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(54) Title: SARS-CoV-2 NEUTRALIZING ANTIBODIES

(57) Abstract: The present invention relates to antibodies or antigen-binding fragments thereof against SARS- related coronavirus, pharmaceutical compositions comprising such antibodies or antigen-binding fragments thereof, kits comprising such antibodies or antigen-binding fragments thereof, and the antibodies or antigen-binding fragments thereof, the pharmaceutical compositions and the kits for use as a medicament, and in the treatment or prevention of a disease caused by SARS-related coronavirus. The present invention further relates to methods of treating, preventing or reducing the severity of an infection with a SARS-related coronavirus, and to nucleic acids encoding such antibodies or antigen-binding fragments thereof, expression vectors comprising such nucleic acids, host cells comprising such nucleic acids or expression vectors, and methods for the production of such antibodies or antigen-binding fragments thereof.

WO 2024/175802 A2

SARS-CoV-2 NEUTRALIZING ANTIBODIES

Technical Field

The present invention relates to antibodies or antigen-binding fragments thereof against SARS-related coronavirus, pharmaceutical compositions comprising such antibodies or antigen-binding fragments thereof, kits comprising such antibodies or antigen-binding fragments thereof, and the antibodies or antigen-binding fragments thereof, the pharmaceutical compositions and the kits for use as a medicament, and in the treatment or prevention of a disease caused by SARS-related coronavirus. The present invention further relates to methods of treating, preventing or reducing the severity of an infection with a SARS-related coronavirus, and to nucleic acids encoding such antibodies or antigen-binding fragments thereof, expression vectors comprising such nucleic acids, host cells comprising such nucleic acids or expression vectors, and methods for the production of such antibodies or antigen-binding fragments thereof.

Technological Background

In the last 3 years, the coronavirus disease-19 (COVID-19) pandemic has led to the loss of over 6.6 million lives worldwide. Although a majority of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections are mild, hospitalizations and death can occur in all age groups and older individuals with co-morbidities are at particular risk. The rapid and successful development of effective SARS-CoV-2 vaccines has been a critical breakthrough. Vaccines can protect from severe disease and death as well as mitigate the spread of infection.

However, unvaccinated individuals and vulnerable groups such as immune-deficient patients who cannot mount adequate immune responses still remain susceptible to infection and severe complications. Moreover, the current rise in SARS-CoV-2 variants with antigenic escape mutations can reduce the efficacy of approved therapeutics as well as vaccines and result in increased incidence of breakthrough infections. This warrants the need for interventions that can effectively treat SARS-CoV-2 infection by preventing severe disease and reducing morbidity.

Neutralizing antibodies (NAbs) are an important part of the humoral immune system for preventing and cleaning viral infections. They can block viral entry into cells and mediate clearance of viral particles through Fc-mediated effector functions. Advanced single B-cell cloning strategies have helped decipher the B-cell response to SARS-CoV-2 and resulted in the isolation of several potent monoclonal antibodies (mAbs) (Andreano, E. et al. (2021). Cell 184, 1821-1835 e1816; Ju, B. et al. (2020). Nature 584, 115-119; Kreer, C. et al. (2020). Cell 182, 843-854 e812; Liu, L. et al. (2020). Nature 584, 450-456; Robbiani, D.F. et al. (2020). Nature 584, 437-442; Rogers, T.F. et al. (2020). Science 369, 956-963; Zost, S.J. et al. (2020). Nat Med 26, 1422-1427.).

These SARS-CoV-2 antibodies are directed against the spike (S) protein expressed on the virus surface, which facilitates viral entry into human cells by binding to the human ACE-2 receptor. On the spike protein, a large fraction of the NAb response is directed at the receptor binding domain (RBD) or the N-terminal domain (NTD) of the SARS-CoV-2 spike S1 domain. The S2 domain of the spike protein is more conserved than the S1 amongst β-coronaviruses (β -CoVs), however, mAbs targeting the S2 domain are rare and less potent (Pinto, D. et al. (2021). Science 373, 1109-1116; Sauer, M.M. et al. (2021). Nat Struct Mol Biol 28, 478-486.).

The highly potent neutralizing capacity of RBD-directed antibodies has led to the clinical development of mAbs for treating and preventing COVID-19. Passive immunization with mAbs can prevent infection in exposed individuals as well as treat COVID-19 and prevent progression to severe disease. Several of these mAbs have been authorized for use by FDA and EMA approval for treatment of COVID-19 or are currently being investigated in phase-III clinical trials.

Despite the success in antibody-mediated treatment of SARS-CoV-2 infection, the recent emergence of SARS-CoV-2 variants with antigenic escape mutations in the spike protein has led to reduced effectiveness or rendered authorized antibodies ineffective due to loss of neutralizing activity. As a result, as of October 2022, for effective treatment against most of the SARS-CoV-2 variants, only the authorized antibody bebtelovimab has been reported to retain its efficacy against all SARS-CoV-2 variants (Cox, M., Peacock, T.P., Harvey, W.T. *et al. SARS-CoV-2 variant evasion of monoclonal antibodies based on in vitro studies*. Nat Rev Microbiol 21, 112–124 (2023)).

However, against the recently emerging SARS-CoV-2 variants such as BQ.1.1, XBB.1, and most recently XBB.1.5, bebtelovimab also lacked the necessary neutralizing capacity, resulting in the revocation of its authorization for emergency use in the United States in November 2022.

One broadly cross-reactive antibody reported to be able to neutralize alpha, beta, delta, epsilon, iota, and omicron variants of the SARS CoV-2 virus has been disclosed which was designated as SP1-77 (Luo, S. *et al. An antibody from single human V_H-rearranging mouse neutralizes all SARS-CoV-2 variants through BA.5 by inhibiting membrane fusion.* Sci. Immunol. 7, eadd5446 (2022)). At the time of publication, SP1-77 was thought to neutralize all known omicron variants and that none of the known mutations would negatively affect binding of the antibody to the variants.

In the meantime, however, new currently circulating variants of the SARS-CoV-2 virus of concern have appeared (e.g. BQ.1.1, XBB.1.5, BF.7, and others) which may not be neutralized by SP1-77 or other antibodies of the prior art.

Therefore, generation and provision of antibodies with broader and superior neutralization characteristics against circulating variants of concern and emerging variants of SARS-CoV-2 are needed.

Therefore, it is essential to develop next-generation mAbs that retain potency and effectiveness against circulating or emerging SARS-CoV-2 variants. There remains a demand for human antibodies directed against SARS-related coronavirus which do not show autoreactivity and have superior neutralization potency against circulating SARS-CoV-2 variants of concern as well as emerging escape variants in comparison to antibodies currently made available to the public.

Thus, it is an object of the present invention to provide novel monoclonal antibodies against SARS-related coronavirus which do not demonstrate autoreactivity and have excellent neutralization potency against circulating SARS-CoV-2 variants of concern as well as emerging escape variants.

It is a further object of the present invention to provide novel monoclonal antibodies against SARS-related coronavirus which can be used in treatment or prevention of a disease caused by SARS-related coronavirus in human or animal subjects as well as in prevention of infection of a human or animal subject with SARS-related coronavirus.

Summary of the invention

These objects have been solved by the present invention as specified hereinafter.

