rabbit serum protein). In some embodiments, the recombinant peptide of the invention may be conjugated to KLH. Methods for conjugating

peptides to carrier proteins, such as KLH, are well-known in the art and commercially available.

In a further aspect, the present invention also provides a nucleic acid comprising a polynucleotide sequence encoding the recombinant peptide, polypeptide or protein according to the present invention. As described above, examples of nucleic acids and/or polynucleotides include, e.g., a recombinant polynucleotide, a vector, an oligonucleotide, an RNA molecule such as an rRNA, an mRNA, an miRNA, an siRNA, or a tRNA, or a DNA molecule such as a cDNA. Preferably, the nucleic acid is an RNA, in particular an mRNA. Nucleic acids, such as RNAs, encoding antigens or antigenic epitopes (such as the recombinant peptide, polypeptide or protein) are well-known in the art for vaccination.

In a further aspect, the present invention also provides a molecule, a virus-like particle or a nanoparticle comprising the recombinant peptide, polypeptide or protein according to the present invention. Such a molecule, a virus-like particle or a nanoparticle may also be useful in vaccination. For example, shorter peptides (such as peptides comprising or consisting of the above-mentioned sequences) may be (covalently or non-covalently) linked to molecules, virus-like particles or nanoparticles in order to increase their immunogenicity.

As used herein, a "Virus-like particle" (also "VLP") refers in particular to a non-replicating, viral shell, derived from any of several viruses. VLPs are generally composed of one or more viral proteins, such as, but not limited to, those proteins referred to as capsid, coat, shell, surface and/or envelope proteins, or particle-forming polypeptides derived from these proteins. VLPs can form spontaneously upon recombinant expression of the protein in an appropriate expression system. Methods for producing particular VLPs are known in the art. The presence of VLPs following recombinant expression of viral proteins can be detected using conventional techniques known in the art, such as by electron microscopy, biophysical characterization, and the like. Further, VLPs can be isolated by known techniques, *e.g.,* density gradient centrifugation and identified by characteristic density banding. See, for example, Baker *et al.* (1991) *Biophys. J.* 60: 1445-1456; and Hagensee *et al.* (1994) *J. Viral.*

68:4503-4505; Vincente, *J Invertebr Pathol.,* 2011; Schneider-Ohrum and Ross, *Curr. Top. Microbial. Immunol.,* 354: 53073, 2012).

A virus-like particle comprising the immunogen according to the present invention as described herein is thus in particular a virus-like particle (VLP) that includes the recombinant peptide, polypeptide or protein as disclosed herein.

VLPs lack the viral components that are required for virus replication and thus represent a highly attenuated form of a virus. The VLP can display a polypeptide *(e.g.,* the recombinant peptide, polypeptide or protein) that is capable of eliciting an immune response to a coronavirus when administered to a subject. Virus like particles and methods of their production are known and familiar to the person of ordinary skill in the art, and viral proteins from several viruses are known to form VLPs, including human papillomavirus, HIV (Kang *et al.,* Biol. Chem. 380: 353-64 (1999)), Semliki-Forest virus (Notka *et al.,* Biol. Chem. 380: 341-52 (1999)), human polyomavirus (Goldmann *et al.,* J. Virol. 73: 4465-9 (1999)), rota virus (Jiang *et al.,* Vaccine 17: 1005-13 (1999)), parvovirus (Casal, Biotechnology and Applied Biochemistry, Vol 29, Part 2, pp 141- 150 (1999)), canine parvovirus (Hurtado *et al.,* J. Viral. 70: 5422-9 (1996)), hepatitis E virus (Li *et al.,* J. Viral. 71: 35 7207-13 (1997)), and Newcastle disease virus. The formation of such VLPs can be detected by any suitable technique. Examples of suitable techniques known in the art for detection of VLPs in a medium include, *e.g.,* electron microscopy techniques, dynamic light scattering (DLS), selective chromatographic separation *(e.g.,* ion exchange, hydrophobic interaction, and/or size exclusion chromatographic separation of the VLPs) and density gradient centrifugation.

As used herein, a "(protein) nanoparticle" refers in particular to a multi-subunit, protein-based polyhedron shaped structure. The subunits are usually each composed of proteins or polypeptides (for example a glycosylated polypeptide), and, optionally of single or multiple features of the following: nucleic acids, prosthetic groups, organic and inorganic compounds. Non-limiting examples of protein nanoparticles include ferritin nanoparticles (see, *e.g.,* Zhang, *Y. Int. J. Mol.* Sci., 12:5406-5421, 2011, incorporated by reference herein), encapsulin nanoparticles (see, *e.g.,* Sutter *et al.,* Nature Struct. and Mol. Biol., 15:939-947, 2008, incorporated by reference herein), Sulfur Oxygenase Reductase (SOR) nanoparticles (see, *e.g.,*

Urich *et al.,* Science, 311 :996-1000, 2006, incorporated by reference herein), lumazine synthase nan op articles (see, *e.g.,* Zhang *et al., J. Mol. Biol.,* 306: 1099-1114, 2001) or pyruvate dehydrogenase nan op articles (see, *e.g.,* Izard et al., PNAS 96: 1240-1245, 1999, incorporated by reference herein). Ferritin, encapsulin, SOR, lumazine synthase, and pyruvate dehydrogenase are monomeric proteins that self-assemble into a globular protein complexes that in some cases consists of 24, 60, 24, 60, and 60 protein subunits, respectively. Preferably, ferritin, encapsulin, SOR, lumazine synthase, or pyruvate dehydrogenase monomers are linked to an immunogen according to the present invention as disclosed herein (for example, the recombinant peptide, polypeptide or protein as described herein) and self-assembled into a protein nanoparticle presenting the disclosed antigens on its surface, which can be administered to a subject to stimulate an immune response to the immunogen.

A protein nanoparticle particle comprising the the recombinant peptide, polypeptide or protein is thus in particular a protein nanoparticle that includes the recombinant peptide, polypeptide or protein as disclosed herein.

Non-limiting example of nanoparticles include ferritin nanoparticles, encapsulin nanoparticles and Sulfur Oxygenase Reductase (SOR) nanoparticles, which are comprised of an assembly of monomeric subunits including ferritin proteins, encapsulin proteins and SOR proteins, respectively. To construct protein nanoparticles including the recombinant peptide, polypeptide or protein, as disclosed herein, is usually linked to a subunit of the protein nanoparticle (such as a ferritin protein, an encapsulin protein or a SOR protein). The fusion protein self-assembles into a nanoparticle under appropriate conditions.

It is also preferred that the recombinant peptide, polypeptide or protein according to the present invention, the virus-like particle according to the present invention, or the nanoparticle according to the present invention specifically bind to the antibodies according to the present invention as described herein, preferably with a K_d of 1 μM or less.

As used herein, "K_d" refers to the dissociation constant for a given interaction, such as a polypeptide-ligand interaction or an antibody-antigen interaction. For example, for the bimolecular interaction of an antibody (such as the antibodies according to the present

invention as described below) and an antigen (such as the peptide according to the present invention or the protein according to the present invention), it is the concentration of the individual components of the bimolecular interaction divided by the concentration of the complex. Methods of determining the K_d of an antibody: antigen interaction are familiar to the person of ordinary skill in the art.

In a further aspect, the present invention also provides a pharmaceutical composition, in particular a vaccine, comprising the recombinant peptide, polypeptide or protein according to the present invention, the peptide conjugate according to the present invention, the nucleic acid according to the present invention or the molecule, virus-like particle or nanoparticle according to the present invention. The detailed description of the pharmaceutical composition comprising the inventive antibodies (and associated subject-matter) as described above, applies accordingly to the pharmaceutical composition, in particular to the vaccine, comprising the recombinant peptide, polypeptide or protein (and associated subject-matter).

Accordingly, the pharmaceutical composition, in particular the vaccine, may optionally also contain a pharmaceutically acceptable carrier, diluent and/or excipient. Although the carrier or excipient may facilitate administration, it should not itself induce the production of antibodies harmful to the individual receiving the composition. Nor should it be toxic. Suitable carriers may be large, slowly metabolized macromolecules such as proteins, polypeptides, liposomes, polysaccharides, polylactic acids, polyglycolic acids, polymeric amino acids, amino acid copolymers and inactive virus particles. In some embodiments, the pharmaceutically acceptable carrier, diluent and/or excipient in the pharmaceutical composition according to the present invention is not an active component in respect to coronavirus infection.

In some embodiments, the pharmaceutical composition, in particular the vaccine, comprises an adjuvant. Adjuvants are well-known in the art.

Accordingly, it is preferred, in particular for vaccines, that the pharmaceutical composition comprises an adjuvant. Examples of adjuvants include aluminum hydroxide

(ALHYDROGEL®, available from Brenntag Biosector, Copenhagen, Denmark and AMPHOGEL®, Wyeth Laboratories, Madison, NJ), Freund's adjuvant, MPL™ (3-0-deacylated monophosphoryl lipid A; Corixa, Hamilton, IN), IL-12 (Genetics Institute, Cambridge, MA), TLR agonists (such as TLR-9 agonists), and QS-21 (a purified plant extract derived from the soap bark tree *Quillaja saponaria*).

As used herein, the term "adjuvant" refers in particular to a vehicle used to enhance antigenicity/immunogenicity. Adjuvants include a suspension of minerals (alum, aluminum hydroxide, or phosphate) on which the antigen is adsorbed; or water-in-oil emulsion, for example, in which antigen solution is emulsified in mineral oil (Freund incomplete adjuvant), sometimes with the inclusion of killed mycobacteria (Freund's complete adjuvant) to further enhance antigenicity (inhibits degradation of antigen and/or causes influx of macrophages). Immunostimulatory oligonucleotides (such as those including a CpG motif) can also be used as adjuvants. Adjuvants include biological molecules (a "biological adjuvant"), such as costimulatory molecules. Exemplary adjuvants include IL-2, RANTES, GM-CSF, TNF-a, IFN-y, G-CSF, LFA-3, CD72, B7-1, B7-2, OX-40L, 4-IBBL and toll-like receptor (TLR) agonists, such as TLR-9 agonists. The person of ordinary skill in the art is familiar with adjuvants (see, *e.g.,* Singh (ed.) Vaccine Adjuvants and Delivery Systems. Wiley-Interscience, 2007), for example, those that can be included in a pharmaceutical composition. Preferably, the adjuvant is selected to elicit a Th1 immune response in a subject administered the pharmaceutical composition. In other words, the adjuvant comprised by the pharmaceutical composition preferably promotes a Th1 immune response. Preferably, the adjuvant is alum, an oil-in water composition, MF59, ASOl, AS03, AS04, MPL, QS21, a CpG oligonucleotide, a TLR7 agonist, a TLR4 agonist, a TLR3 agonist, or a combination of two or more thereof.

The adjuvant may be selected from the group comprising mineral salts, surface-active agents, microparticles, cytokines, hormones, antigen constructs, polyanions, polyacrylics, or water-in-oil emulsions. Accordingly, the inventive composition may comprise one more adjuvants, e.g. one, two, three, four, five, six, seven, eight, nine, or ten or more adjuvants. For example the inventive composition may comprise one, two, three, four, five, six, seven, eight, nine, or ten or more adjuvants selected from aluminum ("Alum"), aluminum hydroxide, aluminum phosphate, calcium phosphate, nonionic block polymer surfactants, virosomes, saponin (QS-

21), meningococcal outer membrane proteins (Proteosomes), immune stimulating complexes (ISCOMs), Cochleates Dimethyl dioctadecyl ammonium bromide (DDA), Avridine (CP20,961), vitamin A, vitamin E, cell wall skeleton of Mycobacterium phlei (Detox®), muramyl dipeptides and tripeptides, Threonyl MDP (SAF-1), Butyl-ester MDP (Murabutide®), Dipalmitoyl phosphatidylethanolamine MTP, Monophosphoryl lipid A, *Klebsiella pneumonia* glycoprotein, *Bordetella pertussis*, Bacillus Calmette-Guérin, *Vibrio cholerae* and *Escherichia coli* heat labile enterotoxin, trehalose dimycolate, CpG oligodeoxynucleotides, interleukin-2, interferon-γ, interferon-β, granulocyte-macrophage colony stimulating factor, dehydroepiandrosterone, Flt3 ligand, 1,25-dihydroxy vitamin D3, interleukin-1, interleukin-6, interleukin-12, human growth hormone, 2-microglobulin, lymphotactin, polyanions, e.g. dextran, double-stranded polynucleotides, polyacrylics, e.g. polymethylmethacrylate, acrylic acid crosslinked with allyl sucrose (Carbopol 934P), or e.g N-acetyl-glucosamine-3yl-acetyl-L-alanyl-D-isoglutamine (CGP-11637), gamma inulin + aluminum hydroxide (Algammulin), human dendritic cells, lysophosphatidyl glycerol, stearyl tyrosine, tripalmitoyl pentapeptide, Carbopol 974P NF polymer, water-in-oil emulsions, mineral oil (Freund's incomplete), vegetable oil (peanut oil), squalene and squalane, oil-in-water emulsions, Squalene + Tween-80 + Span 85 (MF59), or e.g. liposomes, or e.g. biodegradable polymer microspheres, lactide and glycolide, polyphosphazenes, beta-glucan, or e.g. proteinoids. A list of typically used vaccine adjuvants may also be found in "Vaccine Adjuvants", edited by D.T. O'Hogan, Humana Press 2000. The adjuvant comprised in the inventive composition may also include e.g. a synthetic derivative of lipid A, some of which are TLR-4 agonists, and include, but are not limited to: OM174 (2-deoxy-6-o-[2-deoxy-2-[(R)-3-dodecanoyloxytetra-decanoylamino]-4-o-phosphono-D-D-glucopyranosyl]-2-[(R)-3-hydroxy-tetradecanoylamino]-p-D-glucopyranosyldihydrogen-phosphate), (WO 95/14026) OM-294-DP (3S, 9R)-3~[(R)-dodecanoyloxytetradecanoylam, [(R)-3-hydroxytetradecanoylamino]decan-1,10-diol, 1,10-bis(dihydrogenophosphate) (WO 99/64301 and WO 00/0462) OM 197 MP-Ac DP(3S-,9R)-3-D(R)-dodecanoyl-oxytetradecanoylamino]-4-oxo-5-aza-9-[(R)-3-hydroxytetra-decanoylamino]decan-1,10-diol,1-dihydrogenophosphate-10-(6-aminohexanoate) (WO 01/46127). For example the inventive vaccine may comprise only one of the above adjuvants, or e.g. two of the above adjuvants, e.g. combination adjuvants such as e.g. Alum and MPL, or oil-in-water emulsion and MPL and QS-21, or liposomes and MPL and QS21. The adjuvant

can also include mineral salts such as an aluminum or calcium salts, in particular aluminum hydroxide, aluminum phosphate and calcium phosphate.

Combinations of different adjuvants can also be used in the pharmaceutical compositions described herein. For example, as already noted, QS21 can be formulated together with (3D-)MPL. The ratio of QS21 : (3D-)MPL will typically be in the order of 1 : 10 to 10 : 1; such as 1 : 5 to 5 : 1, and often substantially 1 : 1. Typically, the ratio is in the range of 2.5 : 1 to 1 : 1 (3D-)MPL : QS21 (such as AS01 (GlaxoSmithKline)). Another combination adjuvant formulation includes (3D-)MPL and an aluminum salt, such as aluminum hydroxide (such as AS04 (GlaxoSmithKline)). When formulated in combination, this combination can enhance an antigen-specific Th1 immune response. The adjuvant formulation may comprise a mineral salt, such as a calcium or aluminum (alum) salt, for example calcium phosphate, aluminum phosphate or aluminum hydroxide. Moreover, the adjuvant may include an oil and water emulsion, e.g., an oil-in-water emulsion (such as MF59 (Novartis) or AS03 (GlaxoSmithKline)). One example of an oil-in-water emulsion comprises a metabolisable oil, such as squalene, a tocol such as a tocopherol, e.g., alpha-tocopherol, and a surfactant, such as sorbitan trioleate (Span 85) or polyoxyethylene sorbitan monooleate (Tween 80), in an aqueous carrier.

The recombinant peptide, polypeptide or protein according to the present invention; the peptide conjugate according to the present invention; the nucleic acid according to the present invention; the molecule, virus-like particle or nanoparticle according to the present invention; or the vaccine according to the present invention may be for use as a medicament. In general, the medicament may be for (prophylactic or therapeutic) treatment of coronavirus infection, as described in detail above.

Accordingly, the present invention also provides the use of the recombinant peptide, polypeptide or protein according to the present invention; the nucleic acid according to the present invention; the molecule, virus-like particle or nanoparticle according to the present invention; or the vaccine according to the present invention in the manufacture of a medicament for prophylaxis, treatment or attenuation of coronavirus infection. Furthermore, a method of reducing or treating coronavirus infection, or lowering the risk of coronavirus

infection, is provided, the method comprising: administering to a subject in need thereof, a therapeutically effective amount of the recombinant peptide, polypeptide or protein according to the present invention; the nucleic acid according to the present invention; the molecule, virus-like particle or nanoparticle according to the present invention; or the vaccine according to the present invention.

The above detailed description for the medical use of the antibody (and associated subject-matter) applies accordingly to the medical use of the recombinant peptide, polypeptide or protein (and associated subject-matter).

In particular, recombinant peptide, polypeptide or protein according to the present invention; the peptide conjugate according to the present invention; the nucleic acid according to the present invention; the molecule, virus-like particle or nanoparticle according to the present invention; or the vaccine according to the present invention may be combined with a molecule that can mimic binding to a spike protein receptor, in particular binding to ACE2. Without being bound to any theory, it is assumed that the combination with a molecule that can mimic binding to ACE2 can greatly enhance the induction and maturation of fusion-peptide targeting antibodies by the vaccine of the invention, since ACE2-engagement induces an intermediate conformation change that exposes the fusion peptide epitope. Accordingly, the present invention also provides a combination therapy, wherein administration of the recombinant peptide, polypeptide or protein (and associated subject-matter) of the present invention, is combined with administration of a molecule that can mimic binding to a spike protein receptor, in particular binding to ACE2. Accordingly, the present invention also provides a combination (therapy), as well as a kit-of-parts, comprising (i) the recombinant peptide, polypeptide or protein according to the present invention; the peptide conjugate according to the present invention; the nucleic acid according to the present invention; the molecule, virus-like particle or nanoparticle according to the present invention; or the vaccine according to the present invention; and (ii) a molecule that can mimic binding to a spike protein receptor, in particular binding to ACE2. Suitable examples of such molecules that can mimic binding to a spike protein receptor, in particular binding to ACE2, for combination are those as described above for the combination of the antibody of the invention with the molecule that can mimic binding to a spike protein receptor, in particular binding to ACE2.

BRIEF DESCRIPTION OF THE FIGURES

In the following a brief description of the appended figures will be given. The figures are intended to illustrate the present invention in more detail. However, they are not intended to limit the subject matter of the invention in any way.

Figure 1 shows for Example 3 the ELISA binding profiles of recombinant antibodies towards a panel of distinct antigens as indicated. Binding data of various concentrations of the antibodies purified from EXPI293 cells transfected with VH and VL of CLM20_B8 (A), CLM20_C9 (B), CLM20_Bis_B3 (C), CLM20_A7 (D), CLM20_B8_UCA (E), CLM99_G12 (F), CLM99_D10 (G), CLM99_E3 (H), ISR42_E7 (I), CSC3_H1 (J), E371_F8 (K), E2418_G12 (L), E2121_B7 (M), E1373_G3 (N) and CSC3_H1_UCA (O) to the spike proteins of the different coronaviruses as indicated, and EC50 values calculated based on these curves are indicated in the table in ng/ml unit for CLM20_B8 (A) and CLM20_C9 (B).

Figure 2 shows for Example 4 the results of the epitope mapping study, wherein the CLM20_B8 antibody of Example 3 was tested against 118 15-mer peptides (overlapping of 10 peptides) spanning the entire S2 protein, as illustrated in the schematic drawing of the spike protein. The coronavirus spike protein is schematically shown with signal sequence (SS), N-terminal domain (NTD), receptor-binding domain (RBD), subdomains 1 and 2 (SD1 and SD2), S2' protease cleavage site (S2'), fusion peptide (FP), heptad repeat 1 (HR1), central helix (CH), connector domain (CD), heptad repeat 2 (HR2), transmembrane domain (TM), and cytoplasmic tail (CT). The epitope of CLM20_B8 is comprised in the FP.

Figure 3 shows an alignment of the exemplified SARS-CoV-2 epitope (SEQ ID NO: 1) identified in Example 4 with corresponding exemplified sequences of the spike protein fusion peptide of the other coronaviruses (SARS-CoV-1, MERS, OC43, HKU1, NL63 and 229E), to which antibody CLM20_B8 binds to, thereby

indicating the CLM20_B8 epitopes in the other coronaviruses (SEQ ID NOs 1 to 7, respectively).

Figure 4 shows for Example 4 the results of the epitope mapping study for antibodies CLM20_A7 (A), CLM20_C9 (B), CSC3_H1 (C), ISR42_E7 (D), E371_F8 (E), E2418_G12 (F), E1373_G3 (G) and E2121_B7 (H), wherein the antibodies were tested against 118 15-mer peptides (overlapping of 10 peptides) spanning the entire S2 protein, in the same manner as shown in Figure 2 for CLM20_B8.

Figure 5 shows for Example 5 the results of a substitution scan analysis where each amino acid in the fusion peptide sequence K_{811}PSKRSFIEDLLFNKVTLAD$_{830}$ (SEQ ID NO: 266) was substituted stepwise with all 20 main amino acids for antibodies CLM20_C9 (A), ISR42_E7 (B), CLM20_B8 (C), CSC3_H1 (D), E371_F8 (E), E1373_G3 (F), E2121_B7 (G) and E2418_G12 (H). Results are shown as heatmaps with the fusion peptide epitope amino acids at the x-axes and substitution amino acids at the y-axes. The binding affinity (in %) relative to the native residue (KPSKRSFIEDLLFNKVTLAD; SEQ ID NO: 266) is shown.

Figure 6 shows for Example 6 the results for SARS-CoV, SARS-CoV-2, MERS and 229E pseudovirus neutralization for each of the antibodies as indicated in the figure. Titrating doses of purified antibodies were assessed for their ability to neutralize: SARS-CoV-2 pseudotyped particles in 293T-ACE2-TMPRSS2 cell lines; SARS-CoV in 293T-ACE2-TMPRSS2 cell line; MERS-CoV in Huh7-TMPRSS2 cell line; and 229E in Huh7-TMPRSS2 cell line. EC50 neutralization values (µg/ml) are shown.

Figure 7 shows for Example 8 inhibition of fusion of A549-spike and A549-ACE2-TMPRSS2 cells for full length IgG of antibodies E2418_G12 (A) and CSC3_H1 (B) as compared with Fab fragments and scFv formats of the same antibodies.

Figure 8 shows for Example 9 the binding of purified antibodies CLM20_B8 (A), CLM20_A7 (B), CLM20_C9 (C), ISR42_E7 (D), CSC3_H1 (E), E371_F8 (F),

E2418_G12 (G), E1373_G3 (H) and E2121_B7 (I) on 293T cells stably expressing SARS-CoV-2 spike protein (293T-spike) as tested by flow cytometry, in the presence or absence of recombinant ACE2-mFc, as indicated.

Figure 9 shows for Example 10 viral load ("RNA"; quantified by real-time quantitative RT-qPCR) and infectious viral content ("TCID50"; evaluated by end-point titration) in an *in vivo* Syrian Golden hamster infection model, wherein antibodies at indicated concentrations were administered intraperitoneally 24 hours prior to intranasal infection with 1 x 10^4 PFU TCID50 inoculum of SARS-CoV-2. Antibodies CSC3_H1 and E2418_G12 were able to significantly reduce infectious viral titer and viral load.

Figure 10 shows for Example 11 the results for SARS-like coronavirus WIV1 pseudovirus neutralization for antibodies CSC3_H1 and E2418_G12. Titrating doses of purified antibodies were assessed for their ability to neutralize SARS-like coronavirus WIV1 pseudotyped particles in 293T-ACE2-TMPRSS2 cell line. EC50 neutralization values (µg/ml) are shown.

Figure 11 shows for Example 12 (A) the results of binding of antibody CSC3_H1 to the fusion peptide of SARS-CoV-2 and non-human infecting coronaviruses infectious bronchitis virus (IBV) and porcine deltacoronavirus (PdCV). In addition to alpha- and betacoronaviruses, CSC3_H1 can also bind to the fusion peptides of coronaviruses of the gamma (IBV) and delta (PdCV) genera. An alignment of the fusion peptides of the different coronaviruses including IBV, PdCV and WIV-1 is shown in (B).

EXAMPLES

In the following, particular examples illustrating various embodiments and aspects of the invention are presented. The following preparations and examples are given to enable those skilled in the art to more clearly understand and to practice the present invention. The present invention, however, is not limited in scope by the exemplified embodiments, which are intended as illustrations of single aspects of the invention only, and methods which are functionally equivalent are within the scope of the invention. Indeed, various modifications of the invention in addition to those described herein will become readily apparent to those skilled in the art from the foregoing description, accompanying figures and the examples below. All such modifications fall within the scope of the appended claims.