According to a first aspect of the present invention, an antibody or antigen-binding fragment thereof is provided directed against SARS-related coronavirus, wherein the antibody or antigen-binding

fragment thereof comprises the combination of the heavy chain CDR1 to CDR3 and the light chain CDR1 to CDR3 amino acid sequence of one antibody selected from the group comprising TV1t4p2_A5 (having a CDR-H1 amino acid sequence of SEQ ID No. 27, a CDR-H2 amino acid sequence of SEQ ID No. 28, a CDR-H3 amino acid sequence of SEQ ID No. 29, a CDR-L1 amino acid sequence of SEQ ID No. 30, a CDR-L2 amino acid sequence of SEQ ID No. 31, a CDR-L3 amino acid sequence of SEQ ID No. 32), TV1t2p6_D3 (having a CDR-H1 amino acid sequence of SEQ ID No. 33, a CDR-H2 amino acid sequence of SEQ ID No. 34 a CDR-H3 amino acid sequence of SEQ ID No. 35 a CDR-L1 amino acid sequence of SEQ ID No. 36 a CDR-L2 amino acid sequence of SEQ ID No. 37, a CDR-L3 amino acid sequence of SEQ ID No. 38), TV1t4p3_E8 (having a CDR-H1 amino acid sequence of SEQ ID No. 21, a CDR-H2 amino acid sequence of SEQ ID No. 22, a CDR-H3 amino acid sequence of SEQ ID No. 23, a CDR-L1 amino acid sequence of SEQ ID No. 24, a CDR-L2 amino acid sequence of SEQ ID No. 25, a CDR-L3 amino acid sequence of SEQ ID No. 26), and TV1t3p4_E1 (having a CDR-H1 amino acid sequence of SEQ ID No. 39, a CDR-H2 amino acid sequence of SEQ ID No. 40, a CDR-H3 amino acid sequence of SEQ ID No. 41, a CDR-L1 amino acid sequence of SEQ ID No. 42, a CDR-L2 amino acid sequence of SEQ ID No. 43, a CDR-L3 amino acid sequence of SEQ ID No. 44).

In one embodiment of the first aspect of the invention, the antibody or antigen-binding fragment thereof comprises the combination of the heavy chain variable region amino acid sequence and of the light chain variable region amino acid sequence of one antibody selected from the group comprising TV1t4p2_A5 (having the heavy chain variable region amino acid sequence of SEQ ID No. 3 and the light chain variable region amino acid sequence of SEQ ID No. 4), TV1t2p6_D3 (having the heavy chain variable region amino acid sequence of SEQ ID No. 5 and the light chain variable region amino acid sequence of SEQ ID No. 6), TV1t4p3_E8 (having the heavy chain variable region amino acid sequence of SEQ ID No. 1 and the light chain variable region amino acid sequence of SEQ ID No. 2), and TV1t3p4_E1 (having the heavy chain variable region amino acid sequence of SEQ ID No. 7 and the light chain variable region amino acid sequence of SEQ ID No. 8).

In another embodiment of the first aspect of the invention, the amino acid sequences comprised are of one antibody selected from the group comprising TV1t4p2_A5, TV1t2p6_D3, and TV1t4p3_E8, preferably of one antibody from the group comprising TV1t4p2_A5 and TV1t2p6_D3, more preferably of antibody TV1t4p2_A5.

According to an embodiment of the first aspect of the invention, the SARS-related coronavirus strain is severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

In another embodiment of the first aspect of the invention, the amino acid sequences of the CDRs or of the variable regions comprised in the antibody or antigen-binding fragment thereof are from an antibody which is able to neutralize each of the SARS-CoV-2 lineages Wu01, Alpha, Beta, Delta, BA.1, BA.2, BA.2.12.1, BA.4/5, BA.2.75, BA.2.75.2, BQ.1.1, BA.4.6, XBB.1, XBB.1.5, and BF.7 in a pseudovirus neutralization assay as described herein with an 50% inhibitory concentration (IC_{50}) of at most 0.07 µg/ml, preferably at most 0.06 µg/ml, more preferably at most 0.05 µg/ml, even more preferably at most 0.04 µg/ml, even more preferably at most 0.03 µg/ml, particularly preferably at most 0.025 µg/ml.

According to a second aspect of the present invention, a pharmaceutical composition comprising an antibody or antigen-binding fragment thereof according to the first aspect of the invention and at least one pharmaceutically acceptable excipient is provided, preferably wherein the pharmaceutical composition is a vaccination composition for a human subject.

According to a third aspect of the present invention, provided is a kit comprising an antibody or antigen-binding fragment thereof according to the first aspect of the invention and a container.

According to a fourth aspect of the present invention, provided are an antibody or antigen-binding fragment thereof according to the first aspect of the invention, a pharmaceutical composition according to the second aspect of the invention, or a kit according to the third aspect of the invention for use as a medicament.

According to a fifth aspect of the present invention, provided are an antibody or antigen-binding fragment thereof according to the first aspect of the invention, a pharmaceutical composition according to the second aspect of the invention, or a kit according to the third aspect of the invention for use as a vaccine.

According to a sixth aspect of the present invention, provided are an antibody or antigen-binding fragment thereof according to the first aspect of the invention, a pharmaceutical composition according to the second aspect of the invention, or a kit according to the third aspect of the invention for use in the treatment or prevention of a disease caused by SARS-related coronavirus in human subjects, preferably for use in the treatment or prevention of a disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in human subjects.

According to a seventh aspect of the present invention, provided are an antibody or antigen-binding fragment thereof according to the first aspect of the invention, a pharmaceutical composition according to the second aspect of the invention, or a kit according to the third aspect of the invention for use in prevention of infection of a human subject with SARS-related coronavirus, preferably of infection of a human subject with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

In one embodiment of the fourth to seventh aspect of the invention, the antibody or antigen-binding fragment thereof is administered by intravenous infusion, by inhalative application, by subcutaneous injection or intramuscular injection, preferably wherein the antibody or antigen-binding fragment thereof is administered at an absolute dose of up to 4000 mg, preferably up to 2400 mg, more preferably up to 1200 mg, even more preferably up to 600 mg, even more preferably up to 300 mg, particularly preferably up to 150 mg.

According to an eighth aspect of the present invention, a nucleic acid is provided encoding an antibody or antigen-binding fragment thereof according to the first aspect of the invention.
According to a ninth aspect of the present invention, an expression vector is provided comprising the nucleic acid of the eighth aspect of the invention in functional association with an expression control sequence.

According to a tenth aspect of the present invention, a host cell is provided comprising a nucleic acid according to the eighth aspect of the invention or the expression vector according to the ninth aspect of the invention.

According to an eleventh aspect of the present invention, a method of production of an antibody or antigen-binding fragment thereof according to the first aspect of the invention is provided, comprising (a) cultivating the host cell of the tenth aspect of the invention under conditions allowing expression of the antibody or antigen-binding fragment thereof, and (b) recovering the antibody or antigen-binding fragment thereof.

According to a twelfth aspect of the present invention, provided is the antibody of the first aspect of the invention for use in medicine in combination with at least one further antibody directed against SARS-related coronavirus 2 (SARS-CoV-2), wherein said further antibody has a different binding specificity.

Brief description of the figures

The present disclosure will be more readily appreciated by reference to the following detailed description when being considered in connection with the accompanying drawings as follows:

Figure 1 shows mean SARS-CoV-2 bNabs IC_{50} values of duplicates against SARS-CoV-2 variants Wu01, Alpha, Beta, Delta, BA.1, BA.2, BA.2.12.1, BA.4/5, BA.2.75, BA.2.75.2, BQ.1.1, BA.4.6, XBB.1, XBB.1.5, and BF.7, and also against SARS-CoV-1 in pseudo virus neutralization assays; antibodies belonging to the same clonal family are marked on the left.

Figure 2 shows mean SARS-CoV-2 bNabs IC_{50} values based on duplicate measurements of two independent comparative experiments between reference antibody SP1-77 from Luo S et al., 2022, and antibodies TV1t4p2_A5, and TV1t4p3_E8 according to the present invention against SARS-CoV-2 variants Wu01, Alpha, Beta, Delta, BA.1, BA.2, BA.2.12.1, BA.4/5, BA.2.75, BA.2.75.2, BQ.1.1, BA.4.6, XBB.1, XBB.1.5, and BF.7.

Detailed description of preferred embodiments

In the following, the invention will be explained in more detail with reference to the accompanying figures. In the Figures, like elements are denoted by identical reference numerals and repeated description thereof may be omitted in order to avoid redundancies.

In order that the present description can be more readily understood, certain terms are first defined. Additional definitions are set forth throughout the detailed description.

It is to be noted that the term "a" or "an" entity refers to one or more of that entity; for example, "a nucleotide sequence," is understood to represent one or more nucleotide sequences. As such, the terms "a" (or "an"), "one or more," and "at least one" can be used interchangeably herein.

Furthermore, "and/or" where used herein is to be taken as specific disclosure of each of the two specified features or components with or without the other. Thus, the term "and/or" as used in a phrase such as "A and/or B" herein is intended to include "A and B," "A or B," "A" (alone), and "B" (alone). Likewise, the term "and/or" as used in a phrase such as "A, B, and/or C" is intended to encompass each of the following aspects: A, B, and C; A, B, or C; A or C; A or B; B or C; A and C; A and B; B and C; A (alone); B (alone); and C (alone).

It is understood that wherever aspects are described herein with the language "comprising," otherwise analogous aspects described in terms of "consisting of" and/or "consisting essentially of" are also provided.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure is related. For example, the Concise Dictionary of Biomedicine and Molecular Biology, Juo, Pei-Show, 2nd ed., 2002, CRC Press; The Dictionary of Cell and Molecular Biology, 3rd ed., 1999, Academic Press; and the Oxford Dictionary Of Biochemistry And Molecular Biology, Revised, 2000, Oxford University Press, provide one of skill with a general dictionary of many of the terms used in this disclosure.

Units, prefixes, and symbols are denoted in their Système International d'Unités (SI) accepted form. Numeric ranges are inclusive of the numbers defining the range. Unless otherwise indicated, nucleotide sequences are written left to right in 5' to 3' orientation. Amino acid sequences are written left to right in amino to carboxy orientation. The headings provided herein are not limitations of the various aspects of the disclosure, which can be had by reference to the specification as a whole. Accordingly, the terms defined immediately below are more fully defined by reference to the specification in its entirety.

The term "about" is used herein to mean approximately, roughly, around, or in the regions of. When the term "about" is used in conjunction with a numerical range, it modifies that range by extending the boundaries above and below the numerical values set forth. In general, the term "about" can modify a numerical value above and below the stated value by a variance of, e.g., 10 percent, up or down (higher or lower).

The term "antibody" is used herein in the broadest sense to refer to molecules with an immunoglobulin-like domain (for example IgG, IgM, IgA, IgD or IgE) and includes monoclonal, recombinant, polyclonal, chimeric, human, humanized, multispecific antibodies, including bispecific antibodies, and heteroconjugate antibodies; a single variable domain (e.g., VH, VHH, VL, domain antibody), antigen binding antibody fragments, Fab, F(ab')2, Fv, disulphide linked Fv, single chain Fv, disulphide-linked scFv, diabodies, etc. and modified versions of any of the foregoing.

The term "antibody" as used herein refers to a protein, derived from a germline immunoglobulin sequence, which is capable of specifically binding to an antigen or an antigen-binding portion thereof. The term includes full length antibodies of any class or isotype (that is, IgA, IgD, IgE, IgG, IgM and/or IgY) and any single chain or fragment thereof. An antibody that specifically binds to an antigen, or

antigen-binding portion thereof, may bind exclusively to that antigen, or portion thereof, or it may bind to a limited number of homologous antigens, or portions thereof. Full-length antibodies usually comprise at least four polypeptide chains: two heavy (H) chains and two light (L) chains that are interconnected by disulfide bonds.

One immunoglobulin sub-class of particular pharmaceutical interest is the IgG family. In humans, the IgG class may be sub-divided into 4 sub-classes: IgG1, IgG2, IgG3 and IgG4, based on the sequence of their heavy chain constant regions. The light chains can be divided into two types, kappa and lambda, based on differences in their sequence composition. IgG molecules are composed of two heavy chains, interlinked by two or more disulfide bonds, and two light chains, each attached to a heavy chain by a disulfide bond. A heavy chain may comprise a heavy chain variable region (VH) and up to three heavy chain constant (CH) regions: CH1, CH2 and CH3. A light chain may comprise a light chain variable region (VL) and a light chain constant region (CL).

VH and VL regions can be further subdivided into regions of hypervariability, termed complementarity determining regions (CDRs), interspersed with regions that are more conserved, termed framework regions (FR). VH and VL regions are typically composed of three CDRs and four FRs, arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4. The hypervariable regions of the heavy and light chains form a binding domain that is capable of interacting with an antigen, while the constant region of an antibody may mediate binding of the immunoglobulin to host tissues or factors, including but not limited to various cells of the immune system (effector cells), Fc receptors and the first component (C1q) of the classical complement system. Antibodies of the current invention may be isolated.

The term "isolated antibody" refers to an antibody that has been separated and/or recovered from (an)other component(s) in the environment in which it was produced and/or that has been purified from a mixture of components present in the environment in which it was produced. Certain antigen-binding fragments of antibodies may be suitable in the context of the current invention, as it has been shown that the antigen-binding function of an antibody can be performed by fragments of a full-length antibody.

The term "antigen-binding portion", “binding fragment” or “antigen-binding fragment” of an antibody refers to one or more fragment(s) of an antibody that retain the ability to specifically bind to an antigen, such as the spike (S) protein of SARS-CoV-2, as described herein.

Examples of antigen-binding fragments include Fab, Fab', F(ab)2, F(ab')2, F(ab)S, Fv (typically the VL and VH domains of a single arm of an antibody), single-chain Fv (scFv; see, e.g., Bird et al., Science 242:42S-426 (1988); Huston et al., PNAS 85: 5879-5883 (1988)), dsFv, Fd (typically the VH and CH1 domain), and dAb (typically a VH domain) fragments; VH, VL, VHH, and V-NAR domains; monovalent molecules comprising a single VH and a single VL chain; minibodies, diabodies, triabodies, tetrabodies, and kappa bodies (see, e.g., Ill et al., Protein Eng 10:949-57 (1997)); camel IgG; IgNAR; as well as one or more isolated CDRs or a functional paratope, where the isolated CDRs or antigen-binding residues or polypeptides can be associated or linked together so as to form a functional antibody fragment.

Various types of antibody fragments have been described or reviewed in, e.g., Holliger and Hudson, Nat Biotechnol 2S:1126-1136 (2005); International Publ. No. WO 2005/040219, and U.S. Publ. Nos. 2005/0238646 and 2002/0161201. These antibody fragments may be obtained using conventional techniques known to those of skill in the art, and the fragments may be screened for utility in the same manner as intact antibodies.

A "human" antibody (HuMAb) refers to an antibody having variable regions in which both the framework and CDR regions are derived from human germline immunoglobulin sequences. Furthermore, if the antibody contains a constant region, the constant region also is derived from human germline immunoglobulin sequences. The SARS-CoV-2 antibodies described herein can include amino acid residues not encoded by human germline immunoglobulin sequences (e.g., mutations introduced by random or site-specific mutagenesis in vitro or by somatic mutation in vivo).