Example 1: Identification of broadly reactive B cell clones

Broadly cross-reactive antibodies against coronaviruses were identified and isolated from donors with previous SARS-CoV-2 infection. Briefly, total PBMCs were isolated from the donors, plated at 60,000 cells per well in 96-well plate, and cultured in the presence of TLR agonist R848 and IL-2 for five days. On day 5, cell culture supernatants were tested in a primary screening for binding to the spike (S) protein of endemic beta-coronaviruses (OC43 and HKU1) and alpha-coronaviruses (NL63 and 229E) as well as pandemic strains of coronaviruses SARS-CoV-1 and SARS-CoV-2, and for binding to irrelevant antigens such as influenza hemagglutinin (HA) and Tetanus toxoid (TT) for control. To this end, different ELISAs (Enzyme-Linked immunosorbent Assay) were performed. Briefly, plates were coated with antigen(s)-of-interest and later washed and blocked with Casein Blocker (Thermo Scientific). Subsequently, supernatant from each well was added to allow binding of antigen-specific antibodies (if any). The plates were washed, and alkaline-phosphatase conjugated goat anti-human IgG was added to bind to any IgG that remains bound to the antigen. Plates underwent a final wash, and substrate (p-NPP) was added and the plates were read at 405 nm. To identify coronavirus cross-reactive cell cultures (i.e., cultures with antibodies against the distinct coronavirus spike proteins, but not irrelevant antigens HA and TT), the reactivity of the cultures to the different antigens (as obtained by ELISA) was then cross-compared for each

individual well. Thereby, three parent cultures which exhibited quintuple-reactivity to the spike protein of endemic beta-coronaviruses (OC43 and HKU1) and alpha-coronaviruses (NL63 and 229E) as well as pandemic strains of coronaviruses SARS-CoV-1 and SARS-CoV-2, but not to irrelevant antigens such as HA or Tetanus toxoid, were identified. Table 3 below shows the OD values of the ELISAs performed with culture supernatants of the three parent cultures and the indicated antigens.

Table 3. OD values of primary screening (ELISAs performed with PBMC culture supernatants and the indicated antigens)

Culture ID	PBS	OC43	HKU1	NL63	229E	SARS1	SARS2	HA	Teta-nus	Xreac-tivity
CLM20_A7	0.131	3.334	3.338	3.322	3.337	3.336	1.629	0.139	0.187	6
CLM20_B8	0.117	3.198	3.177	3.188	3.185	3.145	2.007	0.146	0.149	6
CLM20_C9	0.134	2.885	2.808	2.694	2.57	2.806	3.004	0.173	0.165	6

To affirm that these parental cultures contain indeed broadly-reactive B cells that broadly target human coronaviruses, the inventors sorted memory B cells from all three cultures and cloned at 0.7 cell per well in complete medium in the absence of feeder cells or other supplements. Two days post cloning, the supernatants of each well were evaluated through secondary ELISA screening for binding to the spike (S) protein of endemic beta-coronaviruses (OC43 and HKU1) and alpha-coronaviruses (NL63 and 229E) as well as pandemic strains of coronaviruses SARS-CoV-1 and SARS-CoV-2, essentially as described above. Results are shown in Table 4 below.

Table 4. OD values of secondary screening (ELISAs performed with B cell culture supernatants and the indicated antigens)

Culture ID	Well	OC43	HKU1	NL63	229E	SARS-CoV-1	SARS-CoV-2
CLM20_A7	C7	1.527	0.826	0.821	0.783	0.668	1.277
		1.224	0.787	0.729	0.727	0.62	1.121
		1.941	1.225	1.347	1.38	1.213	1.741
	E7	2.164	1.441	1.792	1.782	1.876	2.56
		1.245	0.81	0.975	0.891	0.793	1.087
CLM20_B8		1.675	1.114	1.238	1.137	1.137	1.527
		2.676	1.977	2.206	1.875	1.73	2.235
		1.422	0.991	1.074	1.1	1.073	1.391
		1.78	1.27	1.412	1.337	1.224	1.707
		1.338	0.902	0.958	0.935	0.911	1.182
		1.624	1.328	1.27	1.257	1.163	1.618
	J8	1.3	0.919	0.915	0.911	0.825	1.129
		1.608	1.205	1.19	1.236	1.149	1.521

		1.639	1.17	1.351	1.292	1.143	1.408
		2.08	1.518	1.571	1.564	1.45	1.93
	M8	1.676	1.119	1.244	1.137	1.095	1.481
		1.979	1.47	1.571	1.503	1.414	1.876
		1.495	1.015	1.089	1.058	0.976	1.373
		1.835	1.101	1.266	1.209	1.171	1.731
		1.385	0.947	1.029	1.027	0.98	1.329
		2.618	1.738	1.873	1.744	1.521	2.205
		2.397	1.707	1.791	1.691	1.506	2.205
		1.387	0.96	1.008	0.87	0.809	1.004
		1.815	1.357	1.443	1.213	1.083	1.51
CLM20_C9	C21	1.394	1.236	1.28	1.341	1.031	1.354
	H15	1.363	1.247	1.234	1.196	0.8	1.107
		2.104	1.628	1.597	1.666	1.352	1.705

These data show that the selected three independent cultures indeed contained B cell clones that were broadly-reactive to all common coronaviruses.

Example 2: Retrieval of antibody gene sequences

Next, six clones of interest derived from three selected parent cultures of Example 1, Cultures CLM20_A7, CLM20_B8, CLM20_C9 (clones of wells C7, E7, J8, M8, C21 and H15 of Table 4 above), were selected and subjected to RT-PCR to generate cDNA, using three primers specific to the constant regions of IgG, Ig , and Ig , respectively. Native IgG, Ig , and Ig sequences were subsequently amplified by two-step PCR using Q5 High-Fidelity DNA polymerase (NEB) and two sets of Ig-specific primers, one nested within the other. The PCR amplicons were later purified for Sanger sequencing.

Thereby, six paired VH/VL genes were retrieved and sequenced. The VH/VL sequences (VDJ sequences) of daughter clones from different wells derived from within the same parent cultures (i.e., clones C7 and E7 of culture CLM20_A7; clones J8 and M8 of CLM20_B8; and clones C21 and H15 of CLM20_C9 see table above) were identical. Therefore, hereafter the antibodies are referred to by their culture ID only.

Interestingly, antibodies CLM20_B8 and CLM20_A7 had very similar VH/VL sequences (with 7 nucleotide mutations resulting in 2 amino acid differences), suggesting that they were

derived from the same progenitor in the donor, which had undergone somatic hypermutations; whereas two selected clones of CLM20_C9 (clones C21 and H15; see table 4 above) were of completely different lineage than CLM20_B8 and CLM20_A7. In general, all selected cultures (antibodies produced by those cultures) exhibit the same pan-reactive binding patterns to all coronavirus spike protein, as shown in Example 1.

The position of the CDR amino acids are defined according to the IMGT numbering system (IMGT: http://www.imgt.org/; cf. Lefranc, M.-P. et al. (2009) Nucleic Acids Res. 37, D1006-D1012). The following antibody sequences were identified (Tables 5 and 6):

Antibody name	Heavy chain				Light chain			
	CDR1	CDR2	CDR3	VH	CDR1	CDR2	CDR3	VL
CLM20_A7	9	10	11	18	12	13/14	15	19
CLM20_B8	9	10	11	16	12	13/14	15	17
CLM20_C9	20	21	22	26	12	23/24	25	27

Table 5: CDR and VH/VL amino acid sequences (SEQ ID NOs) of antibodies CLM20_A7, CLM20_B8, and CLM20_C9.

Antibody name	Heavy chain				Light chain			
	CDR1	CDR2	CDR3	VH	CDR1	CDR2	CDR3	VL
CLM20_A7	76	77	85	87	79	80/86	82	88
CLM20_B8	76	77	78	83	79	80/81	82	84
CLM20_C9	89	90	91	96	92	93/94	95	97

Table 6: CDR and VH/VL nucleic acid sequences (SEQ ID NOs) of antibodies CLM20_A7, CLM20_B8, and CLM20_C9.

In addition, six further cross-reactive antibodies (CLM20_B8_UCA, CLM99_G12, CLM99_D10, CLM99_E3, CLM13_G9 and CLM20_Bis_B3) against coronaviruses (spike protein) were identified in a similar manner as described above. These additional six antibodies exhibit the following sequences (Tables 7 and 8):

Antibody name	Heavy chain				Light chain			
	CDR1	CDR2	CDR3	VH	CDR1	CDR2	CDR3	VL
CLM20_B8_UCA	28	29	30	34	12	31/32	33	35
CLM99_G12	36	37	38	43	39	40/41	42	44
CLM99_D10	45	46	47	50	48	40/49	42	51
CLM99_E3	52	37	38	54	53	40/41	42	55
CLM13_G9	56	57	58	63	59	60/61	62	64
CLM20_Bis_B3	65	66	67	71	68	40/69	70	72

Table 7: CDR and VH/VL amino acid sequences (SEQ ID NOs) of antibodies CLM20_B8_UCA, CLM99_G12, CLM99_D10, CLM99_E3, CLM13_G9 and CLM20_Bis_B3.

Antibody name	Heavy chain				Light chain			
	CDR1	CDR2	CDR3	VH	CDR1	CDR2	CDR3	VL
CLM20_B8_UCA	98	99	100	104	79	101/102	103	105
CLM99_G12	106	107	108	113	109	110/111	112	114
CLM99_D10	115	116	117	121	118	110/119	120	122
CLM99_E3	123	124	108	128	125	110/126	127	129
CLM13_G9	130	131	132	137	133	134/135	136	138
CLM20_Bis_B3	139	140	141	145	142	110/143	144	146

Table 8: CDR and VH/VL nucleic acid sequences (SEQ ID NOs) of antibodies CLM20_B8_UCA, CLM99_G12, CLM99_D10, CLM99_E3, CLM13_G9 and CLM20_Bis_B3.

In addition, seven further cross-reactive antibodies (ISR42_E7, CSC3_H1, E371_F8, E2418_G12, E2121_B7, E1373_G3, CSC3_H1_UCA) against coronaviruses (spike protein) were identified in a similar manner as described above. These additional seven antibodies exhibit the following sequences (Tables 9 and 10):

Antibody name	Heavy chain				Light chain			
	CDR1	CDR2	CDR3	VH	CDR1	CDR2	CDR3	VL
ISR42_E7	207	208	209	214	210	211/212	213	215
CSC3_H1	216	217	218	223	219	220/221	222	224
E371_F8	225	226	227	232	228	229/230	231	233
E2418_G12	234	235	236	240	237	211/238	239	241
E2121_B7	242	243	244	247	245	31/32	246	248
E1373_G3	249	250	251	256	252	253/254	255	257
CSC3_H1_UCA	258	259	260	262	219	220/221	261	263

Table 9: CDR and VH/VL amino acid sequences (SEQ ID NOs) of antibodies ISR42_E7, CSC3_H1, E371_F8, E2418_G12, E2121_B7, E1373_G3, CSC3_H1_UCA.

Antibody name	Heavy chain				Light chain			
	CDR1	CDR2	CDR3	VH	CDR1	CDR2	CDR3	VL
ISR42_E7	147	148	149	154	150	151/152	153	155
CSC3_H1	156	157	158	163	159	160/161	162	164
E371_F8	165	166	167	172	168	169/170	171	173
E2418_G12	174	175	176	180	177	151/178	179	181
E2121_B7	182	183	184	189	185	186/187	188	190
E1373_G3	191	192	193	198	194	195/196	197	199
CSC3_H1_UCA	200	201	202	205	159	160/203	204	206

Table 10: CDR and VH/VL nucleic acid sequences (SEQ ID NOs) of antibodies ISR42_E7, CSC3_H1, E371_F8, E2418_G12, E2121_B7, E1373_G3, CSC3_H1_UCA.

Example 3: Validation of cross-reactivity of antibodies obtained from selected clones

To confirm cross-reactivity of antibodies obtained from the selected clones, the VDJ sequences (VH/VL sequences) of the nine antibodies of Example 2 were cloned into expression vectors for expression of a light chain (lambda) and of a human IgG1 heavy chain, as described in Tiller T., Meffre E., Yurasov S., Tsuiji M, Nussenzweig M.C., and Wardemann

H. (2008) Efficient generation of monoclonal antibodies from single human B cells by single cell RT-PCR and expression vector cloning. doi: 10.1016/j.jim.2007.09.017.

The IgG antibodies were produced by transient transfection of EXPI293 cells and the supernatants were tested against the same panel of antigens to validate their cross-reactivity. Briefly, EXPI293 cells were co-transfected with expression vectors carrying the VDJ sequences of the IgH and IgL, using polyethylenimine (PEI), a stable cationic polymer as transfection reagent. After overnight incubation, the EXPI293 supernatant was tested in ELISA to validate the reactivity of secreted antibodies to various antigens. Results are shown in Table 11 below:

Table 11: Binding data of the nine recombinantly produced antibodies (OD 405 nm values)

Antibody	OC43	HKU1	NL63	229E	SARS-CoV-1	SARS-CoV-2	MERS	HA
CLM20_B8	4.457	4.461	4.519	4.495	4.408	4.451	4.444	0.131
CLM20_A7	4.391	4.361	4.44	4.34	4.394	4.308	4.447	0.133
CLM20_C9	4.359	4.306	4.39	4.305	4.359	4.318	4.372	0.128
CLM20_B8_UCA	4.227	4.314	4.291	0.338	3.418	2.455	1.532	0.125
CLM99_G12	4.246	4.215	0.115	0.107	4.103	3.428	4.198	0.113
CLM99_D10	4.253	4.199	0.125	0.103	4.23	4.231	4.213	0.102
CLM99_E3	4.179	4.144	0.092	0.087	4.1	4.113	4.118	0.079
CLM13_G9	0.084	0.086	0.084	0.082	4.175	4.142	0.082	0.08
CLM20_Bis_B3	3.616	4.151	0.104	0.095	4.153	2.281	0.223	0.095

Indeed, ectopic expression of VH/VL sequences of CLM20_B8, CLM20_A7 and CLM20_C9 results in production of pan-reactive antibodies to beta-coronavirus (OC43, HKU1, SARS-CoV-1, SARS-CoV-2, MERS) and alpha-coronavirus (NL63, 229E), while no reactivity against unrelated antigens influenza HA and tetanus toxoid was detected. In addition, further six paired VH/VL antibody sequences (CLM20_B8_UCA, CLM99_G12, CLM99_D10, CLM99_E3, CLM13_G9 and CLM20_Bis_B3) were identified that exhibit broad-specificities (Table 9).

Next, antibodies CLM20_B8 and CLM20_C9 were purified and different concentrations of the purified antibodies were tested in an ELISA for binding to spike proteins of the different coronaviruses OC43, HKU1, NL63, 229E, SARS-CoV-1, SARS-CoV-2 and MERS. Results are shown in Fig. 1. Accordingly, Fig. 1 shows the binding data of titrating concentrations of

purified CLM20_B8 and CLM20_C9 antibodies against spike proteins of the different coronaviruses as indicated, as well as the EC50 values calculated based on these curves.

Next, antibodies ISR42_E7, CSC3_H1, E371_F8, E2418_G12, E2121_B7, E1373_G3 and CSC3_H1_UCA of Example 2 were also cloned into expression vectors for expression of a light chain (lambda) and of a human IgG1 heavy chain, as described above, and IgG antibodies were produced by transient transfection of EXPI293 cells. Purified antibodies CLM20_Bis_B3, CLM20_A7, CLM20_B8_UCA, CLM99_G12, CLM99_D10, CLM99_E3, ISR42_E7, CSC3_H1, E371_F8, E2418_G12, E2121_B7, E1373_G3 and CSC3_H1_UCA were tested at different concentrations in an ELISA for binding to spike proteins of the different coronaviruses OC43, HKU1, NL63, 229E, SARS-CoV-1, SARS-CoV-2 and MERS. Results are also shown in Fig. 1. The EC50 values are shown in Table 12 below:

	EC50 (ug/ml)						
	OC43	HKU1	NL63	229E	SARS-CoV-1	SARS-CoV-2	MERS
CLM20_Bis_B3	470	485.3	B.T.	B.T.	94	81.75	
CLM99_G12	30.31	84.35	B.T.	B.T.	49.08	39.35	31.82
CLM99_D10	45.47	69.06	B.T.	B.T.	63.03	45.51	68.34
CLM99_E3	31.45	49.85	B.T.	B.T.	54	36.93	55.86
CLM20_B8_UCA	109.2	77.98	691.5	7671	1652	534.8	218.8
CLM20_A7	24.73	78.49	55.31	51.48	63.51	52.09	29.04
ISR42_E7	41.72	70.65	139.4	92.28	104.6	79.43	52.88
CSC3_H1	31.99	49.78	96.55	98.48	58.12	59.92	50.52
E371_F8	40.02	148.4	46.79	43.36	240.9	69.32	54.28
E2418_G12	54.49	362.7	2497	305.6	386.7	411.7	298.9
E2121_B7	B.T.	B.T.	B.T.	B.T.	205.7	124.4	B.T.
E1373_G3	B.T.	1993	B.T.	B.T.	78.34	57.98	B.T.
CSC3_H1 UCA	258.7	338	6072	118.1	1474	1016	7277

Table 12: Binding data (EC50 in µg/ml) of the recombinantly produced antibodies. B.T. below detection threshold.

In summary, these data confirm that the antibodies according to the present invention are broadly reactive human coronavirus antibodies displaying high affinity to the spike protein of various distinct human coronaviruses.

Example 4: Epitope identification

Purified antibodies were tested against a panel of 118 15-mer peptides (overlapping of 10) spanning the entire SARS-CoV-2 S2 protein (Spike676-Spike1273). Briefly, each well of the plate was coated with 8ug/ml of each of the 118 15-mer peptides. ELISA was performed as described above using 0.6ug/ml of purified CLM20_B8 antibody as primary antibody in each individual well.

Results are shown in Fig. 2. These data show that the antibodies were found to be specific for the peptide of SEQ ID NO: 1 ("KPSKRSFIEDLLFNK") (which comprises the epitope to which the antibodies bind to). As illustrated in Fig. 2, said peptide maps to the fusion peptide (FP) Spike811-Spike825 (S2'). Accordingly, the data show that the epitope of the spike protein, to which the cross-reactive antibody binds to, is located in the fusion peptide of the spike protein.

However, as antibody CLM20_B8 binds not only to the spike protein of SARS-CoV-2, but also to the spike protein of various other coronaviruses (SARS-CoV-1, MERS, OC43, HKU1, NL63 and 229E; see Example 3) the identified peptide of SEQ ID NO: 1 ("KPSKRSFIEDLLFNK") was aligned to the spike protein of those other coronaviruses showing highly conserved sequences in the spike protein fusion peptide. The alignment, which indicates exemplified corresponding epitopes in the other coronaviruses, is shown in Figure 3.

Antibodies CLM20_A7, CLM20_C9, ISR42_E7, CSC3_H1, E371_F8, E2418_G12, E2121_B7 and E1373_G3 were also purified and mapped to the same epitope of SEQ ID NO:1 ("KPSKRSFIEDLLFNK") in the S2 domain of SARS-CoV-2 spike, similarly as antibody CLM20_B8 described above. The results are shown in Figure 4.

Example 5: Epitope footprint identification

Purified antibodies CLM20_B8, CLM20_C9, ISR42_E7, CSC3_H1, E371_F8, E2418_G12, E2121_B7, E1373_G3 were subjected to substitution scan analysis, where each amino acid

in the fusion peptide sequence K_{811}PSKRSFIEDLLFNKVTLAD$_{830}$ (SEQ ID NO: 266) was substituted stepwise with all 20 main amino acids. These peptide variants and wildtype peptide, as well as HA control peptides was printed on a microarray chip in triplicate. Primary antibodies were incubated with the microarray chip for 16 h at 4°C with orbital shaking at 140 rpm. After washing, secondary antibody goat anti-human IgG (H+L) DyLight680 (0.2 µg/ml) was incubated for 45 min at room temperature before reading on Innopsys InnoScan 710-IR Microarray Scanner.

Results are shown as heatmaps in Figure 5. Each amino acid in the fusion peptide epitope (x-axes) was substituted, step-wise, with all amino acids (y-axes), and the binding affinity of the antibody to each peptide variant is measured. Legend shows the binding affinity relative to the native residue. Even though the antibodies were binding to the same FP region, they have heterogeneous binding footprints. However, the footprints revealed a core binding motif at I_{818}EDLLNK$_{825}$ (SEQ ID NO: 264). This motif is highly conserved amongst the *Orthocoronavirinae* subfamily, including the alpha, beta, gamma, and delta coronaviruses, as well as all SARS-CoV-2 variants. Antibodies ISR42_E7 and CSC3_H1 have a 3-amino acid expanded footprint $R_{815}SF_{817}$ at the N-terminus, spanning the S_2' cleavage site at R_{815} (SEQ ID NO: 265).

Example 6: Pseudovirus neutralization

Titrating doses of purified antibodies were assessed for their ability to neutralize: SARS-CoV-2 pseudotyped particles in 293T-ACE2-TMPRSS2 cell lines; SARS-CoV in 293T-ACE2-TMPRSS2 cell line; MERS-CoV in Huh7-TMPRSS2 cell line; and 229E in Huh7-TMPRSS2 cell line as described in Crawford et al. (Crawford, K.H.D., Eguia R., Dingens A.S., Loes A.N., Malone K.D., Wolf C.R., Chu H. Y., Tortorici M.A., Veesler D., Murphy M., Pettie D., King N.P., Balazs A.B., Bloom J.D. (2020) Protocol and Reagents for Pseudotyping Lentiviral Particles with SARS-CoV-2 Spike Protein for Neutralization Assays, doi: 10.3390/v12050513).

Briefly, 293T cells were co-transfected with a lentiviral backbone encoding luciferase reporter (pHAGE-CMV-Luc2-IRES-ZsGreen-W, HIV-based packaging plasmids (Tat, Gag-Pol and Rev)

and various spike expression plasmids (SARS-CoV-2, SARS-CoV, MERS-CoV and 229E) using PEI in Opti-MEM. Supernatants were harvested 36 h post-transfection and pseudotyped viral particles, filtered through 0.22 µm filter and precipitated using 40% (W/V) PEG-8000 and 1.2M NaCl for 4-6 h on a shaker at 4°C, and then was centrifuged for 1 h at 1600g at 4°C. For SARS-CoV-2, SARS-CoV, MERS-CoV and 229E S pseudotyped virus neutralization assay, target cells (293-ACE2-TMPRSS2 for SARS-CoV-2 and SARS-CoV; HuH-7-TMPRSS2 for MERS-CoV and 229E) were seeded in white 96-well plate at 40,000 cells/well the day before infection. Concentrated viruses were titrated in serial dilutions with the respective target cell lines and the luciferase reporter signal was determined 48 h later using Luciferase Assay System on Cytation 3 (BioTek). Virus concentrations that gave signal higher than 10^5RLUs/well were used in neutralization experiments. Serial 1:3 dilutions of mAbs (10-point dilutions starting at 200 µg/ml) were pre-incubated with pseudotyped viruses at 37°C for 30 min. The pseudotyped virus-mAb mixture were then overlayed onto target cell lines in the presence of 5 µg/ml polybrene and analyzed 48 h post-infection.

Results are shown in Figure 6. The IC50 values are shown in Table 13 below.

	IC50 (µg/ml)			
	SARS-CoV-2	SARS-CoV	MERS	229E
CLM20_B8	B.T.	B.T.	155.8	40.22
CLM20_A7	B.T.	B.T.	158.9	33.02
CLM20_C9	B.T.	B.T.	B.T.	183.2
ISR42_E7	113.8	24.05	84.43	13.63
CSC3_H1	28.81	16.1	31.25	2.453
E371_F8	91.62	B.T.	13.23	0.6272
E2418_G12	6.994	37.58	83.24	B.T.
E2121_B7	8.602	19.19	B.T.	B.T.

Table 13: Pseudovirus neutralization data (IC50 in µg/ml) of the recombinantly produced antibodies. B.T. below detection threshold.

Antibodies CLM20_B8 and CLM20_A7 were found to neutralize MERS-CoV and 229E. Antibody CLM20_C9 were found to neutralize 229E. While antibodies ISR42_E7, CSC3_H1, E371_F8, E2418_G12 and E2121_B7 showed neutralization to SARS-CoV-2 S pseudotyped viruses. In particular antibodies ISR42_E7 and CSC3_H1 exhibited unprecedented neutralizing activity against all alpha and betacoronavirus S-pseudotyped viruses.

Example 7: Fusion Inhibition

Titrating doses of purified antibodies CSC3_H1, E371_F8, E2418_G12 and E2121_B7 were assessed for their ability to inhibit the fusion of A549-spike and A549-ACE2-TMPRSS2 cell lines. Briefly, A549-spike and A549-ACE2-TMPRSS2 cells were stained with CFSE and CellTrace ™ Far Red, respectively, according to manufacturer's instruction. Stained cells were resuspended in complete media containing Hoechst 33342 at a final concentration of 5 µg/ml. A549-spike cells were co-cultured in indicated concentrations of mAbs for 30 min at 37°C before addition of stained-A549-ACE2-TMPRSS2. Fusion events were measured 2 h post incubation with Molecular Devices ImageXpress Micro 4 system. Acquisition was performed with a 20x/0.45 Super Plan Fluor ELWD objective, FITC and Cy5 filter and images collected with a Andor Zyla sCMOS camera. 9 fields per well were imaged and were subsequently processed with Metaxpress and Powecore softwares.

The IC50 values are shown in Table 14 below.

antibody	IC50 (µg/ml)
CSC3_H1	89.75
E371_F8	143.6
E2418_G12	53.17
E2121_B7	22.27

Table 14: Fusion inhibition IC50.

These data demonstrate that antibodies CSC3_H1, E371_F8, E2418_G12 and E2121_B7 were found to inhibit the fusion of A549-spike and A549-ACE2-TMPRSS2.

Example 8: Size dependent neutralization activity

Full length IgG antibodies of E2418_G12 and CSC3_H1 were compared with Fab and scFv fragments of E2418_G12 and CSC3_H1, respectively, for their ability the inhibit the fusion of

A549-spike and A549-ACE2-TMPRSS2 cell lines, as described in Example 7, (at equimolar amounts of Fab and scFv fragments).

Results are shown in Figure 7. E2418_G12 Fab and scFv formats and CSC3_H1 scFv formats were more effective in inhibiting the fusion activity compared to their respective full length IgG. This indicates that smaller antibody footprints, such as Fab fragments, scFv or nanobodies have more potent neutralization capacity.

Example 9: Fusion peptide epitope is unmasked by ACE2 binding

Binding of purified antibodies CLM20_B8, CLM20_A7, CLM20_C9, ISR42_E7, CSC3_H1, E371_F8, E2418_G12, E2121_B7 and E1373_G3 on 293T-stably expressing SARS-CoV-2 spike protein (293T-spike) were tested by flow cytometry, in the presence or absence of recombinant ACE2-mFc.