However, the term "human antibody", as used herein, is not intended to include antibodies in which CDR sequences derived from the germline of another mammalian species, such as a mouse, have been grafted onto human framework sequences. The terms "human" antibodies and "fully human" antibodies are used synonymously.

A "humanized" antibody refers to a human/non-human chimeric antibody that contains one or more sequences (CDR regions or parts thereof) that are derived from a non-human immunoglobulin. A humanized antibody is, thus, a human immunoglobulin (recipient antibody) in which at least residues from a hyper-variable region of the recipient are replaced by residues from a hyper-variable region of an antibody from a non-human species (donor antibody) such as from a mouse, rat, rabbit or non-human primate, which have the desired specificity, affinity, sequence composition and functionality. In some instances, FR residues of the human immunoglobulin are replaced by corresponding

non-human residues. An example of such a modification is the introduction of one or more so-called back-mutations, which are typically amino acid residues derived from the donor antibody.

Humanization of an antibody may be carried out using recombinant techniques known to the person skilled in the art (see, e.g., Antibody Engineering, Methods in Molecular Biology, vol. 248, edited by Benny K. C. Lo). A suitable human recipient framework for both the light and heavy chain variable region may be identified by, for example, sequence or structural homology. Alternatively, fixed recipient frameworks may be used, e.g., based on knowledge of structure, biophysical and biochemical properties. The recipient frameworks can be germline derived or derived from a mature antibody sequence. CDR regions from the donor antibody can be transferred by CDR grafting.

The CDR grafted humanized antibody can be further optimized for e.g. affinity, functionality and biophysical properties by identification of critical framework positions where re-introduction (backmutation) of the amino acid residue from the donor antibody has beneficial impact on the properties of the humanized antibody. In addition to donor antibody derived backmutations, the humanized antibody can be engineered by introduction of germline residues in the CDR or framework regions, elimination of immunogenic epitopes, site-directed mutagenesis, affinity maturation, etc.

Furthermore, humanized antibodies can comprise residues that are not found in the recipient antibody or in the donor antibody. These modifications are made to further refine antibody performance. In general, a humanized antibody will comprise at least one--typically two--variable regions, in which all or substantially all of the CDR regions correspond to those of a non-human immunoglobulin and in which all or substantially all of the FR residues are those of a human immunoglobulin sequence. The humanized antibody can, optionally, also comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin. The term "humanized antibody derivative" refers to any modified form of the humanized antibody, such as a conjugate of the antibody and another agent or antibody.

The term "recombinant human antibody," as used herein, includes all human antibodies that are prepared, expressed, created or isolated by recombinant means, such as (a) antibodies isolated from an animal (e.g., a mouse) that is transgenic or transchromosomal for human immunoglobulin genes or a hybridoma prepared therefrom, (b) antibodies isolated from a host cell transformed to express the antibody, e.g., from a transfectoma, (c) antibodies isolated from a recombinant, combinatorial human antibody library, and (d) antibodies prepared, expressed, created or isolated by any other means that involve splicing of human immunoglobulin gene sequences to other DNA sequences.

Such recombinant human antibodies comprise variable and constant regions that utilize particular human germline immunoglobulin sequences are encoded by the germline genes, but include subsequent rearrangements and mutations which occur, for example, during antibody maturation. As known in the art (see, e.g., Lonberg Nature Biotech. 23(9): 1117-1125 (2005)), the variable region contains the antigen binding domain, which is encoded by various genes that rearrange to form an antibody specific for a foreign antigen. In addition to rearrangement, the variable region can be further modified by multiple single amino acid changes (referred to as somatic mutation or hypermutation) to increase the affinity of the antibody to the foreign antigen. The constant region will change in further response to an antigen (i.e., isotype switch).

Therefore, the rearranged and somatically mutated nucleic acid molecules that encode the light chain and heavy chain immunoglobulin polypeptides in response to an antigen cannot have sequence identity with the original nucleic acid molecules, but instead will be substantially identical or similar (i.e., have at least 80% identity).

A "chimeric antibody" refers to an antibody in which the variable regions are derived from one species and the constant regions are derived from another species, such as an antibody in which the variable regions are derived from a mouse antibody and the constant regions are derived from a human antibody.

Alternative antibody formats include alternative scaffolds in which the one or more CDRs of the antigen-binding portion can be arranged onto a suitable non-immunoglobulin protein scaffold or skeleton, such as an affibody, a SpA scaffold, an LDL receptor class A domain, an avimer or an EGF domain.

The term "domain" (interchangeably referred to as "region" herein) refers to a folded protein structure which retains its tertiary structure independent of the rest of the protein. Generally, domains are responsible for discrete functional properties of proteins and in many cases may be added, removed or transferred to other proteins without loss of function of the remainder of the protein and/or of the domain.

The term "single variable domain" refers to a folded polypeptide domain comprising sequences characteristic of antibody variable domains. It, therefore, includes complete antibody variable domains such as VH, VHH and VL and modified antibody variable domains, for example, in which one or more loops have been replaced by sequences which are not characteristic of antibody variable domains, or antibody variable domains which have been truncated or comprise N- or C-terminal

extensions, as well as folded fragments of variable domains which retain at least the binding activity and specificity of the full-length domain.

A single variable (V) domain is capable of binding an antigen or epitope independently of a different variable region or domain. A "domain antibody" or "dAbTM" may be considered the same as a "single variable domain". A single variable domain may be a human single variable domain, but also includes single variable domains from other species such as rodent nurse shark and Camelid VHH dAbsTM. Camelid VHH are immunoglobulin single variable domain polypeptides that are derived from species including camel, llama, alpaca, dromedary, and guanaco, which produce heavy chain antibodies naturally devoid of light chains. Such VHH domains may be humanized according to standard techniques available in the art, and such domains are considered to be "single variable domains". As used herein VH includes camelid VHH domains.

An antigen-binding fragment may be provided by means of arrangement of one or more CDRs on non-antibody protein scaffolds. "Protein Scaffold" as used herein includes but is not limited to an immunoglobulin (Ig) scaffold, for example an IgG scaffold, which may be a four chain or two chain antibody, or which may comprise only the Fc region of an antibody, or which may comprise one or more constant regions from an antibody, which constant regions may be of human or primate origin, or which may be an artificial chimera of human and primate constant regions.

As used herein, "isotype" refers to the antibody class (e.g., IgG1, IgG2, IgG3, IgG4, IgM, IgA1, IgA2, IgD, and IgE antibody) that is encoded by the heavy chain constant region genes.

"Allotype" refers to naturally occurring variants within a specific isotype group, which variants differ in a few amino acids (see, e.g., Jefferis et al., mAbs 1:1 (2009)).

The phrases "an antibody recognizing an antigen" and "an antibody specific for an antigen" are used interchangeably herein with the term "an antibody which binds specifically to an antigen."

By the terms "treat," "treating," or "treatment of" (or grammatically equivalent terms) it is meant that the severity of the subject's condition is reduced or at least partially improved or ameliorated and/or that some alleviation, mitigation or decrease in at least one clinical symptom is achieved and/or there is a delay in the progression of the condition.

As used herein, the terms "prevent," "prevents," or "prevention" and "inhibit," "inhibits," or "inhibition" (and grammatical equivalents thereof) are not meant to imply complete abolition of disease and

encompasses any type of prophylactic treatment that reduces the incidence of the condition, delays the onset of the condition, and/or reduces the symptoms associated with the condition after onset.

An "effective," "prophylactically effective," or "therapeutically effective" amount as used herein is an amount that is sufficient to provide some improvement or benefit to the subject. Alternatively stated, an "effective," "prophylactically effective," or "therapeutically effective" amount is an amount that will provide some delay, alleviation, mitigation, or decrease in at least one clinical symptom in the subject. Those skilled in the art will appreciate that the effects need not be complete or curative, as long as some benefit is provided to the subject.