Briefly, titrating doses of fluorescently labelled antibodies are co-incubated with 293T-spike for 2 h at room temperature in the presence or absence of recombinant ACE2-mFc fusion protein (80 µg/ml).

Results are shown in Figure 8. The bindings of all antibodies are enhanced in the presence of recombinant ACE2-mFc in a dose dependent manner, indicating that the spike protein undergoes a conformational change after ACE2 binding, and the FP epitope is exposed in the intermediate conformation.

Example 10: *In vivo* neutralization of live viruses

Purified antibodies (CSC3_H1 and E2418_G12) were tested for their ability to neutralize live SARS-CoV-2 in an *in vivo* Syrian Golden hamster infection model. Briefly, different groups ofSyrian Golden hamsters received either 50 mg/kg antibody CSC3_H1, 25 mg/kg antibody E2418_G12, 50 mg/kg antibody E2418_G12, or 50 mg/kg of a negative control antibody.

Antibodies were administered intraperitoneally 24 hours prior to intranasal infection with 1 x 10^4 PFU TCID50 inoculum of SARS-CoV-2. Four days later, animals were sacrificed and viral load was quantified by real-time quantitative RT-qPCR. In addition, infectious viral content was evaluated by end-point titration.

Results are shown in Figure 9. Antibodies CSC3_H1 and E2418_G12 were able to significantly reduce infectious viral titer and viral load *in vivo*.

Example 11: Neutralization of non-human infecting coronavirus of pandemic potential

Next, antibodies CSC3_H1 and E2418_G12 were tested for their ability to a neutralize non-human-infecting coronavirus of pandemic potential, namely, SARS-like coronavirus WIV-1 ("WIV-1"; also known as bat SARS-like coronavirus WIV-1). Experiments were performed as described in Example 6 with WIV-1 pseudovirus.

Briefly, 293T cells were co-transfected with a lentiviral backbone encoding luciferase reporter (pHAGE-CMV-Luc2-IRES-ZsGreen-W, HIV-based packaging plasmids (Tat, Gag-Pol and Rev) and WIV-1 spike expression plasmids using PEI in Opti-MEM. Supernatants were harvested 36 h post-transfection and pseudotyped viral particles, filtered through 0.22 µm filter and precipitated using 40% (W/V) PEG-8000 and 1.2M NaCl for 4-6 h on a shaker at 4°C, and then centrifuged for 1 h at 1600g at 4°C. 293-ACE2-TMPRSS2 target cells were seeded in white 96-well plate at 40,000 cells/well the day before infection. Concentrated viruses were titrated in serial dilutions with the respective target cell lines and the luciferase reporter signal was determined 48 h later using Luciferase Assay System on Cytation 3 (BioTek). Virus concentrations that gave signal higher than 10^5RLUs/well were used in neutralization experiments. Serial 1:3 dilutions of antibodies CSC3_H1 and E2418_G12 (10-point dilutions starting at 200 µg/ml) were pre-incubated with pseudotyped viruses at 37°C for 30 min. The pseudotyped virus-mAb mixtures were then overlayed onto target cell lines in the presence of 5 µg/ml polybrene and analyzed 48 h post-infection.

Results are shown in Fig. 10. The data demonstrate that antibodies CSC3_H1 and E2418_G12 are also able to neutralize a non-human-infecting coronavirus of pandemic potential (WIV-1).

Example 12: Binding to coronaviruses of gamma and delta genera

The above data show binding and neutralization of different alpha- and betacoronaviruses. To further extend these findings to coronaviruses of gamma and delta genera, purified antibodies (CSC3_H1) were tested for their ability to bind to the fusion peptides of (i) non-human infecting gammacoronaviruses, namely, infectious bronchitis virus (IBV; SEQ ID NO: 268) and (ii) non-human infecting deltacoronaviruses, namely, porcine deltacoronavirus (PdCV; SEQ ID NO: 269).

Briefly, each well of the plate was coated with 8 ug/ml of IBV FP peptide (SEQ ID NO: 268) or PdCV peptide (SEQ ID NO: 269). ELISA was performed as described above using 10 ug/ml of CSC3_H1.

Results are shown in Figure 11. The obtained OD values (405 nm; Figure 11A) show that CSC3_H1 can also bind to the fusion peptides of IBV and PdCV. An alignment of the fusion peptides of the different coronaviruses including IBV and PdCV is shown in Figure 11B.

TABLE OF SEQUENCES AND SEQ ID NUMBERS (SEQUENCE LISTING):

SEQ ID NO	Sequence	Remarks
SEQ ID NO: 1	KPSKRSFIEDLLFNK	SARS-CoV-2 epitope
SEQ ID NO: 2	KPTKRSFIEDLLFNK	SARS-CoV-1 epitope
SEQ ID NO: 3	SRSARSAIEDLLFDK	MERS epitope
SEQ ID NO: 4	KASSRSAIEDLLFDK	OC43 epitope
SEQ ID NO: 5	GSSSRSLLEDLLFNK	HKU1 epitope
SEQ ID NO: 6	RIAGRSALEDLLFSK	NL63 epitope
SEQ ID NO: 7	RVAGRSAIEDILFSK	229E epitope
SEQ ID NO: 8	SFIEDLLFNK	epitope
CLM20_B8		
SEQ ID NO: 9	GDSISNEDYH	CDRH1
SEQ ID NO: 10	LQYSGNT	CDRH2
SEQ ID NO: 11	ATSIVLTGMSNKIQPFDY	CDRH3
SEQ ID NO: 12	ALPKKY	CDRL1
SEQ ID NO: 13	KDT	CDRL2
SEQ ID NO: 14	VIYKDTERP	CDRL2 long
SEQ ID NO: 15	LSADTSGTWV	CDRL3
SEQ ID NO: 16	QVQLQESGPGLVQPSQTLTLTCTVSGDSISNED YHWTWIRQHPGKGLEWMGYLQYSGNTNYNP SLKSRMTISVDTSKNQFSLRLNSVTAADTAVYFC ATSIVLTGMSNKIQPFDYWGQGTLVTVSS	VH
SEQ ID NO: 17	SYELTQPPSVSVSPGQMARITCSGEALPKKYAYW YQQKGGQFPVLVIYKDTERPSGIPERFSGSSSGTI VTLTISGVQPEDEADYYCLSADTSGTWVFGGGT KLTVL	VL
CLM20_A7		
SEQ ID NO: 18	QVQLQESGPGLVQPSQTLTLTCTVSGDSISNED YHWTWIRQPPGKGLEWMGYLQYSGNTNYNPS LKSRMTISVDTSKNQFSLRLSSVTAADTAVYFCAT SIVLTGMSNKIQPFDYWGQGTLVTVSS	VH
SEQ ID NO: 19	SYELTQPPSVSVSPGQMARITCSGEALPKKYAYW YQQKAGQFPVLVIYKDTERPSGIPERFSGSSSGTI VTLTISGVQPEDEADYYCLSADTSGTWVFGGGT KLTVL	VL
CLM20_C9		
SEQ ID NO: 20	GFTSKNTA	CDRH1
SEQ ID NO: 21	IDISNYIT	CDRH2
SEQ ID NO: 22	AAVGKDDDVLTGGNKYFDH	CDRH3
SEQ ID NO: 23	EDD	CDRL2
SEQ ID NO: 24	VIHEDDKRP	CDRL2 long
SEQ ID NO: 25	YSTDTNDNHA	CDRL3

SEQ ID NO: 26	EVQLVQSGPEVKKPGTSARVSCKASGFTSKNTAL QWVRQARGQPLEWMGWIDISNYITNYAQKFR GRLTITWDLSASMAYMELSSLRSEDTAVYYCAAV GKDDDVLTGGNKYFDHWGQGTLVTVSS	VH
SEQ ID NO: 27	SYELTQPPSVSVSPGQTARITCSGDALPKKYAYW YQQKSGQAPVLVIHEDDKRPSGIPGRFSASSSGT TATLTISGAQVEDEADYYCYSTDTNDNHAFGSG TKLTVL	VL
CLM20_B8_UCA		
SEQ ID NO: 28	GGSISSGGYY	CDRH1
SEQ ID NO: 29	IYYSGST	CDRH2
SEQ ID NO: 30	ATSIVLSGMSNKIQPFDY	CDRH3
SEQ ID NO: 31	KDS	CDRL2
SEQ ID NO: 32	VIYKDSERP	CDRL2 long
SEQ ID NO: 33	LSADSSGTWV	CDRL3
SEQ ID NO: 34	QVQLQESGPGLVKPSQTLSLTCTVSGGSISSGGY YWSWIRQHPGKGLEWIGYIYYSGSTYYNPSLKSR VTISVDTSKNQFSLKLSSVTAADTAVYYCATSIVLS GMSNKIQPFDYWGQGTLVTVSS	VH
SEQ ID NO: 35	SYELTQPPSVSVSLGQMARITCSGEALPKKYAYW YQQKPGQFPVLVIYKDSERPSGIPERFSGSSSGTI VTLTISGVQAEDEADYYCLSADSSGTWVFGGGT KLTV	VL
CLM99_G12		
SEQ ID NO: 36	GFNFSSHG	CDRH1
SEQ ID NO: 37	ISFHGTHP	CDRH2
SEQ ID NO: 38	AKDVVLRYFDAMDV	CDRH3
SEQ ID NO: 39	STGVGSHNL	CDRL1
SEQ ID NO: 40	EVT	CDRL2
SEQ ID NO: 41	IIYEVTKRP	CDRL2 long
SEQ ID NO: 42	CSYAGTGNSWV	CDRL3
SEQ ID NO: 43	EVQLVESGGGVVQPGRSLRLTCVASGFNFSSHG MHWVRQAPGKGLEWVAAISFHGTHPYYVDSV KGRFTISRDNSKNTLYLQMDSLGPDDTAIYYCAK DVVLRYFDAMDVWGQGTTVTISS	VH
SEQ ID NO: 44	QAALTQPASVSGSPGQSITISCTGASTGVGSHNL VSWYQQHPGKAPKLIIYEVTKRPSGVSTRFSGSK SGNTASLTISGLQADDEADYHCCSYAGTGNSW VFGGGTKLTVL	VL
CLM99_D10		
SEQ ID NO: 45	GFTFSSYG	CDRH1
SEQ ID NO: 46	ISYHGTHP	CDRH2
SEQ ID NO: 47	AKDLVLRYFDSMDV	CDRH3
SEQ ID NO: 48	SSGVGSHDL	CDRL1

SEQ ID NO: 49	MIYEVTRRP	CDRL2 long
SEQ ID NO: 50	EVQLVQSGGGVVQPGRSLRLSCAASGFTFSSYG MHWVRQAPGKGLEWVAAISYHGTHPYYVDSV KGRFTISRDNSKNTLYLQMGSLGPDDTAVYYCA KDLVLRYFDSMDVWGQGTTVTVSS	VH
SEQ ID NO: 51	QSALTQPASVSGSPGQSITISCTGTSSGVGSHDL VSWYQQHPGKAPKLMIYEVTRRPSGVSNRFSGS KSGNTASLTISGLQAEDEADYHCCSYAGTGNSW VFGGGTKLTVL	VL
CLM99_E3		
SEQ ID NO: 52	GFSFSSYG	CDRH1
SEQ ID NO: 53	SSGVGSHNL	CDRL1
SEQ ID NO: 54	EVQLVESGGGVVQPGRSLRLSCVASGFSFSSYG MHWVRQAPGKGLEWVAAISFHGTHPFYGDSV KGRFTISRDNSKSTLFLDMGSLGTDDTAVYYCAK DVVLRYFDAMDVWGQGSTVTVSS	VH
SEQ ID NO: 55	QAGQTQPASVSGSPGQSITISCTGASSGVGSHN LVSWYQQHPGKAPKLIIYEVTKRPSGVSDRFSGS KSGNTASLTISGLQAEDEADYHCCSYAGTGNSW VFGGGTKLTVL	VL
CLM13_G9		
SEQ ID NO: 56	GFTFSRYW	CDRH1
SEQ ID NO: 57	TSGDGSIT	CDRH2
SEQ ID NO: 58	ARALYYYDSSDYGVNWFDP	CDRH3
SEQ ID NO: 59	SSNIGAGYD	CDRL1
SEQ ID NO: 60	AST	CDRL2
SEQ ID NO: 61	LIYASTNRP	CDRL2 long
SEQ ID NO: 62	QSYDISLEV	CDRL3
SEQ ID NO: 63	EVQLVESGGGLIQPGGSLRLSCVASGFTFSRYWV HWVRQAPGKGLVWVSRTSGDGSITIYADSVKG RFTISRDNAKNTLFLQMNSLRVEDTAVYYCARAL YYYDSSDYGVNWFDPWGQGTLVTVSS	VH
SEQ ID NO: 64	QAVLTQPPSVSGAPGQRVTISCTGSSSNIGAGY DVHWYQQLPGTAPKLLIYASTNRPSGVPDRFSG SKSGTSASLAITGLRAEDEADYYCQSYDISLEVFG TGTKVTVL	VL
CLM20_Bis_B3		
SEQ ID NO: 65	GFTFNNYA	CDRH1
SEQ ID NO: 66	ISYEGSLK	CDRH2
SEQ ID NO: 67	ARSHGLFELPPFYLDY	CDRH3
SEQ ID NO: 68	SSDVGGYNY	CDRL1
SEQ ID NO: 69	MIYEVTNRP	CDRL2 long
SEQ ID NO: 70	SSFTSRSTHV	CDRL3

SEQ ID NO: 71	EVQLVQSGGGVVQPGRSLRLSCAASGFTFNNY AMHWVRQAPGKGLEWLARISYEGSLKSYAESVE GRFTISRDSSNTLYLQMHSLTVEDTAVYYCARSH GLFELPPFYLDYWGQGTLVTVYS	VH
SEQ ID NO: 72	QSALTQPASVSGSPGQSITMSCTGTSSDVGGYN YVSWYQQHPGKAPKLMIYEVTNRPSGVSNRFS GSKSGNTASLTISGLQAEDEADYYCSSFTSRSTHV FGSGTKVTVL	VL
Constant regions		
SEQ ID NO: 73	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPE PVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVV TVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISR TPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNA KTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYK CKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESNGQPE NNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQG NVFSCSVLHEALHSHYTQKSLSLSPGK	heavy chain
SEQ ID NO: 74	GQPKAAPSVTLFPPSSEELQANKATLVCLISDFYP GAVTVAWKADSSPVKAGVETTTPSKQSNNKYA ASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVA PTECS	lambda light chain
SEQ ID NO: 75	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPR EAKVQWKVDNALQSGNSQESVTEQDSKDSTYS LSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSF NRGEC	kappa light chain
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SEQ ID NO: 79	gcattgccaaaaaaatat	CDRL1
SEQ ID NO: 80	aaagacacc	CDRL2
SEQ ID NO: 81	gtgatatataaagacaccgagaggccc	CDRL2 long
SEQ ID NO: 82	ctatcagcagacaccagtggtacttgggtg	CDRL3

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SEQ ID NO: 191	ggattcactctcaaaaacctctgg	CDRH1
SEQ ID NO: 192	attagaagcaaaattgctggtgggacaaca	CDRH2
SEQ ID NO: 193	accactctattctcc	CDRH3
SEQ ID NO: 194	agcctcagaaactattat	CDRL1
SEQ ID NO: 195	gaggagaac	CDRL2
SEQ ID NO: 196	gtcatctatgaggagaacacccggccc	CDRL2 long
SEQ ID NO: 197	aattcccgggacaccagtgttaatcatctgcta	CDRL3

SEQ ID NO: 198	gaggtgcagctggtggagtctgggggaggcttggtgaagcctgggg ggtcccttagactctcttgtgtagactctggattcactctcaaaaacct ctggatgaactgggtccgccaggctccagggaaggggctggagtg ggttggccgaattagaagcaaaattgctggtgggacaacagactac gctgtacccgtgcaaggtagattcagcatctctagagatgactcaaa aaacacggtgtatctgcagatgaacagcctgaaaaccgaggaca cagccgtgtattattgtaccactctattctcctggggccagggaaccc tggtcaccgtctcctcag	VH
SEQ ID NO: 199	tcttctgagctgactcaggaccctgctgtgtctgtggccttggggcag acagtcaggatcacatgccaaggagacagcctcagaaactattat ccaagttggtaccagcagaagccaggccaggcccctgtacttgtc atctatgaggagaacacccggccctcagggatcccagaccgattc tcagcctccatctcaggaaacacagcttccttgaccatcactgggg cacaggcggaagatgaggctgactattactgtaattcccgggacac cagtgttaatcatctgctattcggcggagggaccaaactgaccgtcc taa	VL
CSC3_H1_UCA		
SEQ ID NO: 200	ggattcaccttcagtagctatgct	CDRH1
SEQ ID NO: 201	attagtagtaatgggggtagcaca	CDRH2
SEQ ID NO: 202	gtgaagaattctgacgtattacgatttcctcacctctacttcgatctc	CDRH3
SEQ ID NO: 203	ctcatctatggtgcatccaccagggcc	CDRL2 long
SEQ ID NO: 204	cagcagtataataactggccttcgatcacc	CDRL3
SEQ ID NO: 205	gaggtgcagctggtggagtctgggggaggcttggtccagcctgggg ggtccctgagactctcctgttcagcctctggattcaccttcagtagct atgctatgcactgggtccgccaggctccagggaagggactggaat atgtttcagctattagtagtaatgggggtagcacatactacgcagact ccgtgaagggcagattcaccatctccagagacaattccaagaaca cgctgtatcttcaaatgagcagtctgagagctgaggacacggctgtg tattactgtgtgaagaattctgacgtattacgatttcctcacctctacttc gatctctggggccgtggcaccctggtcactgtctcctcag	VH
SEQ ID NO: 206	gaaatagtgatgacgcagtctccagccaccctgtctgtgtctccagg ggaaagagccaccctctcctgcagggccagtcagagtgttagcag caacttagcctggtaccagcagaaacctggccaggctcccaggct cctcatctatggtgcatccaccagggccactggtatcccagccagg ttcagtggcagtgggtctgggacagagttcactctcaccatcagcag cctgcagtctgaagattttgcagtttattactgtcagcagtataataact ggccttcgatcaccttcggccaagggacacgactggagattaaac	VL
Amino acid sequences		
ISR42_E7		
SEQ ID NO: 207	GFTFNNYI	CDRH1

SEQ ID NO: 208	IGSDGRNT	CDRH2
SEQ ID NO: 209	VKGLDVLRFLDLSTPSGERLDAFDI	CDRH3
SEQ ID NO: 210	QGISNY	CDRL1
SEQ ID NO: 211	AAS	CDRL2
SEQ ID NO: 212	LIYAASTLQ	CDRL2 long
SEQ ID NO: 213	QQLNSYPLFT	CDRL3
SEQ ID NO: 214	QVQLVQSGGGVVQPGESLRLSCSGSGFTFNNYI MHWVRQAPGQGLDYVSGIGSDGRNTNYGDS VKGRFTISRDNSKDTLYLQMTSLRAEDTAFYYCV KGLDVLRFLDLSTPSGERLDAFDIWGQGTMVTV SS	VH
SEQ ID NO: 215	DIVMTQSPSFLSASVGDRVTITCRASQGISNYLA WYQQKPGKAPHLLIYAASTLQSGVPSRFSGSGS GTEFTLTISSLQPEDFATYYCQQLNSYPLFTFGPG TKVDIE	VL
CSC3_H1		
SEQ ID NO: 216	GFTFSDFS	CDRH1
SEQ ID NO: 217	ITSSGSST	CDRH2
SEQ ID NO: 218	VKNSDVFRFPHLYFDV	CDRH3
SEQ ID NO: 219	QSVSSN	CDRL1
SEQ ID NO: 220	GAS	CDRL2
SEQ ID NO: 221	LIYGASTRA	CDRL2 long
SEQ ID NO: 222	QQYDNWPSIT	CDRL3
SEQ ID NO: 223	EVQLVESGGGLVLPGGSLRLSCSASGFTFSDFSM HWVRQSPGKGLEYVSAITSSGSSTYYPDSVKGRF TISRDNSKNTLYLQMGSLRVEDTAVYWCVKNSD VFRFPHLYFDVWGRGTLVTVSS	VH
SEQ ID NO: 224	DIVMTQSPATLSVSPGDRATLSCRASQSVSSNLA WYQQKPGQAPRLLIYGASTRAAGIPARFSGSGS GTEFTLTISSLQSEDFAVYYCQQYDNWPSITFGQ GTRLEIK	VL
E371_F8		
SEQ ID NO: 225	GDTFTSYT	CDRH1
SEQ ID NO: 226	VNIGSGNI	CDRH2

SEQ ID NO: 227	ATGGETVWLLAFDI	CDRH3
SEQ ID NO: 228	SSDVGGYNY	CDRL1
SEQ ID NO: 229	DVT	CDRL2
SEQ ID NO: 230	VIYDVTKRP	CDRL2 long
SEQ ID NO: 231	SSFSSSRTVL	CDRL3
SEQ ID NO: 232	EVQLVQSGAEVKKPGASVKVSCRASGDTFTSYT VHWVRQAPGQGLEWVGRVNIGSGNINYSQKF QGRVTIIRDTSASTAYMELSSLRFEDTAVYYCATG GETVWLLAFDIWGQGTRVTVSS	VH
SEQ ID NO: 233	QSALTQAASVSGSPGQSITISCTGTSSDVGGYNY VSWYQQHPVKAPKLVIYDVTKRPSGVSNRFSGS KSGNTASLTISGLQAEDEADYYCSSFSSSRTVLFG GGTKLTVL	VL
E2418_G12		
SEQ ID NO: 234	GFTFGSYA	CDRH1
SEQ ID NO: 235	MSSDGHNE	CDRH2
SEQ ID NO: 236	ARGSDYVDDSPPLHY	CDRH3
SEQ ID NO: 237	QDIANK	CDRL1
SEQ ID NO: 238	LIYAASRLQ	CDRL2 long
SEQ ID NO: 239	QQYDSFPFT	CDRL3
SEQ ID NO: 240	EVQLVESGGGVVQPGRSLRISCAVSGFTFGSYA MHWVRQAPGKGLEWVGVMSSDGHNEYYADS VKGRFTISRDNSRNKLYLEMNNLRVDDTAVFYC ARGSDYVDDSPPLHYWGQGTLVTVSS	VH
SEQ ID NO: 241	DIQLTQSPSSLSASIGDRVTITCRASQDIANKLAW FQQAPGKAPKSLIYAASRLQSGVPSQFSGSGSGT DFTLTIESLQAGDFATYFCQQYDSFPFTFGPGTK VDVK	VL
E2121_B7		
SEQ ID NO: 242	GYSFTKYW	CDRH1
SEQ ID NO: 243	IYPGDSDT	CDRH2
SEQ ID NO: 244	ATPGIAASYTGGAFDI	CDRH3
SEQ ID NO: 245	ALAKQY	CDRL1
SEQ ID NO: 246	QSADSSGTFGVI	CDRL3

SEQ ID NO: 247	EVQLVQSGAEVKKPGESLKISCKGSGYSFTKYWI AWVRQMPGKGLEWMGIIYPGDSDTRYSPSFQG HVTISADKSISTAFLQWSSLKASDTAIYYCATPGIA ASYTGGAFDIWGQGTTVIVSP	VH
SEQ ID NO: 248	SYELTQPPSVSVSPGQTARITCSGDALAKQYAY WYQQKPGQAPGVVIYKDSERPSGIPERFSGSSSG TTVTLTISGVQAEDEADYYCQSADSSGTFGVIFG GGTKLTVL	VL
E1373_G3		
SEQ ID NO: 249	GFTLKNLW	CDRH1
SEQ ID NO: 250	IRSKIAGGTT	CDRH2
SEQ ID NO: 251	TTLFS	CDRH3
SEQ ID NO: 252	SLRNYY	CDRL1
SEQ ID NO: 253	EEN	CDRL2
SEQ ID NO: 254	VIYEENTRP	CDRL2 long
SEQ ID NO: 255	NSRDTSVNHLL	CDRL3
SEQ ID NO: 256	EVQLVESGGGLVKPGGSLRLSCVDSGFTLKNLW MNWVRQAPGKGLEWVGRIRSKIAGGTTDYAVP VQGRFSISRDDSKNTVYLQMNSLKTEDTAVYYC TTLFSWGQGTLVTVSS	VH
SEQ ID NO: 257	SSELTQDPAVSVALGQTVRITCQGDSLRNYYPS WYQQKPGQAPVLVIYEENTRPSGIPDRFSASISG NTASLTITGAQAEDEADYYCNSRDTSVNHLLFG GGTKLTVL	VL
CSC3_H1_UCA		
SEQ ID NO: 258	GFTFSSYA	CDRH1
SEQ ID NO: 259	ISSNGGST	CDRH2
SEQ ID NO: 260	VKNSDVLRFPHLYFDL	CDRH3
SEQ ID NO: 261	QQYNNWPSIT	CDRL3
SEQ ID NO: 262	EVQLVESGGGLVQPGGSLRLSCSASGFTFSSYAM HWVRQAPGKGLEYVSAISSNGGSTYYADSVKG RFTISRDNSKNTLYLQMSSLRAEDTAVYYCVKNS DVLRFPHLYFDLWGRGTLVTVSS	VH
SEQ ID NO: 263	EIVMTQSPATLSVSPGERATLSCRASQSVSSNLA WYQQKPGQAPRLLIYGASTRATGIPARFSGSGS GTEFTLTISSLQSEDFAVYYCQQYNNWPSITFGQ GTRLEIK	VL

Fusion peptide and epitope		
SEQ ID NO: 264	IEDLLFNK	fusion peptide epitope
SEQ ID NO: 265	RSFIEDLLFNK	fusion peptide epitope
SEQ ID NO: 266	KPSKRSFIEDLLFNKVTLAD	SARS-CoV-2 fusion peptide
SEQ ID NO: 267	KRSFIEDLLFNK	fusion peptide epitope
SEQ ID NO: 268	SPRRRSFIEDLLFTS	IBV fusion peptide
SEQ ID NO: 269	RLGGRSAIEDLLFNK	PdCV fusion peptide

CLAIMS

1. An antibody, or an antigen-binding fragment thereof, which binds to the spike (S) protein of different sarbecoviruses.