As used herein, a "neutralizing antibody" is any antibody or antigen-binding fragment thereof that binds to a pathogen and interferes with the ability of the pathogen to infect a cell and/or cause disease in a subject.

"Peptide" as used herein includes peptides which are conservative variations of those peptides specifically exemplified herein. "Conservative variations" and "Conservative amino acid substitutions" as used herein denotes the replacement of an amino acid residue by another, biologically similar residue. Examples of conservative variations include, but are not limited to, the substitution of one hydrophobic residue such as isoleucine, valine, leucine, alanine, cysteine, glycine, phenylalanine, proline, tryptophan, tyrosine, norleucine or methionine for another, or the substitution of one polar residue for another, such as the substitution of arginine for lysine, glutamic for aspartic acids, or glutamine for asparagine, and the like. Neutral hydrophilic amino acids which can be substituted for one another include asparagine, glutamine, serine and threonine.

"Conservative variations" also includes the use of a substituted amino acid in place of an unsubstituted parent amino acid provided that antibodies raised to the substituted polypeptide also immunoreact with the unsubstituted polypeptide. Such conservative substitutions are within the definition of the classes of the peptides of the invention. The biological activity of the peptides can be determined by standard methods known to those of skill in the art and described herein.

For polypeptides, the term "substantial homology" indicates that two polypeptides, or designated sequences thereof, when optimally aligned and compared, are identical, with appropriate amino acid insertions or deletions, in at least about 80% of the amino acids, at least about 90% to 95%, or at least about 98% to 99.5% of the amino acids.

The percent identity between two sequences is a function of the number of identical positions shared by the sequences (i.e., % homology = # of identical positions/total # of positions times 100), taking into account the number of gaps, and the length of each gap, which need to be introduced for optimal alignment of the two sequences. The comparison of sequences and determination of percent identity between two sequences can be accomplished using a mathematical algorithm, as described in the non-limiting examples below.

The nucleic acids can be present in whole cells, in a cell lysate, or in a partially purified or substantially pure form. A nucleic acid is "isolated" or "rendered substantially pure" when purified away from other cellular components or other contaminants, e.g., other cellular nucleic acids (e.g., the other parts of the chromosome) or proteins, by standard techniques, including alkaline/SDS treatment, CsCl banding, column chromatography, agarose gel electrophoresis and others well known in the art. See, F. Ausubel, et al., ed. Current Protocols in Molecular Biology, Greene Publishing and Wiley Interscience, New York (1987).

Nucleic acids, e.g., cDNA, can be mutated, in accordance with standard techniques to provide gene sequences. For coding sequences, these mutations, can affect amino acid sequence as desired. In particular, DNA sequences substantially homologous to or derived from native V, D, J, constant, switches and other such sequences described herein are contemplated (where "derived" indicates that a sequence is identical or modified from another sequence).

The term "vector," as used herein, is intended to refer to a nucleic acid molecule capable of transporting another nucleic acid to which it has been linked. One type of vector is a "plasmid," which refers to a circular double stranded DNA loop into which additional DNA segments can be ligated. Another type of vector is a viral vector, wherein additional DNA or RNA segments can be ligated into the viral genome. Certain vectors are capable of autonomous replication in a host cell into which they are introduced (e.g., bacterial vectors having a bacterial origin of replication and episomal mammalian vectors).

Other vectors (e.g., non-episomal mammalian vectors) can be integrated into the genome of a host cell upon introduction into the host cell, and thereby are replicated along with the host genome. Moreover, certain vectors are capable of directing the expression of genes to which they are operatively linked. Such vectors are referred to herein as "recombinant expression vectors" (or simply, "expression vectors"). In general, expression vectors of utility in recombinant DNA techniques are often in the form of plasmids. In the present specification, "plasmid" and "vector" can be used interchangeably as the plasmid is the most commonly used form of vector. However, also included

are other forms of expression vectors, such as viral vectors (e.g., replication defective retroviruses, adenoviruses and adeno-associated viruses), which serve equivalent functions.

The term "recombinant host cell" (or simply "host cell"), as used herein, is intended to refer to a cell that comprises a nucleic acid that is not naturally present in the cell, and can be a cell into which a recombinant expression vector has been introduced. It should be understood that such terms are intended to refer not only to the particular subject cell but to the progeny of such a cell. Because certain modifications can occur in succeeding generations due to either mutation or environmental influences, such progeny cannot, in fact, be identical to the parent cell, but are still included within the scope of the term "host cell" as used herein.

As used herein, the term "linked" refers to the association of two or more molecules. The linkage can be covalent or non-covalent. The linkage also can be genetic (i.e., recombinantly fused). Such linkages can be achieved using a wide variety of art recognized techniques, such as chemical conjugation and recombinant protein production.

An "effector function" refers to the interaction of an antibody Fc region with an Fc receptor or ligand, or a biochemical event that results therefrom. Exemplary "effector functions" include C1q binding, complement dependent cytotoxicity (CDC), Fc receptor binding, FcγR-mediated effector functions such as ADCC and antibody dependent cell-mediated phagocytosis (ADCP), and downregulation of a cell surface receptor (e.g., the B cell receptor; BCR). Such effector functions generally require the Fc region to be combined with a binding domain (e.g., an antibody variable domain).

An "Fc receptor" or "FcR" is a receptor that binds to the Fc region of an immunoglobulin. FcRs that bind to an IgG antibody comprise receptors of the FcγR family, including allelic variants and alternatively spliced forms of these receptors. The FcγR family consists of three activating (FcγRI, FcγRIII, and Fc.RIV in mice; FcγRIA, FcγRIIA, and FcγRIIIA in humans) and one inhibitory (FcγRIIB) receptor. Various properties of human FcγRs are known in the art. The majority of innate effector cell types coexpress one or more activating FcγR and the inhibitory FcγRIIB, whereas natural killer (NK) cells selectively express one activating Fc receptor (FcγRIII in mice and FcγRIIIA in humans) but not the inhibitory FcγRIIB in mice and humans. Human IgG1 binds to most human Fc receptors and is considered equivalent to murine IgG2a with respect to the types of activating Fc receptors that it binds to.

"Fc region" (fragment crystallizable region) or "Fc domain" or "Fc" refers to the C-terminal region of the heavy chain of an antibody that mediates the binding of the immunoglobulin to host tissues or factors, including binding to Fc receptors located on various cells of the immune system (e.g., effector cells) or to the first component (C1q) of the classical complement system. Thus, an Fc region comprises the constant region of an antibody excluding the first constant region immunoglobulin domain (e.g., CH1 or CL).

The constant region may be modified to stabilize the antibody, e.g., to reduce the risk of a bivalent antibody separating into two monovalent VH-VL fragments. For example, in an IgG4 constant region, residue S228 (residue numbering according to the EU index) may be mutated to a proline (P) residue to stabilize inter heavy chain disulphide bridge formation at the hinge (see, e.g., Angal et al., Mol Immunol. 30: 105-8(1995)). Antibodies or fragments thereof can also be defined in terms of their complementarity-determining regions (CDRs).