2. The antibody, or an antigen-binding fragment thereof, according to claim 1, wherein the antibody, or the antigen-binding fragment thereof, binds to the spike (S) protein of SARS-CoV-1 and SARS-CoV-2.

3. The antibody, or an antigen-binding fragment thereof, according to claim 1 or 2, wherein the antibody, or the antigen-binding fragment thereof, binds to the spike (S) protein of sarbecoviruses and non-sarbecovirus betacoronaviruses.

4. The antibody, or an antigen-binding fragment thereof, according to claim 3, wherein the antibody, or the antigen-binding fragment thereof, binds to the spike (S) protein of HKU1 coronavirus, SARS-CoV-1 and SARS-CoV-2.

5. The antibody, or an antigen-binding fragment thereof, according to any one of the previous claims, wherein the antibody, or the antigen-binding fragment thereof, binds to the spike (S) protein of HKU1 coronavirus, OC43 coronavirus, SARS-CoV-1 and SARS-CoV-2.

6. The antibody, or an antigen-binding fragment thereof, according to any one of the previous claims, wherein the antibody, or the antigen-binding fragment thereof, binds to the spike (S) protein of HKU1 coronavirus, OC43 coronavirus, MERS coronavirus, SARS-CoV-1 and SARS-CoV-2.

7. The antibody, or an antigen-binding fragment thereof, according to any one of the previous claims, wherein the antibody, or the antigen-binding fragment thereof, binds to the spike (S) protein of an alphacoronavirus and to the spike (S) protein of a betacoronavirus.

8. The antibody, or an antigen-binding fragment thereof, according to any one of the previous claims, wherein the antibody, or the antigen-binding fragment thereof, binds to the spike (S) protein of 229E coronavirus, NL63 coronavirus, HKU1 coronavirus, OC43 coronavirus, MERS coronavirus, SARS-CoV-1 and SARS-CoV-2.

9. The antibody, or an antigen-binding fragment thereof, according to any one of the previous claims, wherein the antibody, or the antigen-binding fragment thereof, binds to the fusion peptide of the coronavirus spike (S) protein.

10. The antibody, or an antigen-binding fragment thereof, according to claim 8 or 9, wherein the antibody, or the antigen-binding fragment thereof, comprises (i) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 9, SEQ ID NO: 10, and SEQ ID NO: 11, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 12, SEQ ID NO: 13 or 14, and SEQ ID NO: 15, respectively; or (ii) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 20, SEQ ID NO: 21, and SEQ ID NO: 22, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 12, SEQ ID NO: 23 or 24, and SEQ ID NO: 25, respectively; or (iii) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 28, SEQ ID NO: 29, and SEQ ID NO: 30, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 12, SEQ ID NO: 31 or 32, and SEQ ID NO: 33, respectively; or (iv) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 207, SEQ ID NO: 208, and SEQ ID NO: 209, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 210, SEQ ID NO: 211 or 212, and SEQ ID NO: 213, respectively; or (v) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 216, SEQ ID NO: 217, and SEQ ID NO: 218, respectively, and light chain CDR1, CDR2, and

CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 219, SEQ ID NO: 220 or 221, and SEQ ID NO: 222, respectively; or (vi) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 225, SEQ ID NO: 226, and SEQ ID NO: 227, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 228, SEQ ID NO: 229 or 230, and SEQ ID NO: 231, respectively; or (vii) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 234, SEQ ID NO: 235, and SEQ ID NO: 236, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 237, SEQ ID NO: 211 or 238, and SEQ ID NO: 239, respectively; or (viii) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 258, SEQ ID NO: 259 and SEQ ID NO: 260, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 219, SEQ ID NO: 220 or 221, and SEQ ID NO: 261, respectively.

11. The antibody, or an antigen-binding fragment thereof, according to according to claim 10, wherein the antibody, or the antigen-binding fragment thereof, comprises (i) heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 9, SEQ ID NO: 10, and SEQ ID NO: 11, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 12, SEQ ID NO: 13 or 14, and SEQ ID NO: 15, respectively; or (ii) heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 20, SEQ ID NO: 21, and SEQ ID NO: 22, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 12, SEQ ID NO: 23 or 24, and SEQ ID NO: 25, respectively; or (iii) heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 28, SEQ ID NO: 29, and SEQ ID NO: 30, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 12, SEQ ID NO: 31 or 32, and SEQ ID NO: 33, respectively; or (iv) heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 207, SEQ ID NO: 208, and SEQ ID NO: 209, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to

SEQ ID NO: 210, SEQ ID NO: 211 or 212, and SEQ ID NO: 213, respectively; or (v) heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 216, SEQ ID NO: 217, and SEQ ID NO: 218, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 219, SEQ ID NO: 220 or 221, and SEQ ID NO: 222, respectively; or (vi) heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 225, SEQ ID NO: 226, and SEQ ID NO: 227, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 228, SEQ ID NO: 229 or 230, and SEQ ID NO: 231, respectively; or (vii) heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 234, SEQ ID NO: 235, and SEQ ID NO: 236, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 237, SEQ ID NO: 211 or 238, and SEQ ID NO: 239, respectively; or (viii) heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 258, SEQ ID NO: 259 and SEQ ID NO: 260, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 219, SEQ ID NO: 220 or 221, and SEQ ID NO: 261, respectively.

12. The antibody, or an antigen-binding fragment thereof, according to any one of the previous claims, wherein the antibody, or the antigen-binding fragment thereof, also binds to the spike (S) protein of SARS-like coronavirus WIV-1.

13. The antibody, or an antigen-binding fragment thereof, according to any one of the previous claims, wherein the antibody, or the antigen-binding fragment thereof, binds to the spike (S) protein of an alphacoronavirus, to the spike (S) protein of a betacoronavirus, to the spike (S) protein of a gammacoronavirus, and to the spike (S) protein of a deltacoronavirus.

14. The antibody, or an antigen-binding fragment thereof, according to claim 13, wherein the antibody, or the antigen-binding fragment thereof, binds to the spike (S) protein of 229E coronavirus, NL63 coronavirus, HKU1 coronavirus, OC43 coronavirus, MERS coronavirus, SARS-CoV-1, SARS-CoV-2, infectious bronchitis virus (IBV) and porcine deltacoronavirus (PdCV).

15. The antibody, or an antigen-binding fragment thereof, according to any one of the previous claims, wherein the antibody, or the antigen-binding fragment thereof, binds to an amino acid sequence according to any one of SEQ ID NOs 1 – 8 and 264 – 269.

16. The antibody, or an antigen-binding fragment thereof, according to any one of the previous claims, wherein the antibody, or the antigen-binding fragment thereof, binds to an amino acid sequence according to each of SEQ ID NOs 1 – 7; and, optionally, additionally to an amino acid sequence according to SEQ ID NO: 268 and to an amino acid sequence according to SEQ ID NO: 269.

17. An antibody, or an antigen-binding fragment thereof, which binds to the fusion peptide (FP) of the coronavirus spike (S) protein.

18. The antibody, or an antigen-binding fragment thereof, according to any one of the previous claims, wherein the antibody, or the antigen-binding fragment thereof, binds to an amino acid sequence according to SEQ ID NO: 266 or to a sequence variant thereof having at least 70% sequence identity; preferably to an amino acid sequence according to SEQ ID NO: 1 or to a sequence variant thereof having at least 70% sequence identity; more preferably to an amino acid sequence according to SEQ ID NO: 265 or to a sequence variant thereof having at least 70% sequence identity; even more preferably to an amino acid sequence according to SEQ ID NO: 8 or to a sequence variant thereof having at least 70% sequence identity; and still more preferably to an amino acid sequence according to SEQ ID NO: 264 or to a sequence variant thereof having at least 70% sequence identity.

19. The antibody, or an antigen-binding fragment thereof, according to claim 17 or 18, wherein the antibody or the antigen-binding fragment thereof comprises (i) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 9, SEQ ID NO: 10, and SEQ ID NO: 11, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 12, SEQ ID NO: 13, and SEQ ID NO: 15, respectively; or (ii) heavy chain CDR1, CDR2, and CDR3

sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 9, SEQ ID NO: 10, and SEQ ID NO: 11, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 12, SEQ ID NO: 14, and SEQ ID NO: 15, respectively; or (iii) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 20, SEQ ID NO: 21, and SEQ ID NO: 22, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 12, SEQ ID NO: 23, and SEQ ID NO: 25, respectively; or (iv) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 20, SEQ ID NO: 21, and SEQ ID NO: 22, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 12, SEQ ID NO: 24, and SEQ ID NO: 25, respectively; or (v) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 207, SEQ ID NO: 208, and SEQ ID NO: 209, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 210, SEQ ID NO: 211 or 212, and SEQ ID NO: 213, respectively; or (vi) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 216, SEQ ID NO: 217, and SEQ ID NO: 218, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 219, SEQ ID NO: 220 or 221, and SEQ ID NO: 222, respectively; or (vii) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 225, SEQ ID NO: 226, and SEQ ID NO: 227, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 228, SEQ ID NO: 229 or 230, and SEQ ID NO: 231, respectively; or (viii) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 234, SEQ ID NO: 235, and SEQ ID NO: 236, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 237, SEQ ID NO: 211 or 238, and SEQ ID NO: 239, respectively; or

(ix) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 242, SEQ ID NO: 243, and SEQ ID NO: 244, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 245, SEQ ID NO: 31 or 32, and SEQ ID NO: 246, respectively; or (x) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 249, SEQ ID NO: 250, and SEQ ID NO: 251, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 252, SEQ ID NO: 253 or 254, and SEQ ID NO: 255, respectively.

20. An antibody, or an antigen-binding fragment thereof, which binds to the coronavirus spike (S) protein, wherein the antibody or the antigen-binding fragment thereof comprises (i) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 9, SEQ ID NO: 10, and SEQ ID NO: 11, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 12, SEQ ID NO: 13 or 14, and SEQ ID NO: 15, respectively; or (ii) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 20, SEQ ID NO: 21, and SEQ ID NO: 22, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 12, SEQ ID NO: 23 or 24, and SEQ ID NO: 25, respectively; or (iii) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 28, SEQ ID NO: 29, and SEQ ID NO: 30, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 12, SEQ ID NO: 31 or 32, and SEQ ID NO: 33, respectively; or (iv) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 36, SEQ ID NO: 37, and SEQ ID NO: 38, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 39, SEQ ID NO: 40 or 41, and SEQ ID NO: 42, respectively; or (v) heavy chain CDR1, CDR2, and CDR3

sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 45, SEQ ID NO: 46, and SEQ ID NO: 47, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 48, SEQ ID NO: 40 or 49, and SEQ ID NO: 42, respectively; or (vi) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 52, SEQ ID NO: 37, and SEQ ID NO: 38, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 53, SEQ ID NO: 40 or 41, and SEQ ID NO: 42, respectively; or (vii) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 56, SEQ ID NO: 57, and SEQ ID NO: 58, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 59, SEQ ID NO: 60 or 61, and SEQ ID NO: 62, respectively; or (viii) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 65, SEQ ID NO: 66, and SEQ ID NO: 67, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 68, SEQ ID NO: 40 or 69, and SEQ ID NO: 70, respectively; or (ix) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 207, SEQ ID NO: 208, and SEQ ID NO: 209, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 210, SEQ ID NO: 211 or 212, and SEQ ID NO: 213, respectively; or (x) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 216, SEQ ID NO: 217, and SEQ ID NO: 218, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 219, SEQ ID NO: 220 or 221, and SEQ ID NO: 222, respectively; or (xi) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 225, SEQ ID NO: 226, and SEQ ID NO: 227, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 228, SEQ ID NO: 229 or 230, and SEQ ID NO: 231, respectively; or

(xii) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 234, SEQ ID NO: 235, and SEQ ID NO: 236, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 237, SEQ ID NO: 211 or 238, and SEQ ID NO: 239, respectively; or (xiii) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 242, SEQ ID NO: 243, and SEQ ID NO: 244, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 245, SEQ ID NO: 31 or 32, and SEQ ID NO: 246, respectively; or (xiv) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 249, SEQ ID NO: 250, and SEQ ID NO: 251, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 252, SEQ ID NO: 253 or 254, and SEQ ID NO: 255, respectively; or (xv) heavy chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 258, SEQ ID NO: 259 and SEQ ID NO: 260, respectively, and light chain CDR1, CDR2, and CDR3 sequences having at least 70% sequence identity with the amino acid sequences of SEQ ID NO: 219, SEQ ID NO: 220 or 221, and SEQ ID NO: 261, respectively.

21. The antibody, or an antigen-binding fragment thereof, according to any one of the previous claims, wherein the antibody or the antigen-binding fragment thereof comprises (i) heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 9, SEQ ID NO: 10, and SEQ ID NO: 11, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 12, SEQ ID NO: 13 or 14, and SEQ ID NO: 15, respectively; or (ii) heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 20, SEQ ID NO: 21, and SEQ ID NO: 22, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 12, SEQ ID NO: 23 or 24, and SEQ ID NO: 25, respectively; or (iii) heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 28, SEQ ID NO: 29, and SEQ ID NO: 30, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 12, SEQ ID NO: 31 or 32, and SEQ ID NO: 33, respectively; or (iv) heavy chain

CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 36, SEQ ID NO: 37, and SEQ ID NO: 38, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 39, SEQ ID NO: 40 or 41, and SEQ ID NO: 42, respectively; or (v) heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 45, SEQ ID NO: 46, and SEQ ID NO: 47, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 48, SEQ ID NO: 40 or 49, and SEQ ID NO: 42, respectively; or (vi) heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 52, SEQ ID NO: 37, and SEQ ID NO: 38, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 53, SEQ ID NO: 40 or 41, and SEQ ID NO: 42, respectively; or (vii) heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 56, SEQ ID NO: 57, and SEQ ID NO: 58, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 59, SEQ ID NO: 60 or 61, and SEQ ID NO: 62, respectively; or (viii) heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 65, SEQ ID NO: 66, and SEQ ID NO: 67, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 68, SEQ ID NO: 40 or 69, and SEQ ID NO: 70, respectively; or (ix) heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 207, SEQ ID NO: 208, and SEQ ID NO: 209, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 210, SEQ ID NO: 211 or 212, and SEQ ID NO: 213, respectively; or (x) heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 216, SEQ ID NO: 217, and SEQ ID NO: 218, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 219, SEQ ID NO: 220 or 221, and SEQ ID NO: 222, respectively; or (xi) heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 225, SEQ ID NO: 226, and SEQ ID NO: 227, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 228, SEQ ID NO: 229 or 230, and SEQ ID NO: 231, respectively; or (xii) heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 234, SEQ ID NO: 235, and SEQ ID NO: 236, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 237, SEQ ID NO: 211 or 238, and SEQ ID NO: 239, respectively; or (xiii) heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 242, SEQ ID NO: 243, and SEQ ID NO: 244, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to

SEQ ID NO: 245, SEQ ID NO: 31 or 32, and SEQ ID NO: 246, respectively; or (xiv) heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 249, SEQ ID NO: 250, and SEQ ID NO: 251, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 252, SEQ ID NO: 253 or 254, and SEQ ID NO: 255, respectively; or (xv) heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 258, SEQ ID NO: 259 and SEQ ID NO: 260, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 219, SEQ ID NO: 220 or 221, and SEQ ID NO: 261, respectively.

22. The antibody, or an antigen-binding fragment thereof, according to any one of the previous claims, wherein the antibody or the antigen-binding fragment thereof comprises heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 9, SEQ ID NO: 10, and SEQ ID NO: 11, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 12, SEQ ID NO: 13 or 14, and SEQ ID NO: 15, respectively.

23. The antibody, or an antigen-binding fragment thereof, according to any one of the previous claims, wherein the antibody or the antigen-binding fragment thereof comprises heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 20, SEQ ID NO: 21, and SEQ ID NO: 22, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 12, SEQ ID NO: 23 or 24, and SEQ ID NO: 25, respectively.

24. The antibody, or an antigen-binding fragment thereof, according to any one of the previous claims, wherein the antibody or the antigen-binding fragment thereof comprises heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 28, SEQ ID NO: 29, and SEQ ID NO: 30, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 12, SEQ ID NO: 31 or 32, and SEQ ID NO: 33, respectively.

25. The antibody, or an antigen-binding fragment thereof, according to any one of the previous claims, wherein the antibody or the antigen-binding fragment thereof

comprises heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 36, SEQ ID NO: 37, and SEQ ID NO: 38, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 39, SEQ ID NO: 40 or 41, and SEQ ID NO: 42, respectively.

26. The antibody, or an antigen-binding fragment thereof, according to any one of the previous claims, wherein the antibody or the antigen-binding fragment thereof comprises heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 45, SEQ ID NO: 46, and SEQ ID NO: 47, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 48, SEQ ID NO: 40 or 49, and SEQ ID NO: 42, respectively.

27. The antibody, or an antigen-binding fragment thereof, according to any one of the previous claims, wherein the antibody or the antigen-binding fragment thereof comprises heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 52, SEQ ID NO: 37, and SEQ ID NO: 38, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 53, SEQ ID NO: 40 or 41, and SEQ ID NO: 42, respectively.

28. The antibody, or an antigen-binding fragment thereof, according to any one of the previous claims, wherein the antibody or the antigen-binding fragment thereof comprises heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 56, SEQ ID NO: 57, and SEQ ID NO: 58, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 59, SEQ ID NO: 60 or 61, and SEQ ID NO: 62, respectively.

29. The antibody, or an antigen-binding fragment thereof, according to any one of the previous claims, wherein the antibody or the antigen-binding fragment thereof comprises heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 65, SEQ ID NO: 66, and SEQ ID NO: 67, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 68, SEQ ID NO: 40 or 69, and SEQ ID NO: 70, respectively.

30. The antibody, or an antigen-binding fragment thereof, according to any one of the previous claims, wherein the antibody or the antigen-binding fragment thereof comprises heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 207, SEQ ID NO: 208, and SEQ ID NO: 209, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 210, SEQ ID NO: 211 or 212, and SEQ ID NO: 213, respectively.

31. The antibody, or an antigen-binding fragment thereof, according to any one of the previous claims, wherein the antibody or the antigen-binding fragment thereof comprises heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 216, SEQ ID NO: 217, and SEQ ID NO: 218, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 219, SEQ ID NO: 220 or 221, and SEQ ID NO: 222, respectively.

32. The antibody, or an antigen-binding fragment thereof, according to any one of the previous claims, wherein the antibody or the antigen-binding fragment thereof comprises heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 225, SEQ ID NO: 226, and SEQ ID NO: 227, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 228, SEQ ID NO: 229 or 230, and SEQ ID NO: 231, respectively.

33. The antibody, or an antigen-binding fragment thereof, according to any one of the previous claims, wherein the antibody or the antigen-binding fragment thereof comprises heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 234, SEQ ID NO: 235, and SEQ ID NO: 236, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 237, SEQ ID NO: 211 or 238, and SEQ ID NO: 239, respectively.

34. The antibody, or an antigen-binding fragment thereof, according to any one of the previous claims, wherein the antibody or the antigen-binding fragment thereof comprises heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO:

242, SEQ ID NO: 243, and SEQ ID NO: 244, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 245, SEQ ID NO: 31 or 32, and SEQ ID NO: 246, respectively.

35. The antibody, or an antigen-binding fragment thereof, according to any one of the previous claims, wherein the antibody or the antigen-binding fragment thereof comprises heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 249, SEQ ID NO: 250, and SEQ ID NO: 251, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 252, SEQ ID NO: 253 or 254, and SEQ ID NO: 255, respectively.

36. The antibody, or an antigen-binding fragment thereof, according to any one of the previous claims, wherein the antibody or the antigen-binding fragment thereof comprises heavy chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 258, SEQ ID NO: 259 and SEQ ID NO: 260, respectively, and light chain CDR1, CDR2, and CDR3 sequences according to SEQ ID NO: 219, SEQ ID NO: 220 or 221, and SEQ ID NO: 261, respectively.

37. The antibody, or an antigen-binding fragment thereof, according to any one of the previous claims, wherein the antibody or the antigen-binding fragment thereof comprises (i) a heavy chain variable region comprising an amino acid sequence having at least 70% identity to SEQ ID NO: 16 and a light chain variable region comprising an amino acid sequence having at least 70% identity to SEQ ID NO: 17; or (ii) a heavy chain variable region comprising an amino acid sequence having at least 70% identity to SEQ ID NO: 18 and a light chain variable region comprising an amino acid sequence having at least 70% identity to SEQ ID NO: 19; or (iii) a heavy chain variable region comprising an amino acid sequence having at least 70% identity to SEQ ID NO: 26 and a light chain variable region comprising an amino acid sequence having at least 70% identity to SEQ ID NO: 27; or (iv) a heavy chain variable region comprising an amino acid sequence having at least 70% identity to SEQ ID NO: 34 and a light chain variable region comprising an amino acid sequence having at least 70% identity to SEQ ID NO: 35; or (v) a heavy chain variable region comprising an amino acid

sequence having at least 70% identity to SEQ ID NO: 43 and a light chain variable region comprising an amino acid sequence having at least 70% identity to SEQ ID NO: 44; or (vi) a heavy chain variable region comprising an amino acid sequence having at least 70% identity to SEQ ID NO: 50 and a light chain variable region comprising an amino acid sequence having at least 70% identity to SEQ ID NO: 51; or (vii) a heavy chain variable region comprising an amino acid sequence having at least 70% identity to SEQ ID NO: 54 and a light chain variable region comprising an amino acid sequence having at least 70% identity to SEQ ID NO: 55; or (viii) a heavy chain variable region comprising an amino acid sequence having at least 70% identity to SEQ ID NO: 63 and a light chain variable region comprising an amino acid sequence having at least 70% identity to SEQ ID NO: 64; or (ix) a heavy chain variable region comprising an amino acid sequence having at least 70% identity to SEQ ID NO: 71 and a light chain variable region comprising an amino acid sequence having at least 70% identity to SEQ ID NO: 72; or (x) a heavy chain variable region comprising an amino acid sequence having at least 70% identity to SEQ ID NO: 214 and a light chain variable region comprising an amino acid sequence having at least 70% identity to SEQ ID NO: 215; or (xi) a heavy chain variable region comprising an amino acid sequence having at least 70% identity to SEQ ID NO: 223 and a light chain variable region comprising an amino acid sequence having at least 70% identity to SEQ ID NO: 224; or (xii) a heavy chain variable region comprising an amino acid sequence having at least 70% identity to SEQ ID NO: 232 and a light chain variable region comprising an amino acid sequence having at least 70% identity to SEQ ID NO: 233; or (xiii) a heavy chain variable region comprising an amino acid sequence having at least 70% identity to SEQ ID NO: 240 and a light chain variable region comprising an amino acid sequence having at least 70% identity to SEQ ID NO: 241; or (xiv) a heavy chain variable region comprising an amino acid sequence having at least 70% identity to SEQ ID NO: 247 and a light chain variable region comprising an amino acid sequence having at least 70% identity to SEQ ID NO: 248; or (xv) a heavy chain variable region comprising an amino acid sequence having at least 70% identity to SEQ ID NO: 256 and a light chain variable region comprising an amino acid sequence having at least 70% identity to SEQ ID NO: 257; or (xvi) a heavy chain variable region comprising an amino acid sequence

having at least 70% identity to SEQ ID NO: 262 and a light chain variable region comprising an amino acid sequence having at least 70% identity to SEQ ID NO: 263.

38. The antibody, or an antigen-binding fragment thereof, according to any one of the previous claims, wherein the antibody or the antigen-binding fragment thereof comprises (i) a heavy chain variable region comprising an amino acid sequence according to SEQ ID NO: 16 and a light chain variable region comprising an amino acid sequence according to SEQ ID NO: 17; or (ii) a heavy chain variable region comprising an amino acid sequence according to SEQ ID NO: 18 and a light chain variable region comprising an amino acid sequence according to SEQ ID NO: 19; or (iii) a heavy chain variable region comprising an amino acid sequence according to SEQ ID NO: 26 and a light chain variable region comprising an amino acid sequence according to SEQ ID NO: 27; or (iv) a heavy chain variable region comprising an amino acid sequence according to SEQ ID NO: 34 and a light chain variable region comprising an amino acid sequence according to SEQ ID NO: 35; or (v) a heavy chain variable region comprising an amino acid sequence according to SEQ ID NO: 43 and a light chain variable region comprising an amino acid sequence according to SEQ ID NO: 44; or (vi) a heavy chain variable region comprising an amino acid sequence according to SEQ ID NO: 50 and a light chain variable region comprising an amino acid sequence according to SEQ ID NO: 51; or (vii) a heavy chain variable region comprising an amino acid sequence according to SEQ ID NO: 54 and a light chain variable region comprising an amino acid sequence according to SEQ ID NO: 55; or (viii) a heavy chain variable region comprising an amino acid sequence according to SEQ ID NO: 63 and a light chain variable region comprising an amino acid sequence according to SEQ ID NO: 64; or (ix) a heavy chain variable region comprising an amino acid sequence according to SEQ ID NO: 71 and a light chain variable region comprising an amino acid sequence according to SEQ ID NO: 72; or (x) a heavy chain variable region comprising an amino acid sequence according to SEQ ID NO: 214 and a light chain variable region comprising an amino acid sequence according to SEQ ID NO: 215; or (xi) a heavy chain variable region comprising an amino acid sequence according to SEQ ID NO: 223 and a light chain variable region comprising an amino acid sequence according to SEQ ID NO: 224; or (xii) a heavy chain variable region

comprising an amino acid sequence according to SEQ ID NO: 232 and a light chain variable region comprising an amino acid sequence according to SEQ ID NO: 233; (xiii) a heavy chain variable region comprising an amino acid sequence according to SEQ ID NO: 240 and a light chain variable region comprising an amino acid sequence according to SEQ ID NO: 241; or (xiv) a heavy chain variable region comprising an amino acid sequence according to SEQ ID NO: 247 and a light chain variable region comprising an amino acid sequence according to SEQ ID NO: 248; or (xv) a heavy chain variable region comprising an amino acid sequence according to SEQ ID NO: 256 and a light chain variable region comprising an amino acid sequence according to SEQ ID NO: 257; or (xvi) a heavy chain variable region comprising an amino acid sequence according to SEQ ID NO: 262 and a light chain variable region comprising an amino acid sequence according to SEQ ID NO: 263.

39. The antibody, or an antigen-binding fragment thereof, according to any one of the previous claims, wherein the antibody, or the antigen-binding fragment thereof, binds to the spike (S) protein of alphacoronaviruses and betacoronaviruses.

40. The antibody, or an antigen-binding fragment thereof, according to any one of the previous claims, wherein the antibody, or the antigen-binding fragment thereof, neutralizes infection with a coronavirus.

41. The antibody, or an antigen-binding fragment thereof, according to claim 40, wherein the antibody, or the antigen-binding fragment thereof, neutralizes infection with a human coronavirus selected from the group consisting of 229E, NL63, OC43, HKU1, WIV-1, MERS, SARS-CoV and/or SARS-CoV-2.

42. The antibody, or an antigen-binding fragment thereof, according to claim 40 or 41, wherein the antibody, or the antigen-binding fragment thereof, neutralizes infection with at least two distinct coronaviruses.

43. The antibody, or an antigen-binding fragment thereof, according to any one of the previous claims, wherein the antibody, or the antigen-binding fragment thereof, inhibits or reduces fusion of the coronavirus spike protein with ACE2.

44. The antibody, or an antigen-binding fragment thereof, according to any one of the previous claims, wherein the antibody, or the antigen-binding fragment thereof, is a human antibody.

45. The antibody, or an antigen-binding fragment thereof, according to any one of the previous claims, wherein the antibody, or the antigen-binding fragment thereof, is a monoclonal antibody.

46. The antibody according to any one of the previous claims, wherein the antibody comprises an Fc moiety.

47. The antibody according to any one of the previous claims, wherein the antibody is of the IgG type.

48. The antibody according to any one of the previous claims, wherein the antibody is of the IgG1 type.

49. The antibody, or an antigen-binding fragment thereof, according to any one of the previous claims, wherein the antibody, or the antigen-binding fragment thereof, is purified.

50. The antibody, or an antigen-binding fragment thereof, according to any one of the previous claims, wherein the antibody, or the antigen-binding fragment thereof, is a single-chain antibody.

51. The antibody, or an antigen-binding fragment thereof, according to any one of the previous claims, wherein the antibody, or the antigen-binding fragment thereof, is selected from Fab, Fab', F(ab')2, Fv, nanobodies or scFv.

52. The antibody, or an antigen-binding fragment thereof, according to any one of the previous claims for use as a medicament.

53. The antibody, or an antigen-binding fragment thereof, for use according to any one of the previous claims in prophylaxis or treatment of coronavirus infection.

54. A nucleic acid molecule comprising a polynucleotide encoding the antibody, or an antigen-binding fragment thereof, according to any one of claims 1 to 51.

55. The nucleic acid molecule of claim 54, wherein the polynucleotide encoding the antibody, or an antigen-binding fragment thereof, is codon-optimized.

56. The nucleic acid molecule of claim 54 or 55 comprising a nucleic acid sequence as set forth in any one of SEQ ID NOs 76 – 206; or a sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity.

57. A combination of a first and a second nucleic acid molecule, wherein the first nucleic acid molecule comprises a polynucleotide encoding the heavy chain of the antibody, or an antigen-binding fragment thereof, according to any one of claims 1 to 51; and the second nucleic acid molecule comprises a polynucleotide encoding the corresponding light chain of the same antibody, or the same antigen-binding fragment thereof.

58. The combination of nucleic acid molecules of claim 57, wherein one or both of the polynucleotides encoding the heavy and/or light chain(s) of the antibody, or an antigen-binding fragment thereof, is/are codon-optimized.

59. The combination of nucleic acid molecules of claim 57 or 58 comprising a nucleic acid sequence as set forth in any one of SEQ ID NOs 76 – 206; or a sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%,

at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity.

60. A combination of a first and a second nucleic acid molecule, wherein

(i) the first nucleic acid molecule comprises a polynucleotide encoding the heavy chain of an antibody, or an antigen-binding fragment thereof, the polynucleotide comprising: (a) nucleotide sequences according to SEQ ID NOs 76, 77 and 78; or (b) nucleotide sequences according to SEQ ID NOs 76, 77 and 85; or (c) nucleotide sequences according to SEQ ID NOs 89, 90 and 91; or (d) nucleotide sequences according to SEQ ID NOs 98, 99 and 100; or (e) nucleotide sequences according to SEQ ID NOs 106, 107 and 108; or (f) nucleotide sequences according to SEQ ID NOs 115, 116 and 117; or (g) nucleotide sequences according to SEQ ID NOs 123, 124 and 108; or (h) nucleotide sequences according to SEQ ID NOs 130, 131 and 132; or (i) nucleotide sequences according to SEQ ID NOs 139, 140 and 141; or (j) nucleotide sequences according to SEQ ID NOs 147, 148 and 149; or (k) nucleotide sequences according to SEQ ID NOs 156, 157 and 158; or (l) nucleotide sequences according to SEQ ID NOs 165, 166 and 167; or (m) nucleotide sequences according to SEQ ID NOs 174, 175 and 176; or (n) nucleotide sequences according to SEQ ID NOs 182, 183 and 184; or (o) nucleotide sequences according to SEQ ID NOs 191, 192 and 193; or (p) nucleotide sequences according to SEQ ID NOs 200, 201 and 202; and

(ii) the second nucleic acid molecule comprises a polynucleotide encoding the light chain of an antibody, or an antigen-binding fragment thereof, the polynucleotide comprising: (A) nucleotide sequences according to SEQ ID NOs 79, 80 (or 81), and 82; or (B) nucleotide sequences according to SEQ ID NOs 79, 80 (or 86), and 82; or (C) nucleotide sequences according to SEQ ID NOs 92, 93 (or 94), and 95; or (D) nucleotide sequences according to SEQ ID NOs 79, 101 (or 102), and 103; or (E) nucleotide sequences according to SEQ ID NOs 109, 110 (or 111), and 112; or (F) nucleotide sequences according to SEQ ID NOs 118, 110 (or 119), and 120; or (G) nucleotide sequences according to SEQ ID NOs 125, 110 (or 126), and 127; or (H) nucleotide sequences according to SEQ ID NOs 133, 134

(or 135), and 136; or (I) nucleotide sequences according to SEQ ID NOs 142, 110 (or 143), and 144; or (J) nucleotide sequences according to SEQ ID NOs 150, 151 (or 152), and 153; or (K) nucleotide sequences according to SEQ ID NOs 159, 160 (or 161), and 162; or (L) nucleotide sequences according to SEQ ID NOs 168, 169 (or 170), and 171; or (M) nucleotide sequences according to SEQ ID NOs 177, 151 (or 178), and 179; or (N) nucleotide sequences according to SEQ ID NOs 185, 186 (or 187), and 188; or (O) nucleotide sequences according to SEQ ID NOs 194, 195 (or 196), and 197; or (P) nucleotide sequences according to SEQ ID NOs 159, 160 (or 203), and 204.

61. A vector comprising the nucleic acid molecule according to any one of claims 54 to 56 or the combination of nucleic acid molecules according to any one of claims 57 to 60.

62. A combination of a first and a second vector, wherein the first vector comprises a first nucleic acid molecule as defined in any one of claims 57 to 60 and the second vector comprises the corresponding second nucleic acid molecule as defined in any one of claims 57 to 60.

63. A cell expressing the antibody, or an antigen-binding fragment thereof, according to any one of claims 1 to 52, or comprising the vector according to claim 61 or the combination of vectors according to claim 62.

64. A pharmaceutical composition comprising the antibody, or an antigen-binding fragment thereof, according to any one of claims 1 to 51, the nucleic acid according to any one of claims 54 to 56, the combination of nucleic acids according to any one of claims 57 to 60, the vector according to claim 61, the combination of vectors according to claim 62, or the cell according to claim 63, and, optionally, a pharmaceutically acceptable excipient, diluent or carrier.

65. The antibody, or an antigen-binding fragment thereof, according to any one of claims 1 to 51, the nucleic acid according to any one of claims 54 to 56, the combination of nucleic acids according to any one of claims 57 to 60, the vector according to claim

61, the combination of vectors according to claim 62, the cell according to claim 63, or the pharmaceutical composition according to claim 64 for use as a medicament; optionally in the prophylaxis or treatment of coronavirus infection.

66. Use of the antibody, or an antigen-binding fragment thereof, according to any one of claims 1 to 51 in (*in-vitro*) diagnosis of coronavirus infection.

67. Use of the antibody, or an antigen-binding fragment thereof, according to any one of claims 1 to 51 in a method for detecting coronavirus antigens.

68. Use of the antibody, or an antigen-binding fragment thereof, according to any one of claims 1 to 51 for monitoring the quality of anti-coronavirus vaccines by checking the antigen of said vaccine.

69. The use according to claim 68, wherein the conformation of the antigen, or an epitope thereof, of said vaccine is checked.

70. Use of the antibody, or an antigen-binding fragment thereof, according to any one of claims 1 to 51, the nucleic acid according to any one of claims 54 to 56, the combination of nucleic acids according to any one of claims 57 to 60, the vector according to claim 61, the combination of vectors according to claim 62, the cell according to claim 63, or the pharmaceutical composition according to claim 64 in the manufacture of a medicament for prophylaxis, treatment or attenuation of coronavirus infection.

71. A method of reducing or treating coronavirus infection, or lowering the risk of coronavirus infection, comprising: administering to a subject in need thereof, a therapeutically effective amount of the antibody, or an antigen-binding fragment thereof, according to any one of claims 1 to 51, the nucleic acid according to any one of claims 54 to 56, the combination of nucleic acids according to any one of claims 57 to 60, the vector according to claim 61, the combination of vectors according to claim

62, the cell according to claim 63, or the pharmaceutical composition according to claim 64.

72. A method of reducing or inhibiting fusion of the coronavirus spike protein with ACE2 using the antibody, or an antigen-binding fragment thereof, according to any one of claims 1 to 51, the nucleic acid according to any one of claims 54 to 56, the combination of nucleic acids according to any one of claims 57 to 60, the vector according to claim 61, the combination of vectors according to claim 62, the cell according to claim 63, or the pharmaceutical composition according to claim 64.

73. A recombinant peptide, polypeptide or protein comprising the amino acid sequence according to SEQ ID NO: 264, or a sequence variant thereof preferably having at least 75% sequence identity.

74. A recombinant peptide, polypeptide or protein comprising the amino acid sequence according to SEQ ID NO: 8, or a sequence variant thereof having at least 70% sequence identity.

75. The recombinant peptide, polypeptide or protein according to claim 73 or 74 comprising the amino acid sequence according to SEQ ID NO: 265, or a sequence variant thereof preferably having at least 70% sequence identity.

76. The recombinant peptide, polypeptide or protein according to any one of claims 73 to 75 comprising the amino acid sequence according to SEQ ID NO: 1, or a sequence variant thereof having at least 70% sequence identity.

77. A peptide conjugate comprising the recombinant peptide according to any one of claims 73 to 76.

78. A nucleic acid comprising a polynucleotide sequence encoding the recombinant peptide, polypeptide or protein according to any one of claims 73 to 76.

79. A molecule, a virus-like particle or a nanoparticle comprising the recombinant peptide, polypeptide or protein according to any one of claims 73 to 76.

80. A vaccine comprising the recombinant peptide, polypeptide or protein according to any one of claims 73 to 76, the peptide conjugate according to claim 77, the nucleic acid according to claim 78 or the molecule, virus-like particle or nanoparticle according to claim 79.

81. The recombinant peptide, polypeptide or protein according to any one of claims 73 to 76; the peptide conjugate according to claim 77; the nucleic acid according to claim 78; the molecule, virus-like particle or nanoparticle according to claim 79; or the vaccine according to claim 80 for use as a medicament.

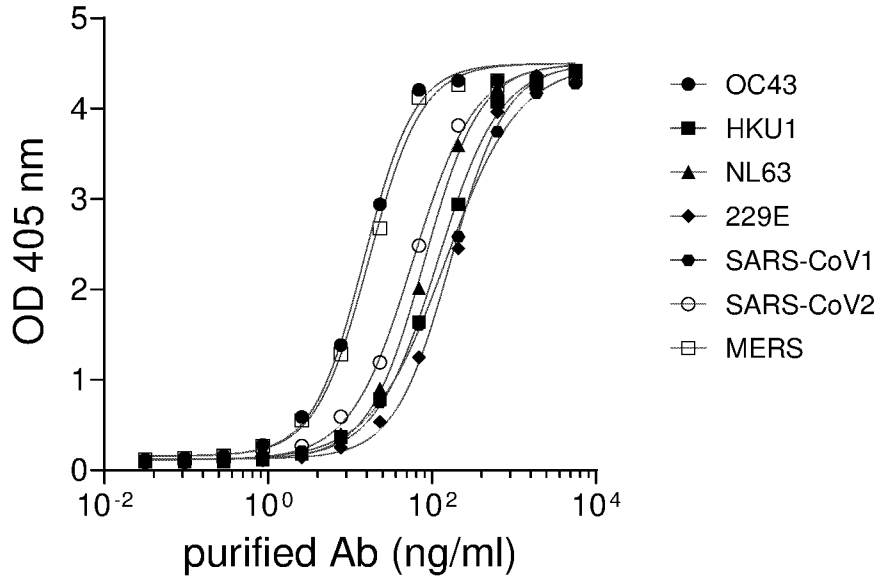
82. Use of the recombinant peptide, polypeptide or protein according to any one of claims 73 to 76; the peptide conjugate according to claim 77; the nucleic acid according to claim 78; the molecule, virus-like particle or nanoparticle according to claim 79; or the vaccine according to claim 80in the manufacture of a medicament for prophylaxis, treatment or attenuation of coronavirus infection.

83. A method of reducing or treating coronavirus infection, or lowering the risk of coronavirus infection, comprising: administering to a subject in need thereof, a therapeutically effective amount of the recombinant peptide, polypeptide or protein according to any one of claims 73 to 76; the peptide conjugate according to claim 77; the nucleic acid according to claim 78; the molecule, virus-like particle or nanoparticle according to claim 79; or the vaccine according to claim 80.

A

Purified CLM20_B8 (@60min)

	OC43	HKU1	NL63	229E	SARS-CoV1	SARS-CoV2	MERS
EC50	14.75	117.1	80.65	168.5	145.7	58.10	16.98



B

Purified CLM20_C9 (@60min)

	OC43	HKU1	NL63	229E	SARS-CoV1	SARS-CoV2	MERS
EC50	23.48	145.1	138.8	213.1	305.1	117.3	31.20

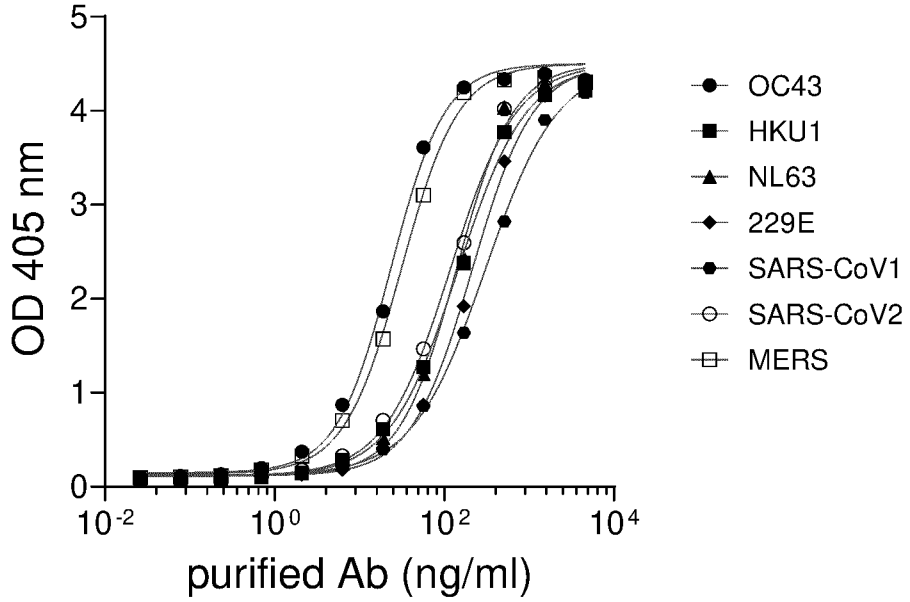
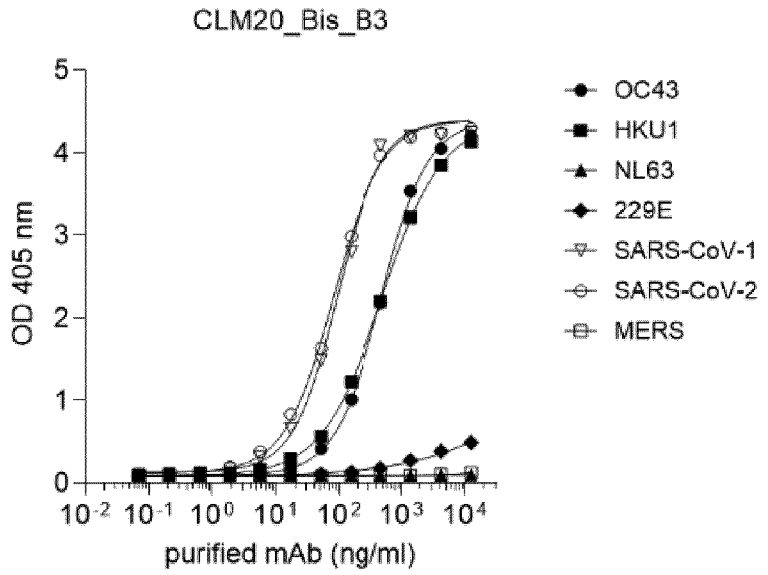


Figure 1

C



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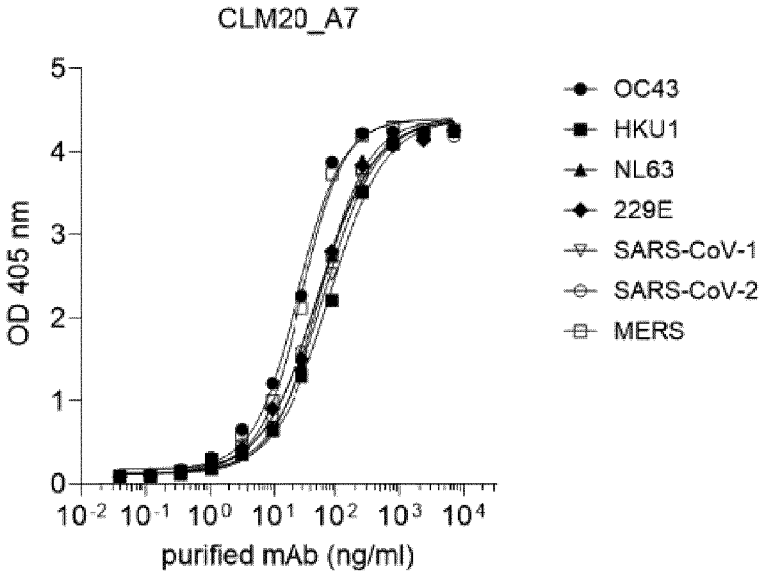

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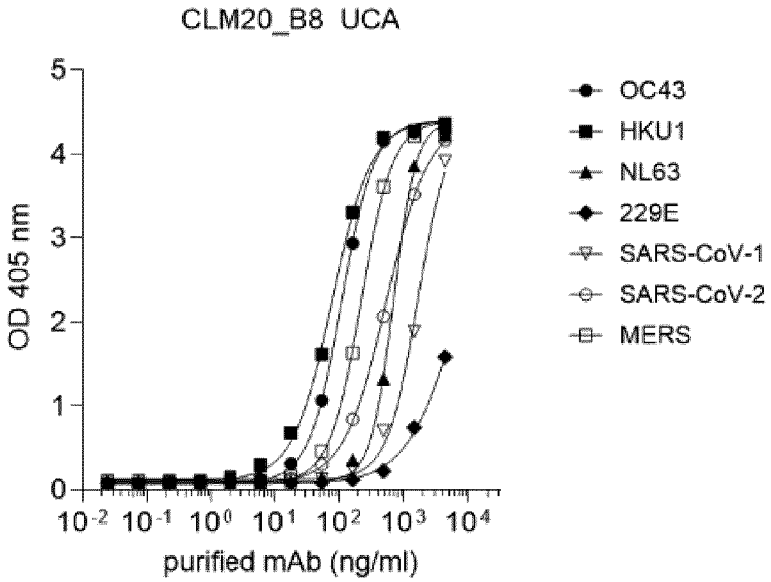
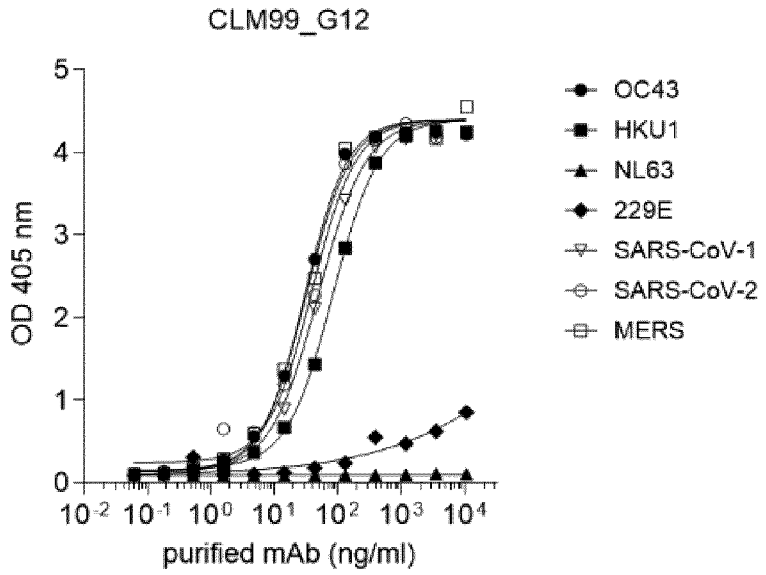


Figure 1 continued

F



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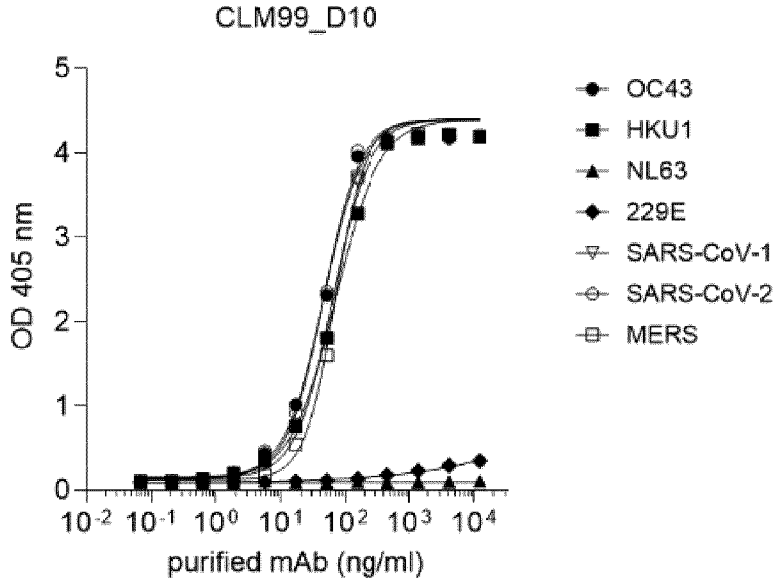


H

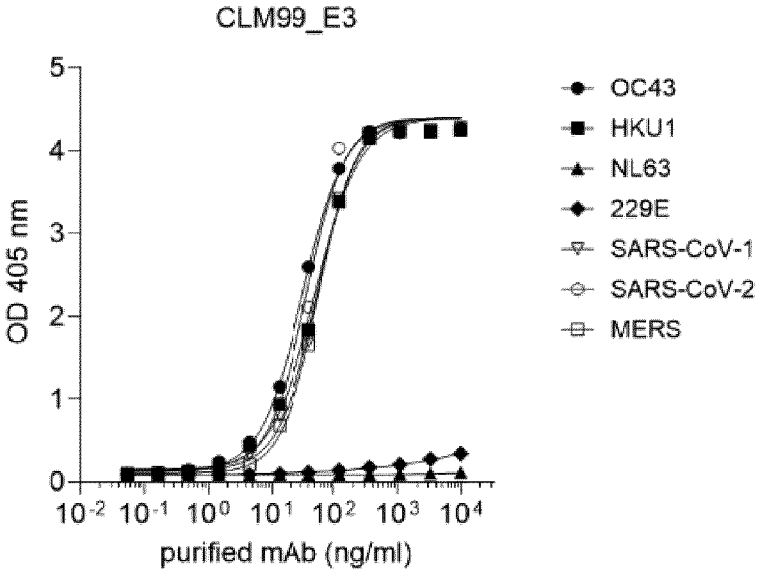
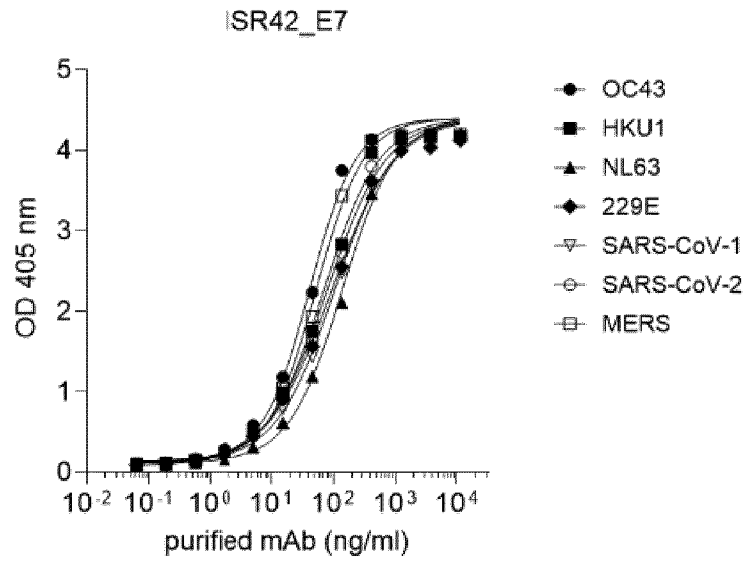