The term "complementarity-determining region" or "hypervariable region", when used herein, refers to the regions of an antibody in which amino acid residues involved in antigen binding are situated. The region of hypervariability or CDRs can be identified as the regions with the highest variability in amino acid alignments of antibody variable domains. Databases can be used for CDR identification such as the Kabat database, the CDRs e.g., being defined as comprising amino acid residues 24-34 (CDR1), 50-59 (CDR2) and 89-97 (CDR3) of the light-chain variable region, and 31-35 (CDR1), 50-65 (CDR2) and 95-102 (CDR3) in the heavy-chain variable region; (Kabat et al. 1991; Sequences of Proteins of Immunological Interest, Fifth Edition, U.S. Department of Health and Human Services, NIH Publication No. 91-3242). Alternatively, CDRs can be defined as those residues from a "hypervariable loop" (residues 26-33 (L1), 50-52 (L2) and 91-96 (L3) in the light-chain variable region and 26-32 (H1), 53-55 (H2) and 96-101 (H3) in the heavy-chain variable region (Chothia and Lesk, J. Mol. Biol 196: 901-917 (1987)).

The CDR regions of the antibody sequences described herein are preferably defined according to the numbering scheme of IMGT which is an adaptation of the numbering scheme of Chothia (ImMunoGeneTics information system®; Lefranc, M.-P. et al. IMGT, the international ImMunoGeneTics database. Nucleic Acids Res 27, 209–212 (1999).; http://imgt.org).

As used herein, the terms "specific binding," "selective binding," "selectively binds," and "specifically binds," refer to antibody binding to an epitope on a predetermined antigen. Preferably, the antibody binds to the predetermined antigen with an affinity that is at least two-fold greater than its affinity for

binding to a non-specific antigen (e.g., BSA, casein) other than the predetermined antigen or a closely-related antigen.

The term "binding affinity" herein refers to a measurement of the strength of a non-covalent interaction between two molecules, e.g. an antibody, or fragment thereof, and an antigen. The term "binding affinity" is used to describe monovalent interactions (intrinsic activity).

The binding affinity between two molecules, e.g. an antibody, or fragment thereof, and an antigen, through a monovalent interaction may be quantified by determination of the equilibrium dissociation constant (KD). In turn, KD can be determined by measurement of the kinetics of complex formation and dissociation, e.g. by the SPR method. The rate constants corresponding to the association and the dissociation of a monovalent complex are referred to as the association rate constant ka (or kon) and dissociation rate constant kd (or koff), respectively. KD is related to ka and kd through the equation KD=kd/ka. Following the above definition, binding affinities associated with different molecular interactions, such as comparison of the binding affinity of different antibodies for a given antigen, may be compared by comparison of the KD values for the individual antibody/antigen complexes.

The term "binding specificity" herein refers to the interaction of a molecule such as an antibody, or fragment thereof, with a single exclusive antigen, or with a limited number of highly homologous antigens (or epitopes). In contrast, antibodies that are capable of specifically binding to the spike (S) protein of SARS-CoV-2 are not capable of binding dissimilar molecules.

The specificity of an interaction and the value of an equilibrium binding constant can be determined directly by well-known methods. Standard assays to evaluate the ability of ligands (such as antibodies) to bind their targets are known in the art and include, for example, ELISAs, Western blots, RIAs, and flow cytometry analysis. The binding kinetics and binding affinity of the antibody also can be assessed by standard assays known in the art, such as SPR.

The term "naturally-occurring" as used herein as applied to an object refers to the fact that an object can be found in nature. For example, a polypeptide or polynucleotide sequence that is present in an organism (including viruses) that can be isolated from a source in nature and which has not been intentionally modified by man in the laboratory is naturally-occurring.

A "polypeptide" refers to a chain comprising at least two consecutively linked amino acid residues, with no upper limit on the length of the chain. One or more amino acid residues in the protein can

contain a modification such as, but not limited to, glycosylation, phosphorylation or disulfide bond formation. A "protein" can comprise one or more polypeptides.

The term "nucleic acid molecule," as used herein, is intended to include DNA molecules and RNA molecules. A nucleic acid molecule can be single-stranded or double-stranded, and can be cDNA.

The term "subject" includes human and other mammalian subjects that receive either prophylactic or therapeutic treatment. As used herein, the term "subject" includes any human or non-human animal. The term "non-human animal" includes all vertebrates, e.g., mammals and non-mammals, such as non-human primates, sheep, dog, cow, chickens, amphibians, reptiles, etc.

As used herein, the terms "ug" and "uM" are used interchangeably with "µg" and "µM," respectively.

As used herein, "administering" refers to the physical introduction of a composition comprising a therapeutic agent to a subject, using any of the various methods and delivery systems known to those skilled in the art. Different routes of administration for the antibodies described herein include intravenous, intraperitoneal, intramuscular, subcutaneous, spinal or other parenteral routes of administration, for example by injection or infusion.

The phrase "parenteral administration" as used herein means modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intraperitoneal, intramuscular, intraarterial, intrathecal, intralymphatic, intralesional, intracapsular, intraorbital, intracardiac, intradermal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal, epidural and intrasternal injection and infusion, as well as in vivo electroporation.

Alternatively, an antibody described herein can be administered via a non-parenteral route, such as a topical, epidermal or mucosal route of administration, for example, intranasally, orally, vaginally, rectally, sublingually or topically. Administering can also be performed, for example, once, a plurality of times, and/or over one or more extended periods.

As used herein “vaccination composition” means a pharmaceutical composition comprising at least one antibody or antigen-binding portion thereof of the present invention which is capable of providing active and/or passive immunity. “Active immunity” as used herein means inducing or enhancing a subject’s immune response to an antigen. “Passive immunity” as used and preferred herein means

supplementing a subject's immune response to an antigen or pathogen by providing antibodies and/or antigen-binding portions thereof which neutralize an antigen.

The present inventors have dedicated themselves to solving the problem of the present invention and were successful to find novel human monoclonal antibodies against SARS-related coronavirus having superior neutralization potency against all currently circulating SARS-CoV-2 variants of concern, most importantly including XBB.1.5, as well as emerging variants in comparison to publicly available neutralizing antibodies.

To date, more than half of the world's population has received a vaccination based on the ancestral severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Wu01 strain. However, with SARS-CoV-2 continuously evolving, each individual must adapt to cope with current and future viral variants.

It is generally known that SARS-CoV-2 humoral immunity matures continuously in the months following infection, e.g. due to memory B cells acquiring somatic mutations within 6 months after infection, leading to more potently neutralizing antibodies. Moreover, longitudinal analyses of serum antibodies showed that renewed antigen contact expands the response against SARS-CoV-2 in potency and breadth. In addition, breakthrough infections with newly emerging variants of concern (VOC) can also increase and improve the plasma antibody response.

The present inventors addressed the need for broadly neutralizing antibodies effective against a wide range of emerging variants by longitudinally investigating the humoral immune response on a molecular level following repeated vaccination and Omicron breakthrough infection.

To this end, the inventors isolated and characterized 656 monoclonal antibodies (mAbs) from SARS-CoV-2-specific memory B cells to identify the antibodies of the present invention which are able to neutralize an extensive range of SARS-CoV-2 variants with high potency and superiority in breadth compared to antibodies that are already used in the clinic. These new bNAbs may hold great therapeutic or prophylactic potential with a chance to also react against future variants.

The particular characteristics and unprecedented neutralization strength of antibodies of the present invention can be seen from the data presented in Figure 2. Therein, antibodies TV1t4p2_A5 and TV1t4p3_E8 of the present invention have been tested in comparative experiments against a reference antibody SP1-77 which was previously reported as supposedly being capable of neutralizing a high diversity of variants of SARS-CoV-2 (cf. (Luo, S. *et al. An antibody from single*

human V_H-rearranging mouse neutralizes all SARS-CoV-2 variants through BA.5 by inhibiting membrane fusion. Sci. Immunol. 7, eadd5446 (2022)).