Figure 1 continued

I



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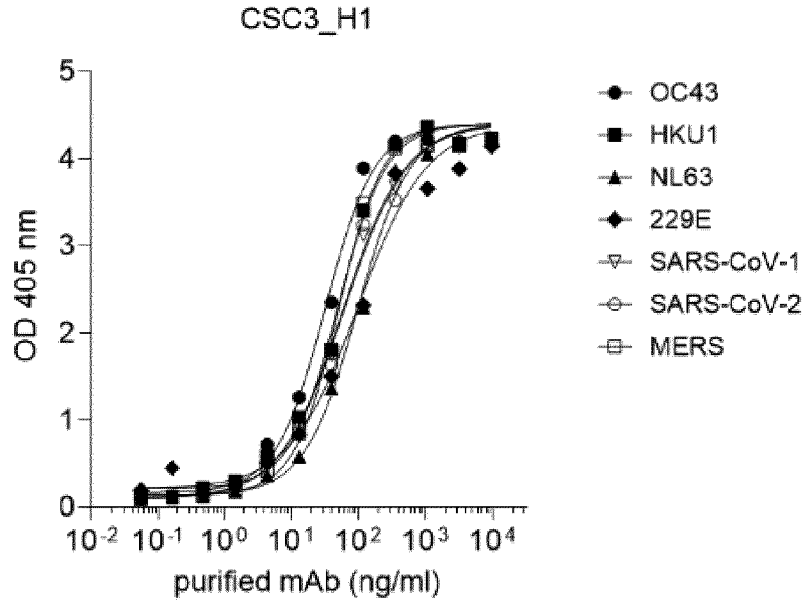

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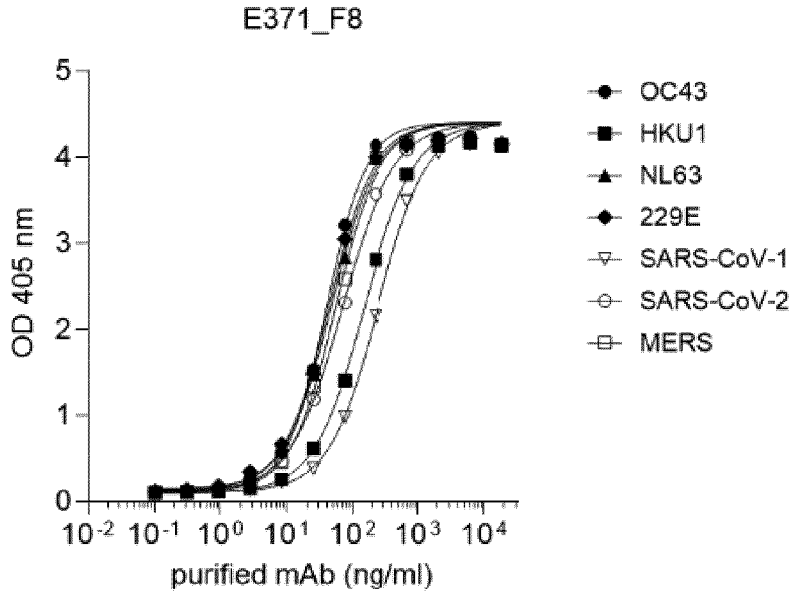
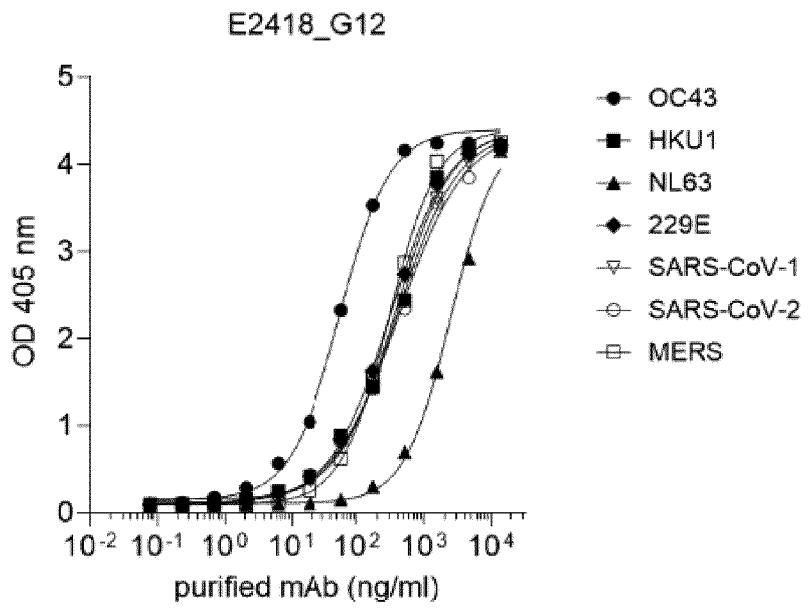


Figure 1 continued

L



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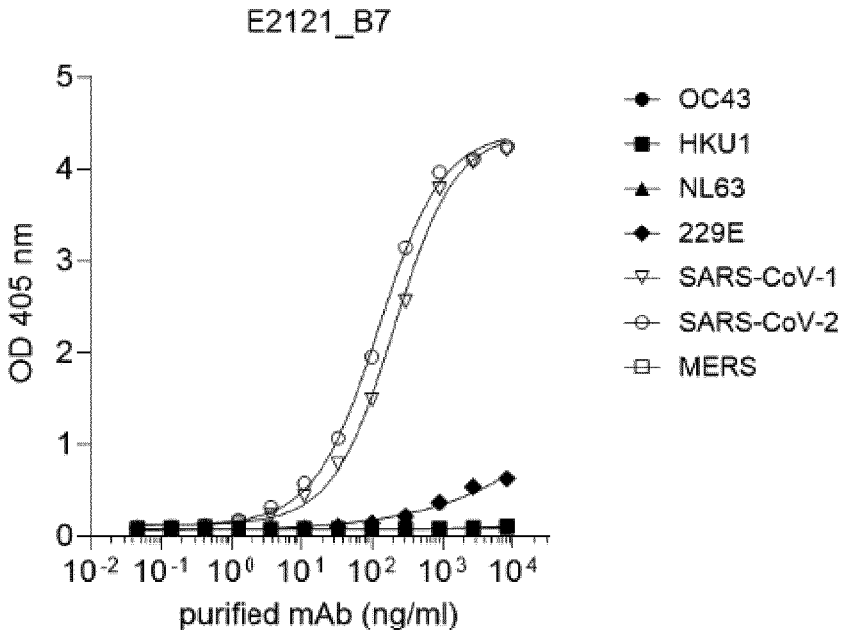
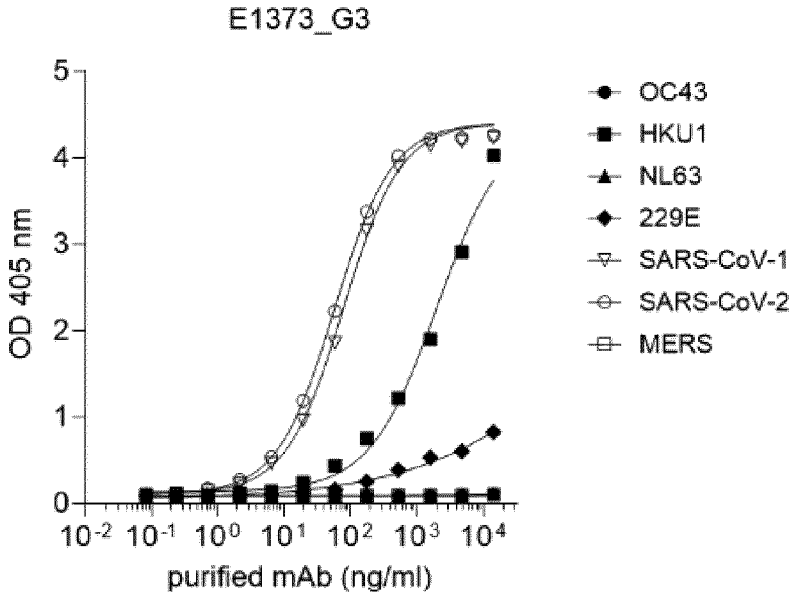


Figure 1 continued

N



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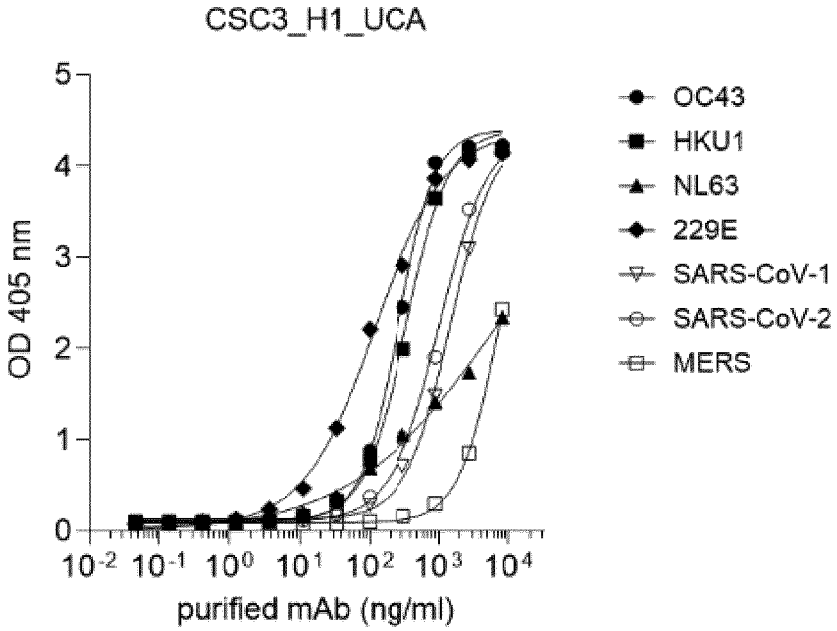
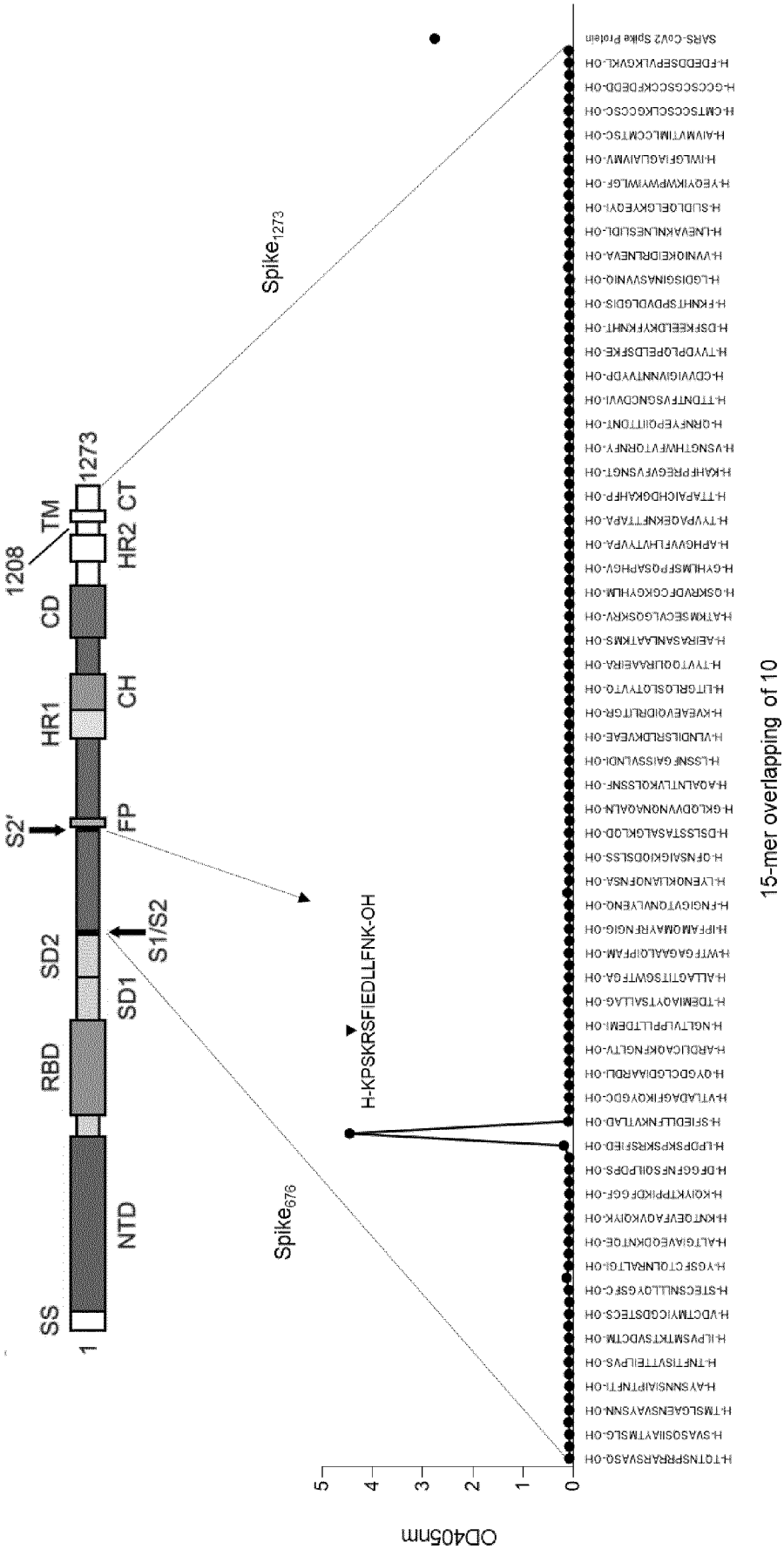


Figure 1 continued


SS
NTD
RBD
SD1
SD2
S1/S2
S2'
FP
HR1
CH
CD
HR2
CT
TM
1
1208
1273
Spike1273
Spike676
H-KPSKRSFIEDLLFNK-OH
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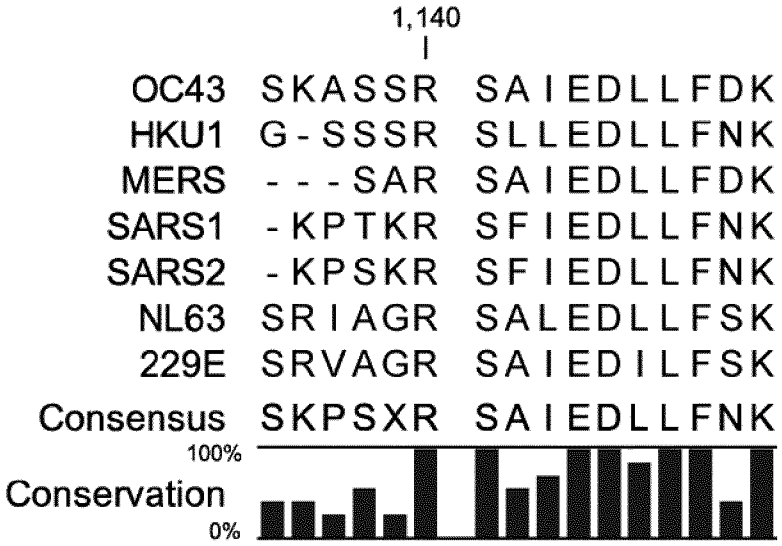
OD405nm
0
1
2
3
4
5

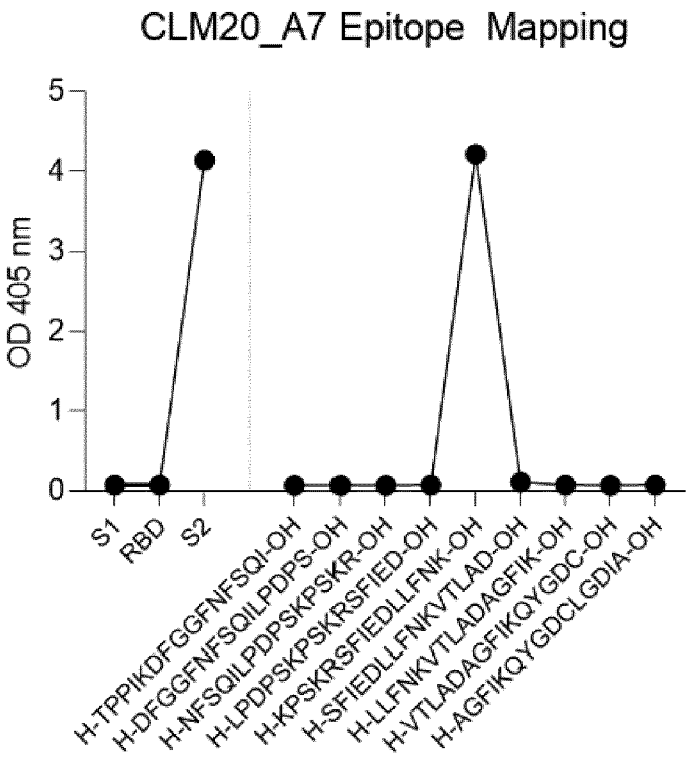
Figure 2




```
NL63            RIAGRSALEDLLFSK  15
229E            RVAGRSAIEDILFSK  15
HKU1            GSSSRSLLEDLLFNK  15
SARS-CoV2       KPSKRSFIEDLLFNK  15
SARS-CoV1       KPTKRSFIEDLLFNK  15
MERS            SRSARSAIEDLLFDK  15
OC43            KASSRSAIEDLLFDK  15
                  : ** :**:**.*
```

Figure 3

A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OD 405 nm
0
1
2
3
4
5
S1
RBD
S2
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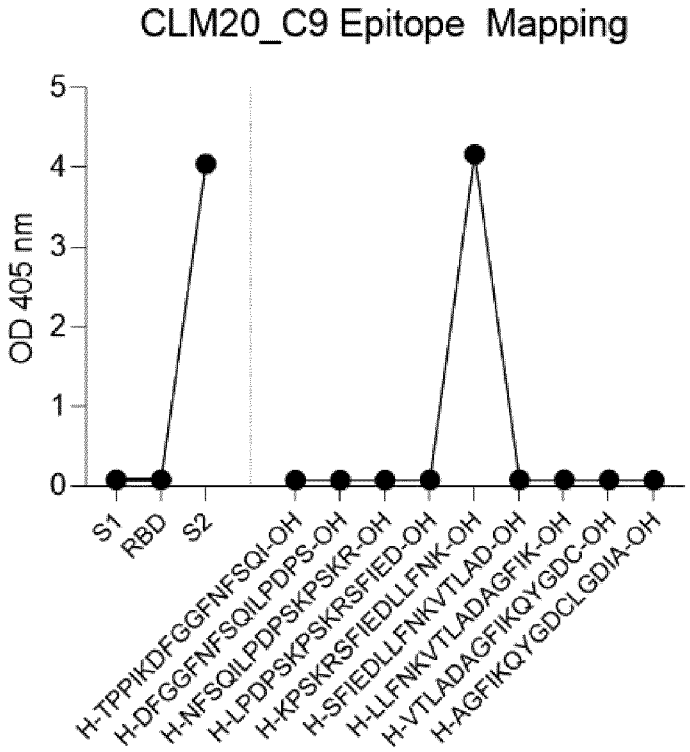
H-DFGGFNFSQILPDPS-OH
H-NFSQILPDPSKPSKR-OH
H-LPDPSKPSKRSFIED-OH
H-KPSKRSFIEDLLFNK-OH
H-SFIEDLLFNKVTLAD-OH
H-LLFNKVTLADAGFIK-OH
H-VTLADAGFIKQYGDC-OH
H-AGFIKQYGDCLGDIA-OH

B


CLM20_C9 Epitope Mapping
OD 405 nm
0
1
2
3
4
5
S1
RBD
S2
H-TPPIKDFGGFNFSQI-OH
H-DFGGFNFSQILPDPS-OH
H-NFSQILPDPSKPSKR-OH
H-LPDPSKPSKRSFIED-OH
H-KPSKRSFIEDLLFNK-OH
H-SFIEDLLFNKVTLAD-OH
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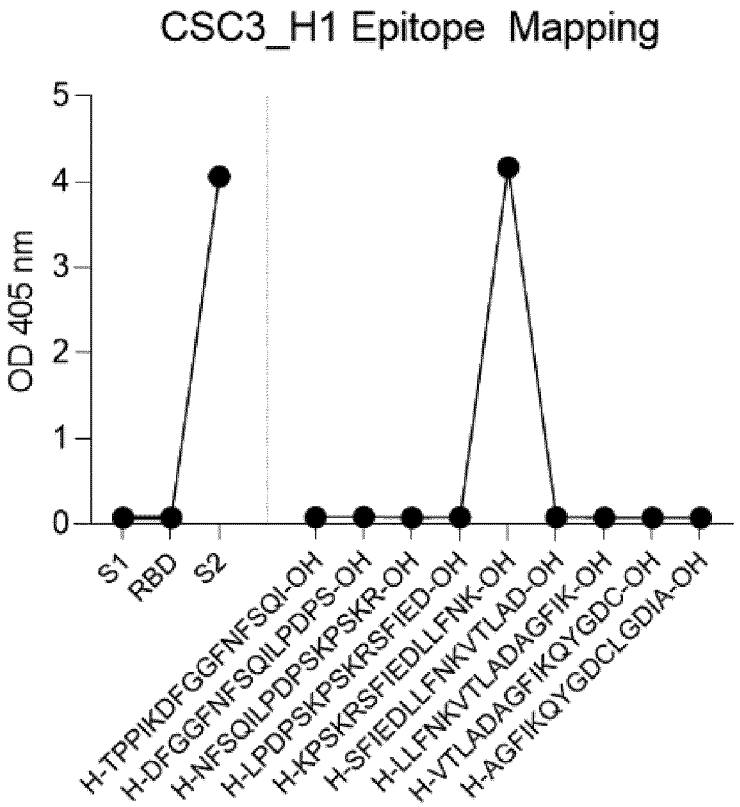
H-VTLADAGFIKQYGDC-OH
H-AGFIKQYGDCLGDIA-OH

Figure 4

C



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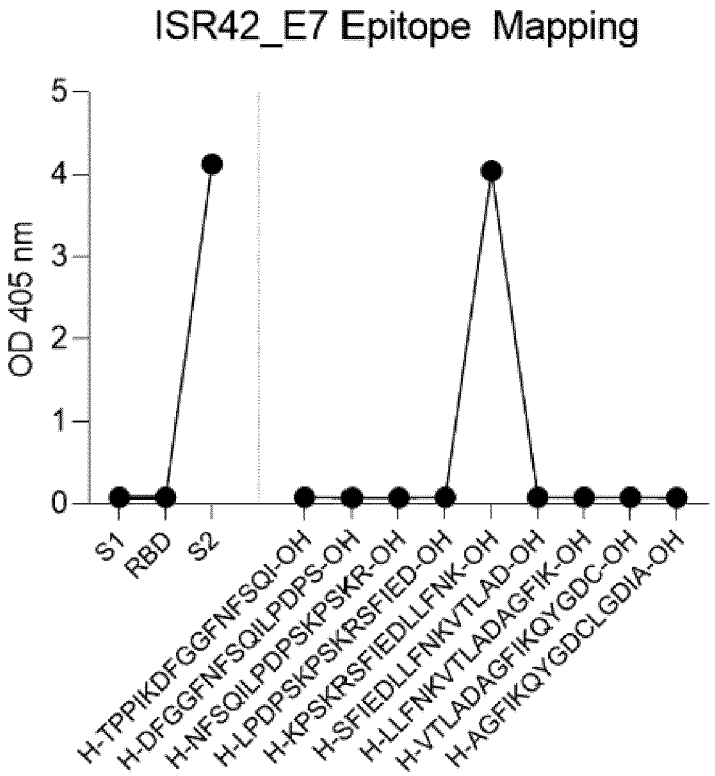
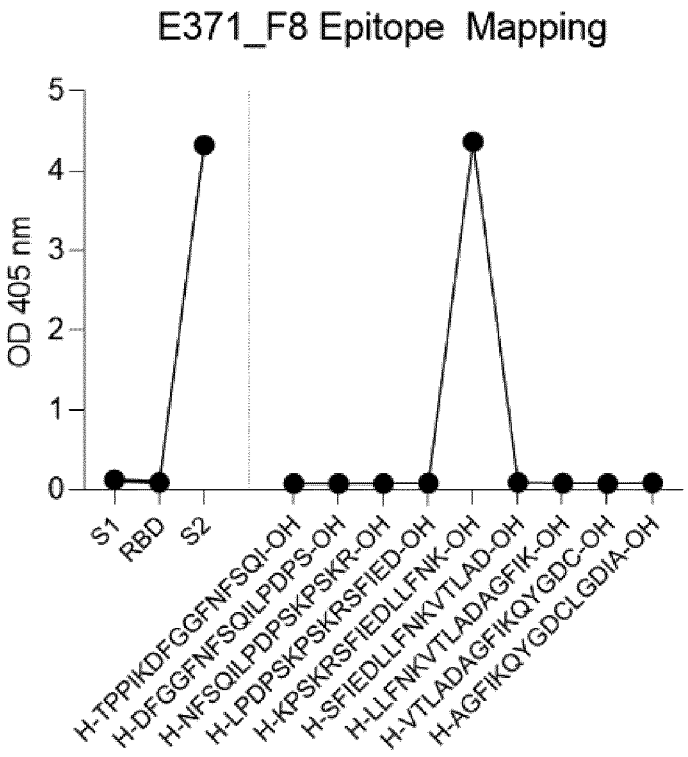


Figure 4 continued

E



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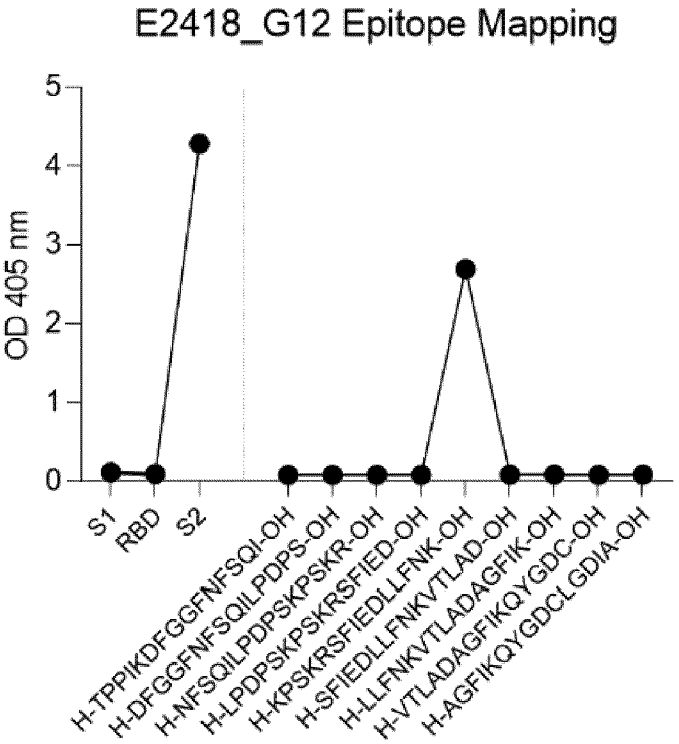
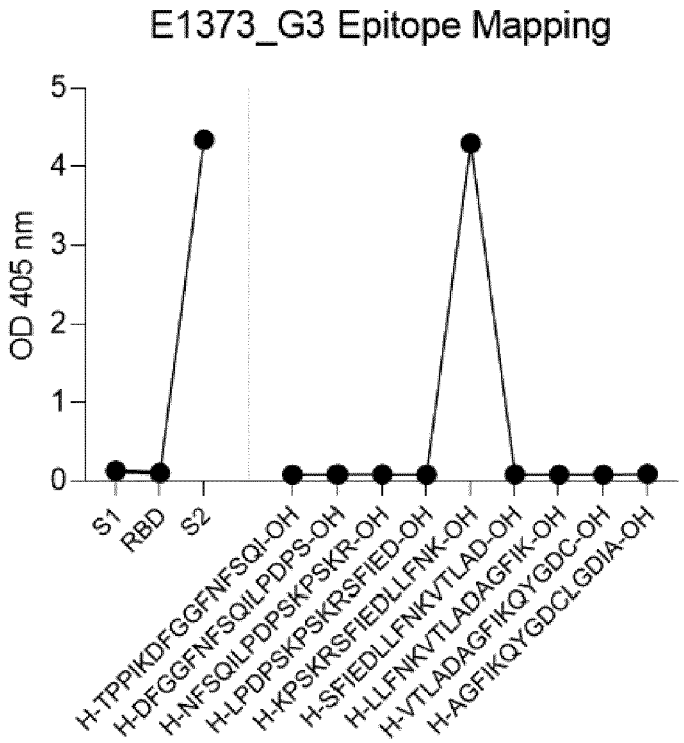


Figure 4 continued

G



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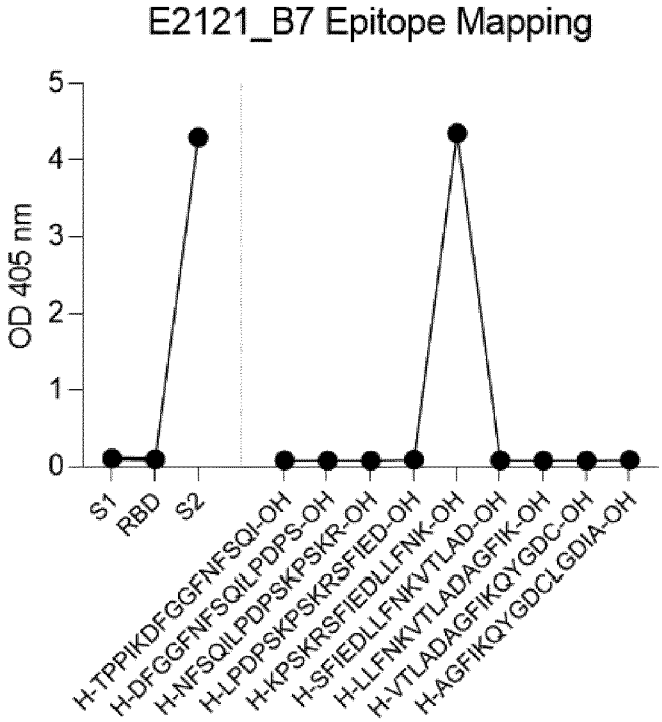
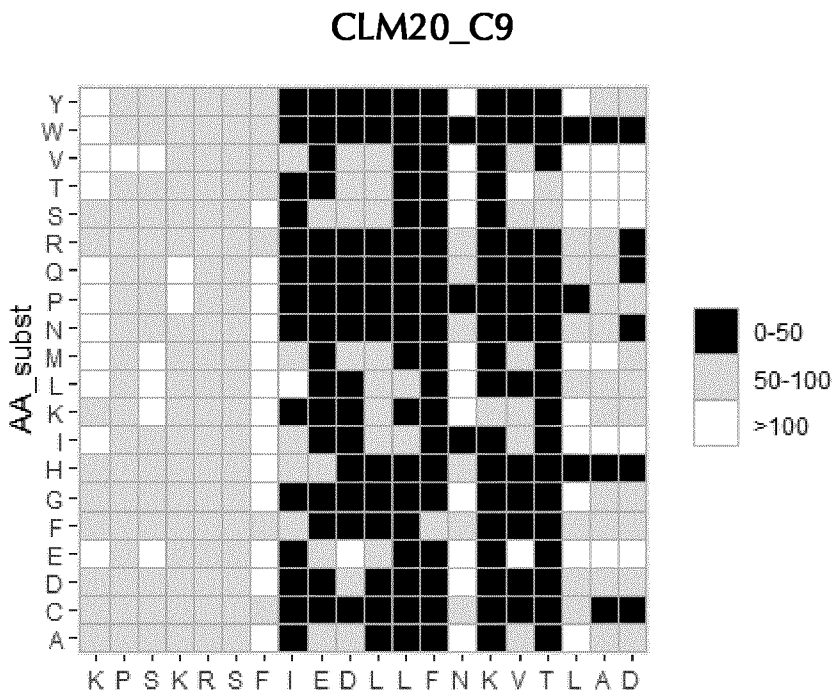


Figure 4 continued

A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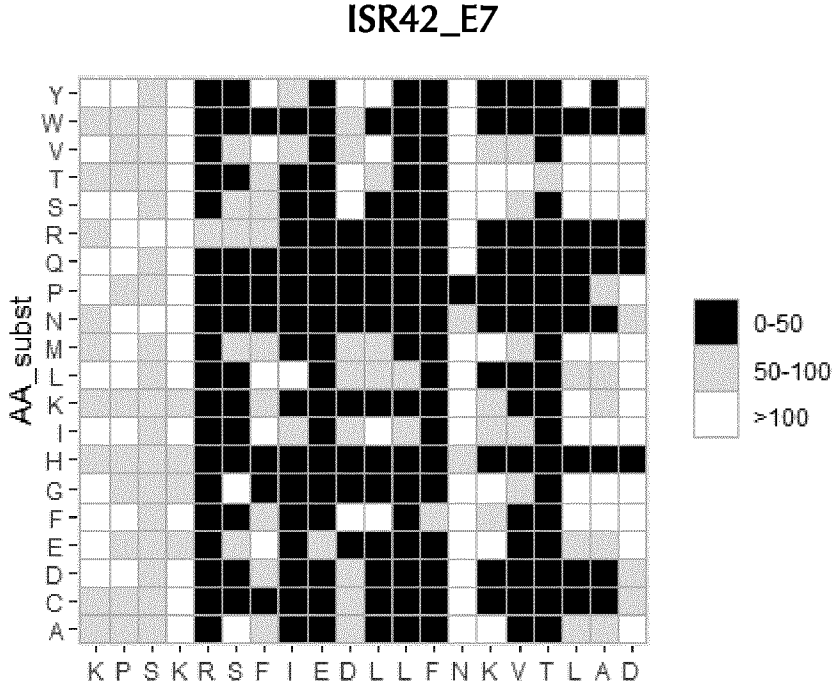
AA_subst
Y W V T S R Q P N M L K I H G F E D C A
K P S K R S F I E D L L F N K V T L A D
0-50
50-100
>100

B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AA_subst
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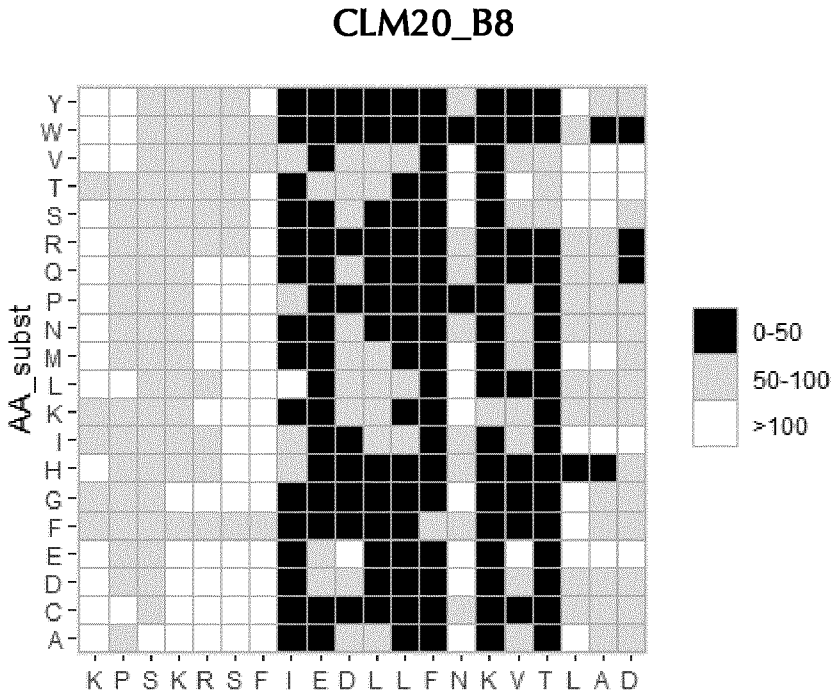
K P S K R S F I E D L L F N K V T L A D
0-50
50-100
>100

Figure 5

C



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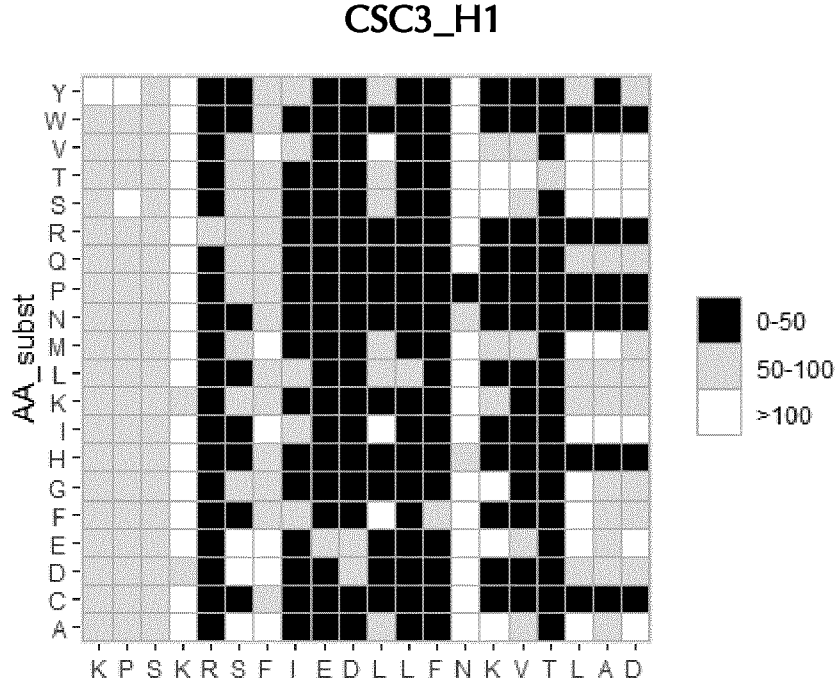

Figure 5 continued

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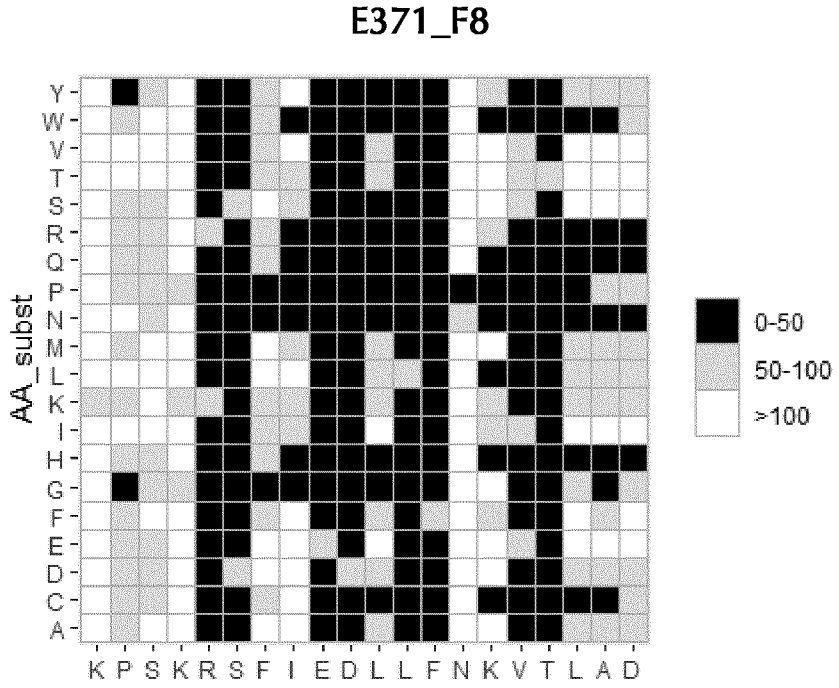

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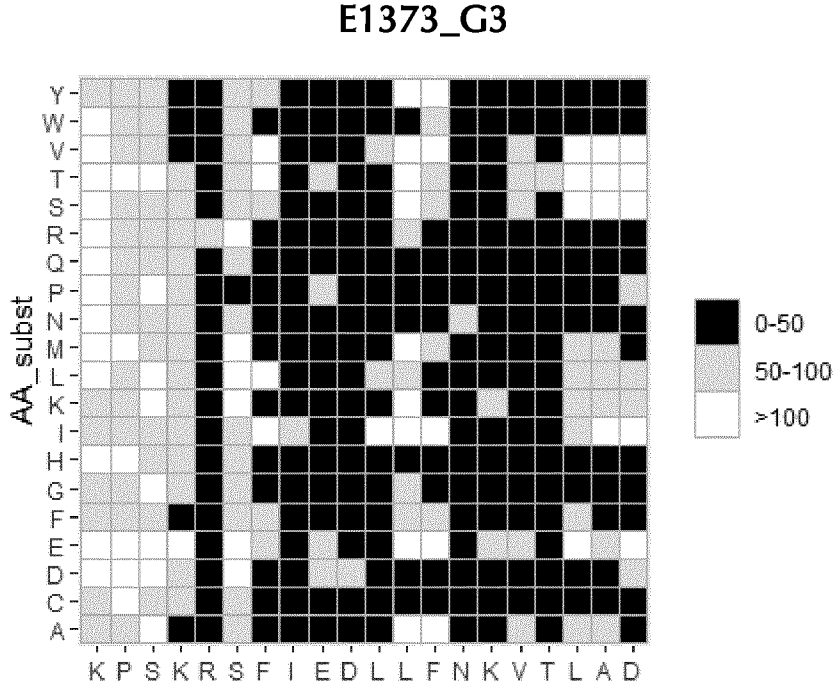

Figure 5 continued

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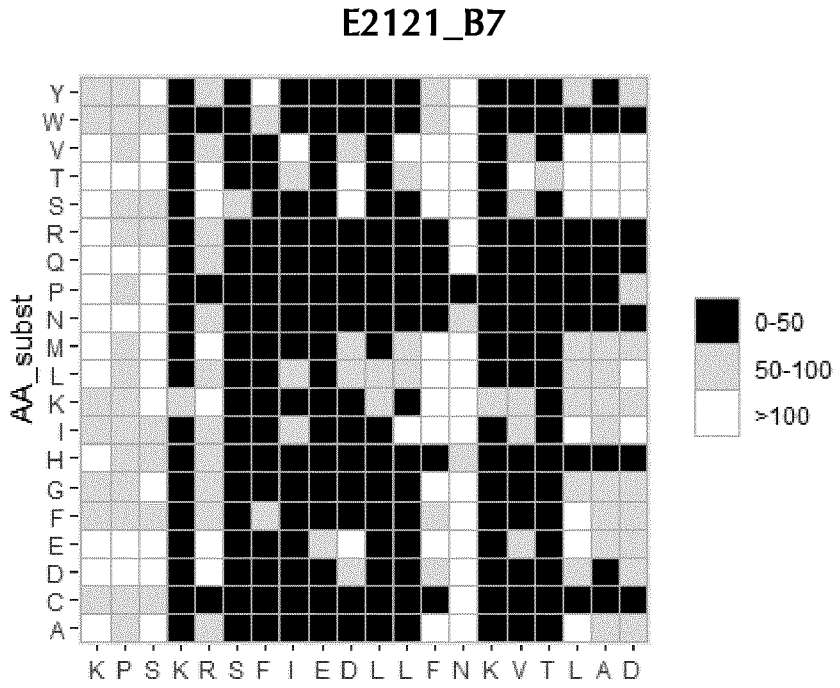
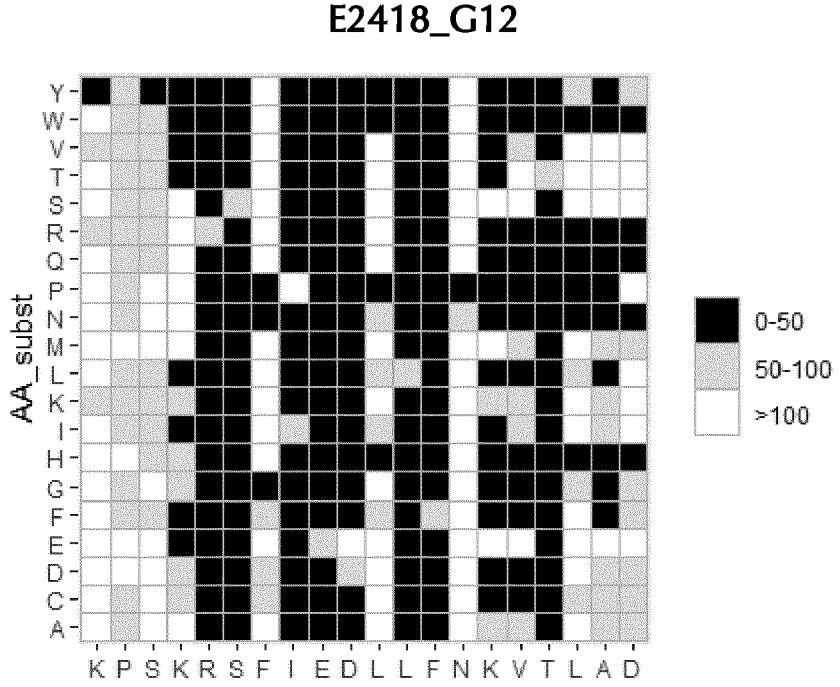


H



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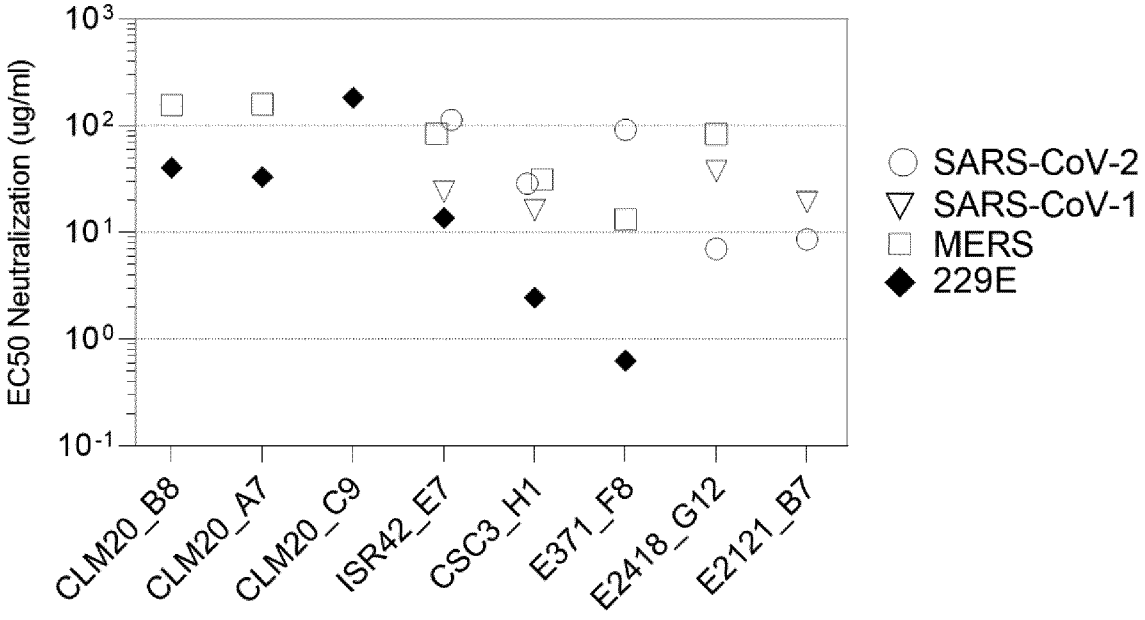
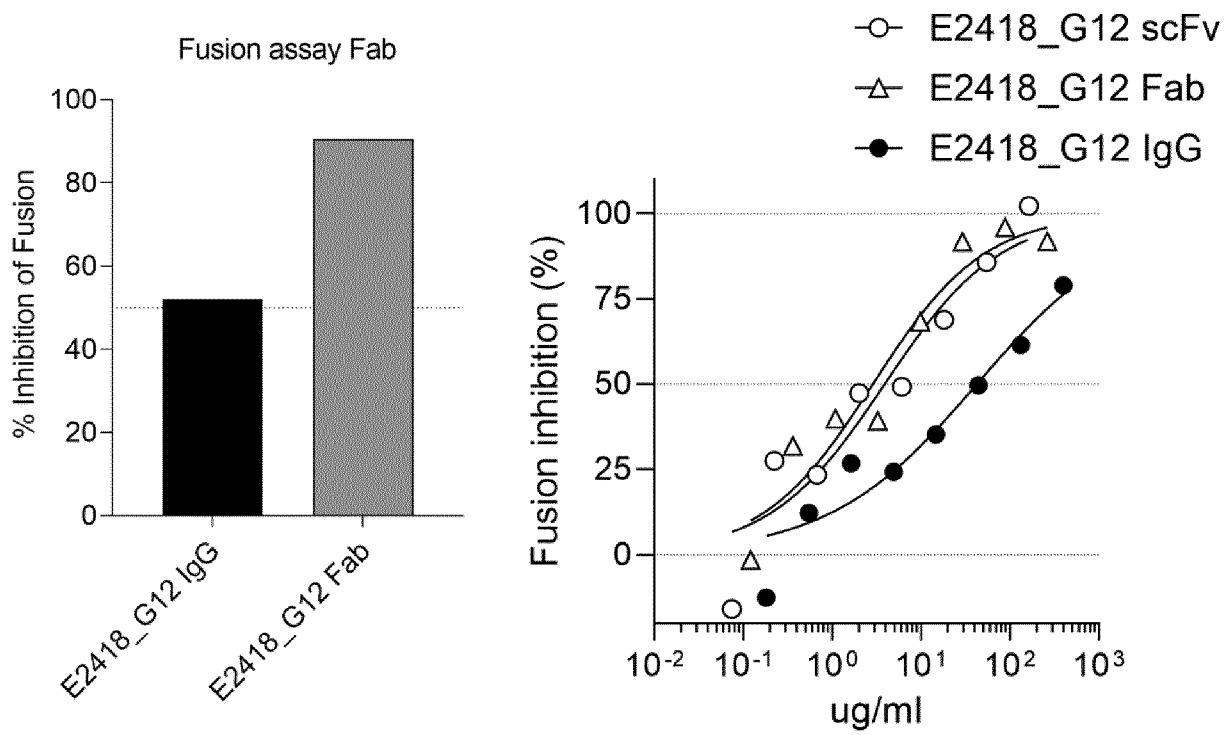

EC50 Neutralization (ug/ml)
10^3
10^2
10^1
10^0
10^-1
CLM20_B8
CLM20_A7
CLM20_C9
ISR42_E7
CSC3_H1
E371_F8
E2418_G12
E2121_B7
SARS-CoV-2
SARS-CoV-1
MERS
229E

Figure 6

A


Fusion assay Fab
% Inhibition of Fusion
100
80
60
40
20
0
E2418_G12 IgG
E2418_G12 Fab
E2418_G12 scFv
E2418_G12 Fab
E2418_G12 IgG
Fusion inhibition (%)
100
75
50
25
0
10-2 10-1 100 101 102 103
ug/ml