In these comparative experiments, SP1-77 proved to be unable to neutralize SARS-CoV-2 variants BA.2.75.2, BQ1.1, BA.4.6, XBB.1, XBB.1.5, and BF.7, while antibodies TV1t4p2_A5 and TV1t4p3_E8 of the present invention maintained high neutralization strength and breadth also against these new variants. These experiments already demonstrate superior results of the antibodies of the present invention in comparison to reference antibodies of the prior art.

Accordingly, the present invention provides antibodies or antigen-binding fragments thereof directed against SARS-related coronavirus, wherein the antibody or antigen-binding fragment thereof comprises the combination of the heavy chain CDR1 to CDR3 and the light chain CDR1 to CDR3 amino acid sequence of one antibody selected from the group comprising TV1t4p2_A5 (having a CDR-H1 amino acid sequence of SEQ ID No. 27, a CDR-H2 amino acid sequence of SEQ ID No. 28, a CDR-H3 amino acid sequence of SEQ ID No. 29, a CDR-L1 amino acid sequence of SEQ ID No. 30, a CDR-L2 amino acid sequence of SEQ ID No. 31, a CDR-L3 amino acid sequence of SEQ ID No. 32), TV1t2p6_D3 (having a CDR-H1 amino acid sequence of SEQ ID No. 33, a CDR-H2 amino acid sequence of SEQ ID No. 34 a CDR-H3 amino acid sequence of SEQ ID No. 35 a CDR-L1 amino acid sequence of SEQ ID No. 36 a CDR-L2 amino acid sequence of SEQ ID No. 37, a CDR-L3 amino acid sequence of SEQ ID No. 38), TV1t4p3_E8 (having a CDR-H1 amino acid sequence of SEQ ID No. 21, a CDR-H2 amino acid sequence of SEQ ID No. 22, a CDR-H3 amino acid sequence of SEQ ID No. 23, a CDR-L1 amino acid sequence of SEQ ID No. 24, a CDR-L2 amino acid sequence of SEQ ID No. 25, a CDR-L3 amino acid sequence of SEQ ID No. 26), and TV1t3p4_E1 (having a CDR-H1 amino acid sequence of SEQ ID No. 39, a CDR-H2 amino acid sequence of SEQ ID No. 40, a CDR-H3 amino acid sequence of SEQ ID No. 41, a CDR-L1 amino acid sequence of SEQ ID No. 42, a CDR-L2 amino acid sequence of SEQ ID No. 43, a CDR-L3 amino acid sequence of SEQ ID No. 44).

Within the context of the present invention, the antibodies, which have been generated and described herein, may be used and claimed as the complete monoclonal human antibody or as any functional or antigen-binding fragment thereof. Preferably, the antibody or any kind of functional or antigen-binding fragment thereof should at least comprise the complementarity determining regions (CDR) 1 to 3 of the heavy chain and CDR 1 to 3 of the light chain of the antibody.

The CDR regions of the antibody sequences described herein are preferably defined according to the numbering scheme of IMGT which is an adaptation of the numbering scheme of Chothia

(ImMunoGeneTics information system®; Lefranc, M.-P. et al. IMGT, the international ImMunoGeneTics database. Nucleic Acids Res 27, 209–212 (1999); http://imgt.org).

Based on the common general knowledge and the information given herein on the heavy chain variable region amino acid sequences and the light chain variable region amino acid sequences of the antibodies of the invention, the CDRs can be easily and unambiguously determined by a skilled person.

According to one preferred embodiment of the present invention, the light and heavy chain variable region sequences of the preferred antibodies and antigen-binding fragments thereof described herein with the internal designations TV1t4p3_E8, TV1t4p2_A5, TV1t2p6_D3, and TV1t3p4_E1 are as follows (CDRs marked in bold):

SEQ ID NO	Source	Sequence
1	Heavy chain variable domain TV1t4p3_E8	EVQLVESGGGLVQPGRSLRLSCVAS**GFPFEDYA**IHWVRQPPGK GLEWVSS**ISWDSGSLA**YADSVKGRFTISRDNAKNSVYLQMNSLR AEETALYYC**AKGPYPGYSSAWYYGMDV**WGQGTTVTVSS
2	Light chain variable domain TV1t4p3_E8	QSALTQPASVSGSPGQSITISCTGT**SSDIGYYNY**VSWYQQHPGK APKLLIY**EVSN**RPSGVSNRFSGSKSGNTASLTISGLQAEDEADYY C**SSYTTRNFGV**FGGGTKLTV
3	Heavy chain variable domain TV1t4p2_A5	QVQLVQSGAEVKKPGSSVKVSCKAS**GGTFSSYA**VSWVRQAPGQ GLEWMGG**IIPQFGTAN**YAQKFQGRVTITADESTSTAYMDLSSLRS EDTAVYYC**ARDRGYCSGTSPSCVGPRYYFYGADV**WGQGTTVAV S
4	Light chain variable domain TV1t4p2_A5	EIVLTQSPATLSLSPGERATLSCRAS**QSVSSS**LAWYQQKPGQAP RLLIY**DASN**RATAIPARFSGSGSGTDFTLTISSLEPEDFAVYYC**QQ RINWPLT**FGGGTKVEIK
5	Heavy chain variable domain TV1t2p6_D3	QVQLVQSGTEVKKPGSSVKVSCKAS**GGTFSTYA**VSWVRQAPGQ GLEWMGG**IIPQFGTAN**YAQKFQGRVTITADESTSTAYMELSSLRS EDTAVYYC**ARDRGHCSGTSSSCVGPRYYFYGTDV**WGQGTTVAV S
6	Light chain variable domain TV1t2p6_D3	EIVLTQSPATLSLSPGERATLSCRAS**QSVSYS**LAWYQQKPGQAP RLLIY**DASN**RATAIPARFSGSGSGTDFTLTISSLEPEDFAVYYC**QQ RINWPLT**FGGGTKVEIK

7	Heavy chain variable domain TV1t3p4_E1	EVQLVESGGGLIQPGGSLRLSCAAS**EIIVSRNY**MSWVRQAPGKG LEWVSV**IYSGGSTF**YSDSVKGRFTISRDSSKNTLYLQMNSLRAED TAVYYC**ARDLMEFGGMDV**WGQGTTVTVSS
8	Light chain variable domain TV1t3p4_E1	DIQMTQSPSTLSASVGDRVSITCRAS**QSVNNW**LAWYQQKPGSAP KLLIY**KASS**LQSGVPSRFSGSGSGTEFTLTITGLQPDDIATYYC**QL YNSYSST**FGQGTKVEIK

According to one embodiment of the present invention, the antibody or antigen-binding fragment thereof comprises a heavy chain variable region amino acid sequence of antibody TV1t4p2_A5 (SEQ ID No. 3), or a heavy chain variable region amino acid sequence of antibody TV1t2p6_D3 (SEQ ID No. 5), or a heavy chain variable region amino acid sequence of antibody TV1t4p3_E8 (SEQ ID No. 1), or a heavy chain variable region amino acid sequence of antibody TV1t3p4_E1 (SEQ ID No. 7).

According to an embodiment of the present invention, the antibody or antigen-binding fragment thereof comprises a light chain variable region amino acid sequence of antibody TV1t4p2_A5 (SEQ ID No. 4), or a light chain variable region amino acid sequence of antibody TV1t2p6_D3 (SEQ ID No. 6), or a light chain variable region amino acid sequence of antibody TV1t4p3_E8 (SEQ ID No. 2), or a light chain variable region amino acid sequence of antibody TV1t3p4_E1 (SEQ ID No. 8).