B

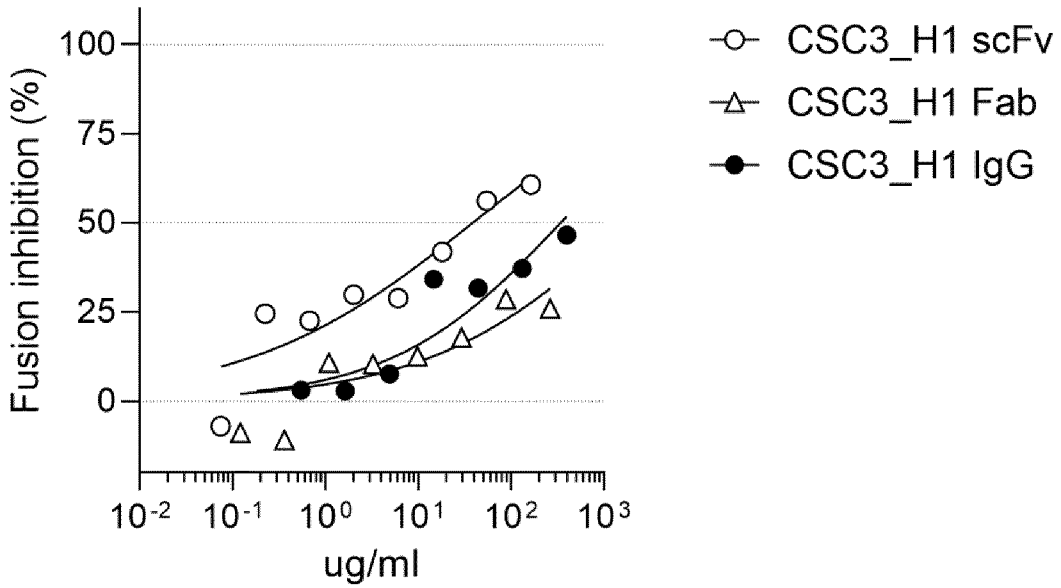
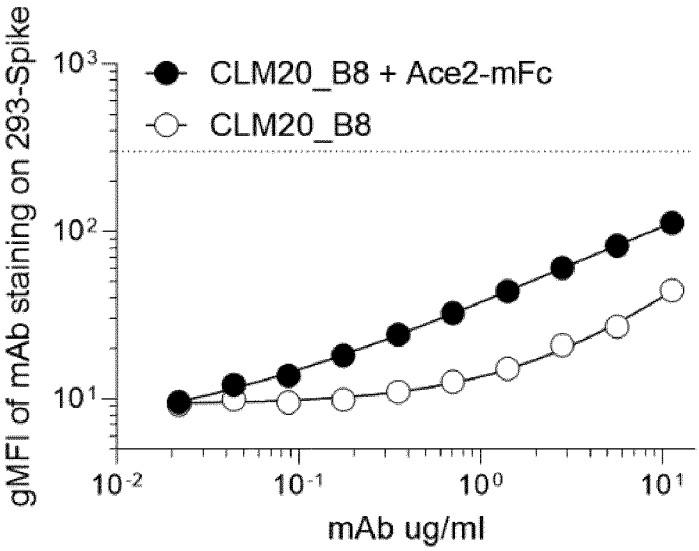
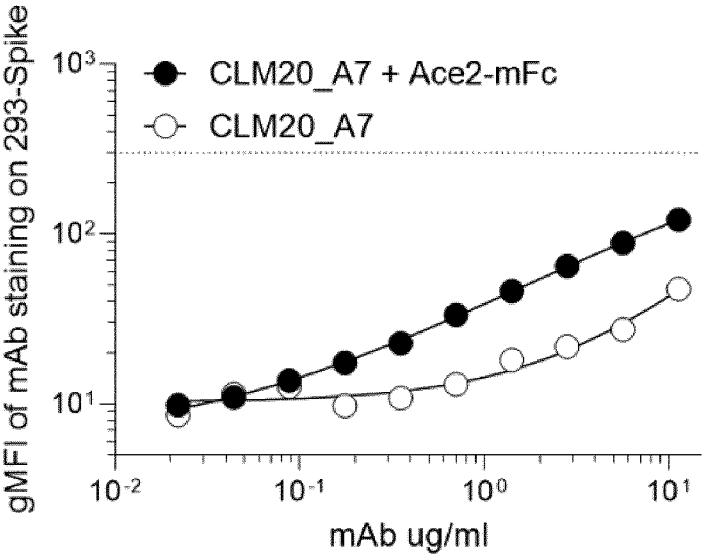

Fusion inhibition (%)
100
75
50
25
0
10-2 10-1 100 101 102 103
ug/ml
CSC3_H1 scFv
CSC3_H1 Fab
CSC3_H1 IgG

Figure 7

A


CLM20_B8 + Ace2-mFc
CLM20_B8
gMFI of mAb staining on 293-Spike
mAb ug/ml

B


CLM20_A7 + Ace2-mFc
CLM20_A7
gMFI of mAb staining on 293-Spike
mAb ug/ml

C

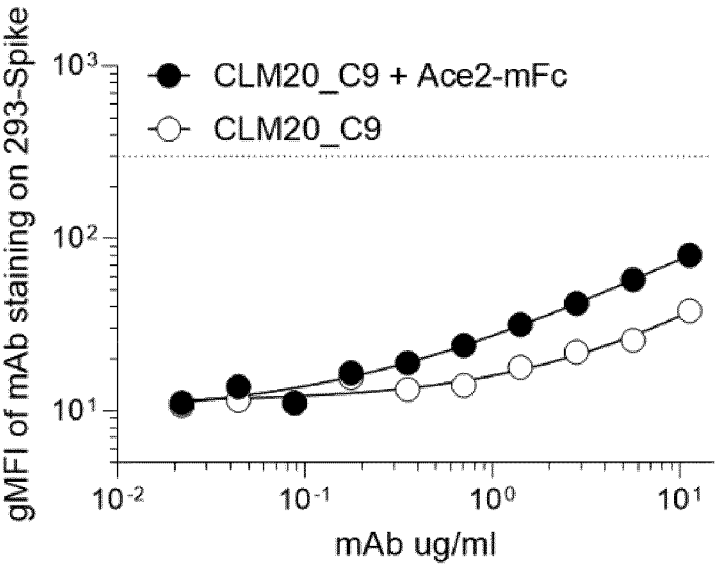
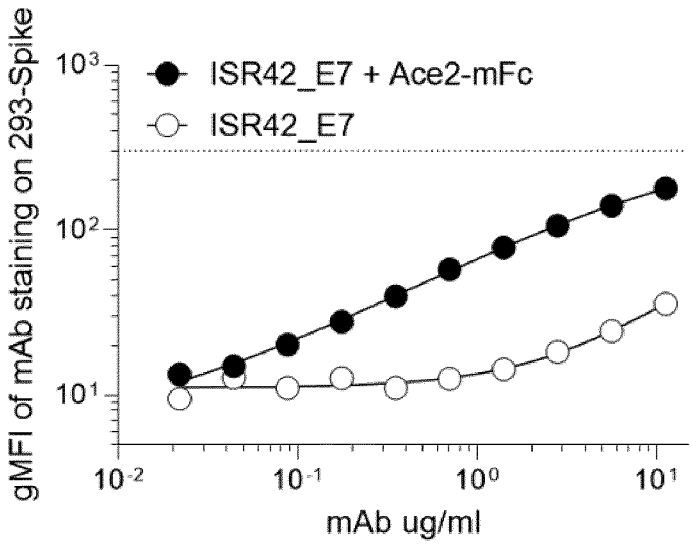
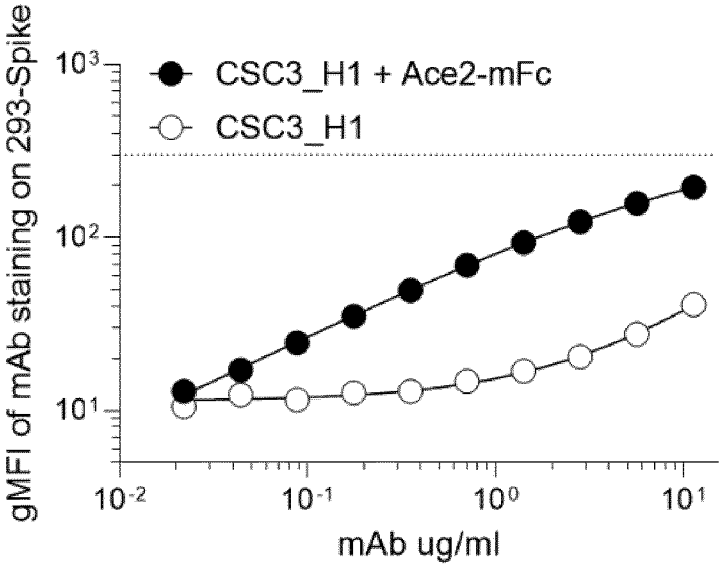

CLM20_C9 + Ace2-mFc
CLM20_C9
gMFI of mAb staining on 293-Spike
mAb ug/ml

Figure 8

D



E



F

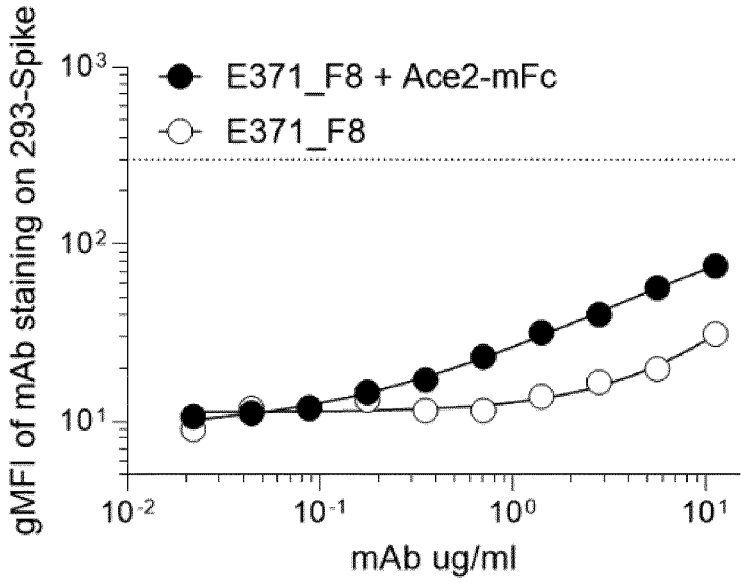
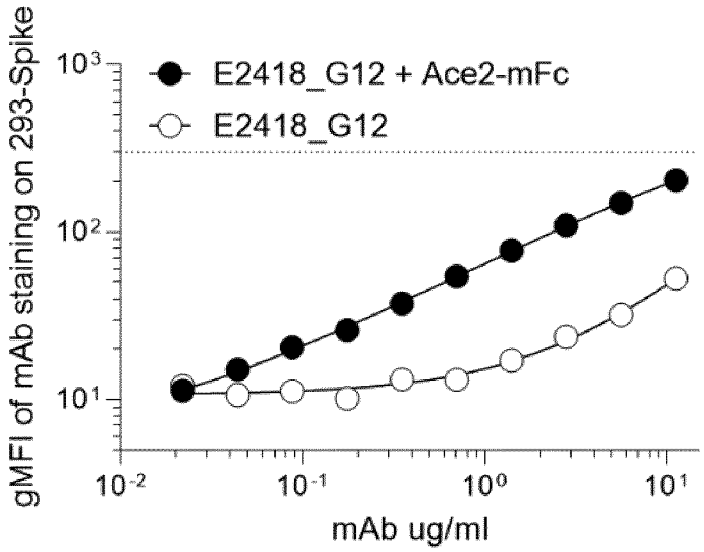
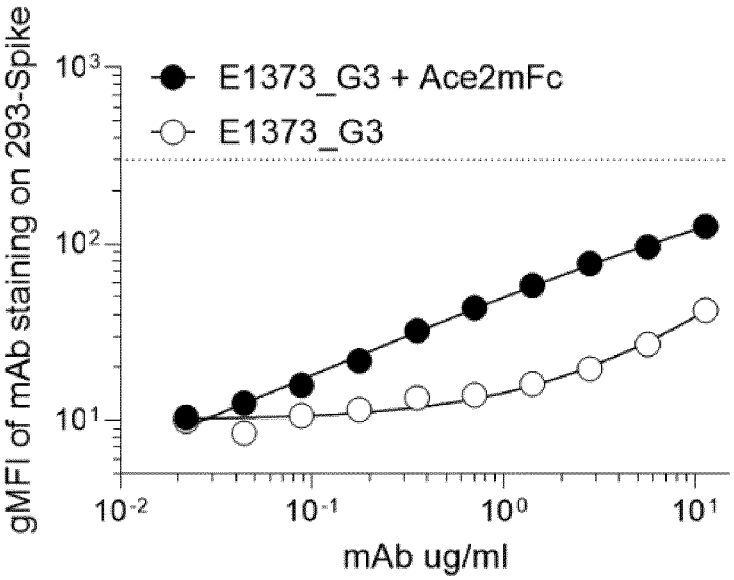


Figure 8 continued

G



H



I

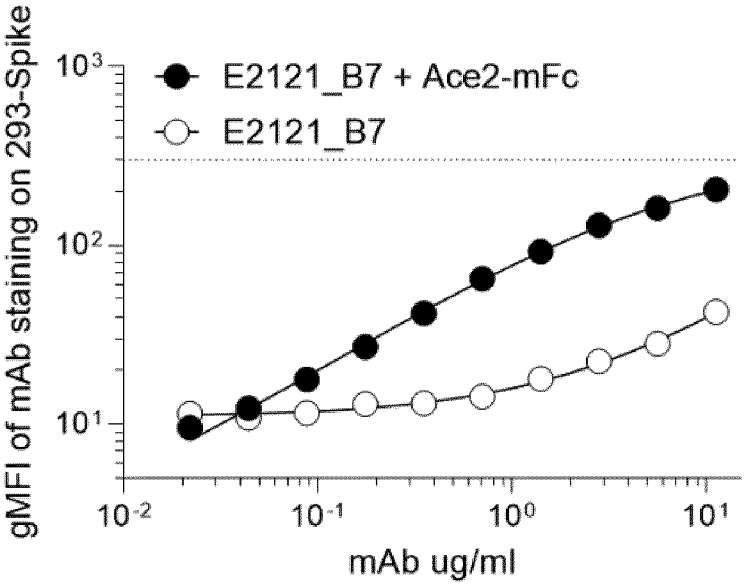


Figure 8 continued

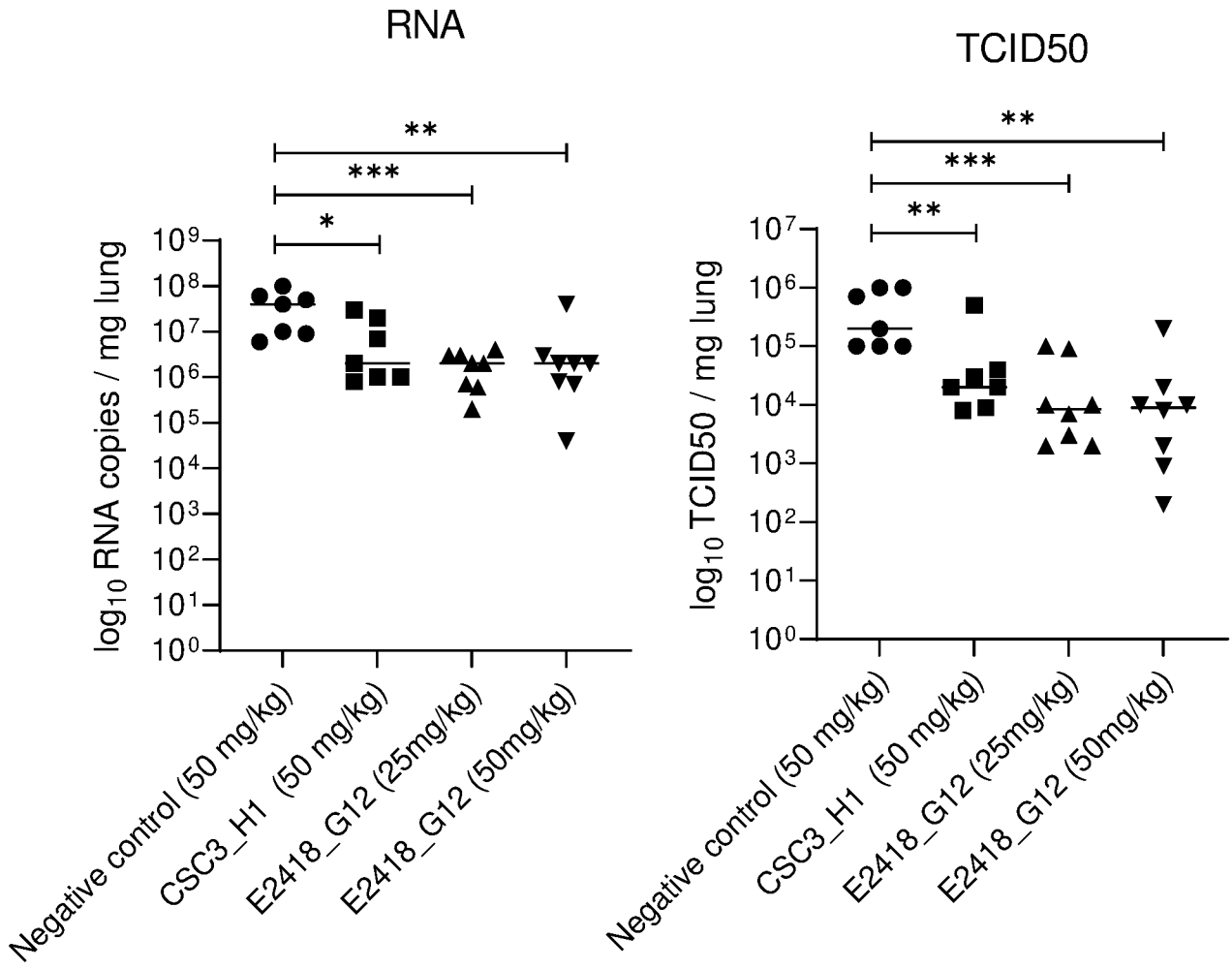

RNA
TCID50
log10 RNA copies / mg lung
log10 TCID50 / mg lung
*
**
***
Negative control (50 mg/kg)
CSC3_H1 (50 mg/kg)
E2418_G12 (25mg/kg)
E2418_G12 (50mg/kg)

Figure 9

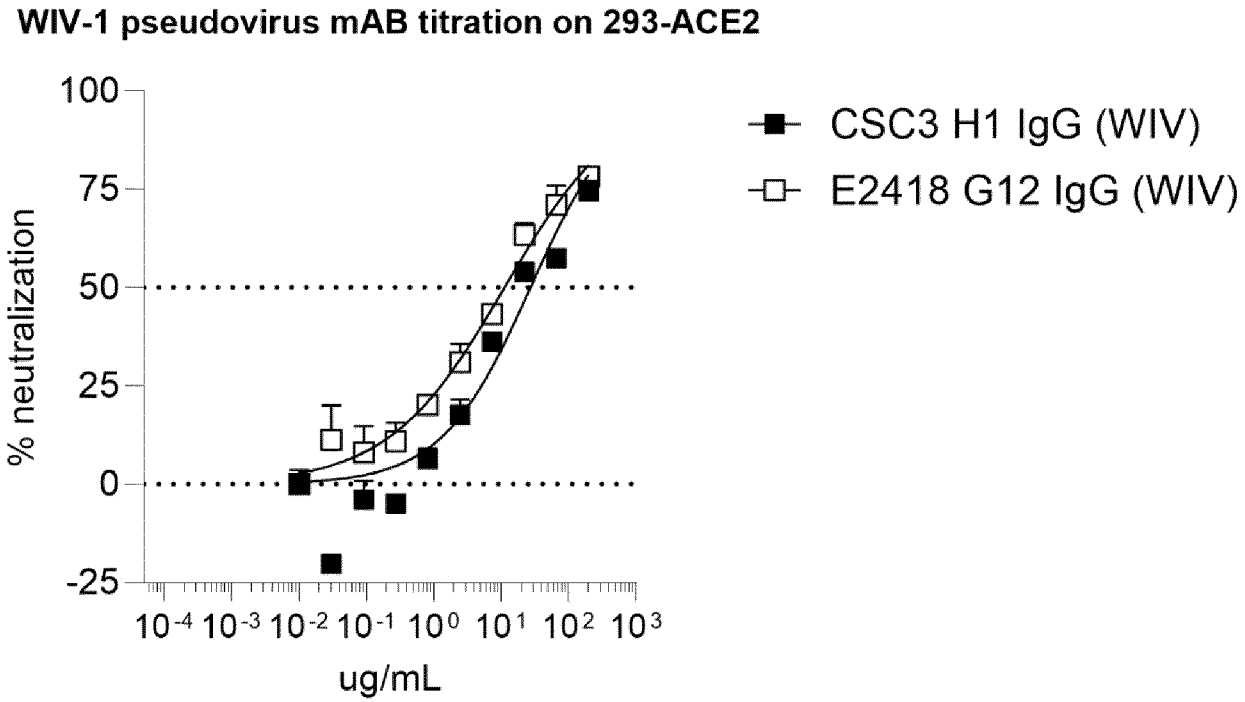
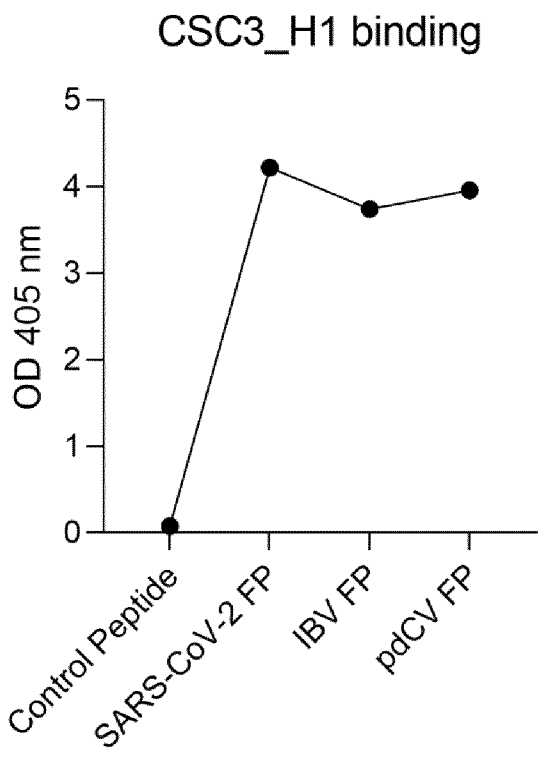

WIV-1 pseudovirus mAB titration on 293-ACE2
% neutralization
100
75
50
25
0
-25
10-4 10-3 10-2 10-1 100 101 102 103
ug/mL
CSC3 H1 IgG (WIV)
E2418 G12 IgG (WIV)

Figure 10

A


CSC3_H1 binding
OD 405 nm
5
4
3
2
1
0
Control Peptide
SARS-CoV-2 FP
IBV FP
pdCV FP

B

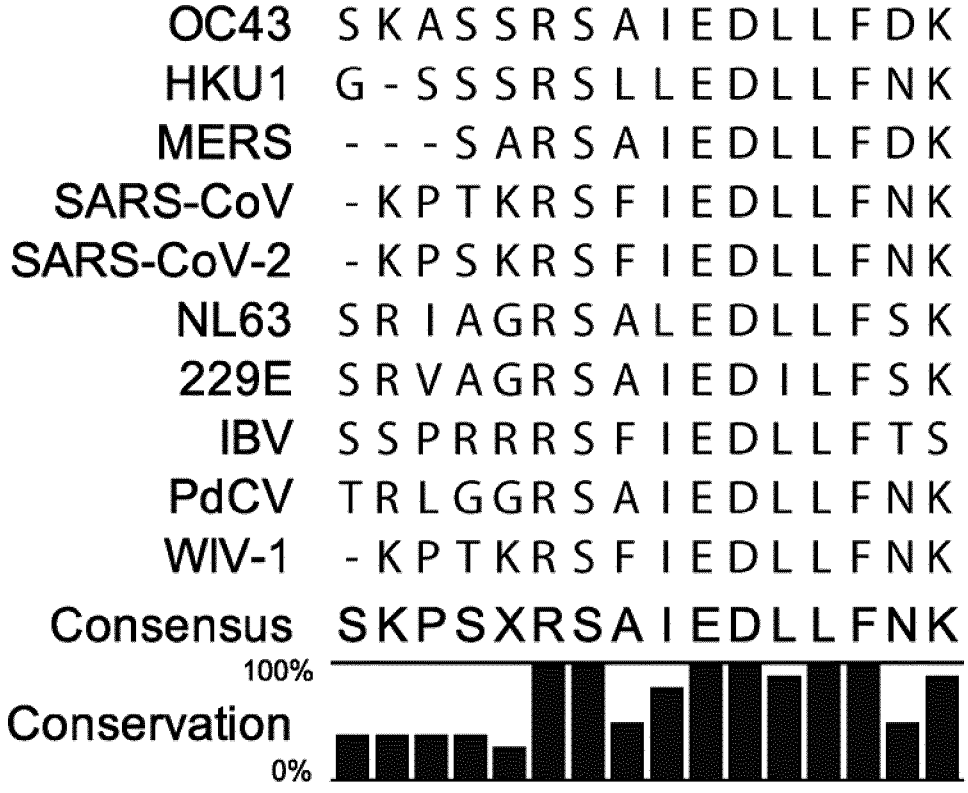

OC43 S K A S S R S A I E D L L F D K
HKU1 G - S S S R S L L E D L L F N K
MERS - - - S A R S A I E D L L F D K
SARS-CoV - K P T K R S F I E D L L F N K
SARS-CoV-2 - K P S K R S F I E D L L F N K
NL63 S R I A G R S A L E D L L F S K
229E S R V A G R S A I E D I L F S K
IBV S S P R R R S F I E D L L F T S
PdCV T R L G G R S A I E D L L F N K
WIV-1 - K P T K R S F I E D L L F N K
Consensus S K P S X R S A I E D L L F N K
100%
Conservation
0%

Figure 11