According to a preferred embodiment of the present invention, the antibody comprises a heavy chain variable region amino acid sequence of SEQ ID No. 3 and a light chain variable region amino acid sequence of SEQ ID No. 4, or the antibody comprises a heavy chain variable region amino acid sequence of SEQ ID No. 5 and a light chain variable region amino acid sequence of SEQ ID No. 6, or the antibody comprises a heavy chain variable region amino acid sequence of SEQ ID No. 1 and a light chain variable region amino acid sequence of SEQ ID No. 2, or the antibody comprises a heavy chain variable region amino acid sequence of SEQ ID No. 7 and a light chain variable region amino acid sequence of SEQ ID No. 8.

According to a specific embodiment of the present invention, the antibody consists of two heavy chains of sequence SEQ ID NO. 3 and two light chains of sequence SEQ ID NO. 4, or the antibody consists of two heavy chains of sequence SEQ ID NO. 5 and two light chains of sequence SEQ ID NO. 6, or the antibody consists of two heavy chains of sequence SEQ ID NO. 1 and two light chains of sequence SEQ ID NO. 2, or the antibody consists of two heavy chains of sequence SEQ ID NO. 7 and two light chains of sequence SEQ ID NO. 8.

According to one preferred embodiment of the present invention, the CDR sequences of the light and heavy chain variable region sequences of the antibodies and antigen-binding fragments thereof described herein are as follows:

Source	CDR1	SEQ ID CDR1	CDR2	SEQ ID CDR2	CDR3	SEQ ID CDR3
Heavy chain TV1t4p3_E8	GFPFEDYA	21	ISWDSGSLA	22	AKGPYPGYSSAWYYGMDV	23
Light chain TV1t4p3_E8	SSDIGYYNY	24	EVSN	25	SSYTTRNFGV	26
Heavy chain TV1t4p2_A5	GGTFSSYA	27	IIPQFGTAN	28	ARDRGYCSGTSPSCVGPRYYFYGADV	29
Light chain TV1t4p2_A5	QSVSSS	30	DASN	31	QQRINWPLT	32
Heavy chain TV1t2p6_D3	GGTFSTYA	33	IIPQFGTAN	34	ARDRGHCSGTSSSCVGPRYYFYGTDV	35
Light chain TV1t2p6_D3	QSVSYS	36	DASN	37	QQRINWPLT	38
Heavy chain TV1t3p4_E1	EIIVSRNY	39	IYSGGSTF	40	ARDLMEFGGMDV	41
Light chain TV1t3p4_E1	QSVNNW	42	KASS	43	QLYNSYSST	44

According to a preferred embodiment of the present invention, the antibody used as a source for sequences comprised in the antibody or antigen-binding fragment thereof according to the present invention is selected from the group comprising TV1T4p2_A5, TV1t2p6_D3, and TV1t4p3_E8, preferably from the group comprising TV1t4p2_A5 and TV1t2p6_D3, more preferably of antibody TV1t4p2_A5.

In another embodiment of the present invention, the antibody used as a source for sequences comprised in the antibody of the invention is TV1t4p2_A5. In another embodiment of the present invention, the antibody used as a source for sequences comprised in the antibody of the invention is TV1t2p6_D3. In one embodiment of the present invention, the antibody used as a source for

sequences comprised in the antibody of the invention is TV1t4p3_E8. In another embodiment of the present invention, the antibody used as a source for sequences comprised in the antibody of the invention is TV1t3p4_E1.

According to another preferred embodiment of the present invention, the SARS-related coronavirus strain is severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

According to one embodiment of the present invention, the amino acid sequences of the CDRs or of the variable regions comprised in the antibody or antigen-binding fragment thereof according to the present invention are from an antibody which is able to neutralize each of the SARS-CoV-2 lineages Wu01, Alpha, Beta, Delta, BA.1, BA.2, BA.2.12.1, BA.4/5, BA.2.75, BA.2.75.2, BQ.1.1, BA.4.6, XBB.1, XBB.1.5, and BF.7 in a pseudovirus neutralization assay as described in the description with an IC_{50} of at most 0.07 µg/ml, preferably at most 0.06 µg/ml, more preferably at most 0.05 µg/ml, even more preferably at most 0.04 µg/ml, even more preferably at most 0.03 µg/ml, particularly preferably at most 0.025 µg/ml.

According to the present invention, the pseudovirus neutralization assay for determining IC_{50} values is to be carried out as described in the section “Pseudovirus assay to determine IgG and plasma SARS-CoV-2 neutralizing activity ” below.

According to the present invention, additional antibodies or antigen-binding fragments thereof are provided which are directed against SARS-related coronavirus, wherein the amino acid sequences of the CDRs or of the variable regions comprised therein are from an antibody which is also able to neutralize each of the SARS-CoV-2 lineages Wu01, Alpha, Beta, Delta, BA.1, BA.2, BA.2.12.1, BA.4/5, BA.2.75, BA.2.75.2, BQ.1.1, BA.4.6, XBB.1, XBB.1.5, and BF.7 in a pseudovirus neutralization assay as described in the description. These antibodies carry the internal designations TV1t4p2_H8, TV1t2p7_F11, TV1t4p1_F7, and TV1t2p4_D11.

According to one embodiment, the light and heavy chain variable region sequences of these additional antibodies and antigen-binding fragments thereof described herein are as follows (CDRs marked in bold):

SEQ ID NO	Source	Sequence
9	Heavy chain variable domain TV1t4p2_H8	EVQLVESGGGLIQPGGSLRLSCAAS**EIIVSRNY**MSWVRQAPGKG LEWVSV**IYSGGSTF**YSDSVKGRFTISRDSSKNTLYLQMNSLRAED TAVYYC**ARDLMEFGGMDV**WGQGTTVTVSS
10	Light chain variable domain TV1t4p2_H8	DIQMTQSPSTLSASVGDRVSITCRAS**QSVNNW**LAWYQQKPGSA PKLLIY**KASS**LQSGVPSRFSGSGSGTEFTLTITGLQPDDIATYYC**Q LYNSYSST**FGQGTKVEIK
11	Heavy chain variable domain TV1t2p7_F11	EVQLVESGGGLIQPGGSLRLSCAAS**EIIVSRNY**MSWVRQAPGKG LEWVSV**IYSGGSTF**YSDSVKGRFTISRDSSKNTLYLQMNSLRAED TAVYYC**ARDLMEFGGMDV**WGQGTTVTVSS
12	Light chain variable domain TV1t2p7_F11	DIQMTQSPSTLSASVGDRVSITCRAS**QSVNNW**LAWYQQKPGSA PKLLIY**KASS**LQSGVPSRFSGSGSGTEFTLTITGLQPDDIATYYC**Q LYNSYSST**FGQGTKVEIK
13	Heavy chain variable domain TV1t4p1_F7	EVQLVESGGGLIQPGGSLRLSCAAS**EIIVSRNY**MSWVRQAPGKG LEWVSV**IYSGGSTF**YADSVKGRFTISRDNSKNTLYLQMNSLRAED TAVYYC**ARDLMEFGGMDV**WGQGTTVTVSS
14	Light chain variable domain TV1t4p1_F7	DIQMTQSPSTLSASVGDRVSITCRAS**QSINNW**LAWYQQKPGSAP KLLMY**KASS**LQSGVPSRFSGSGSGTEFTLTITGLQPDDFGTYYC **QLYNSYSST**FGQGTKVEIK
15	Heavy chain variable domain TV1t2p4_D11	QVQLQESGPGLVKPSGTLSLTCAVS**GGSISSPNW**WSWVRQSPG KGLEWIGE**IHHGGSTQ**YNPSLKSRVTMSVDMSKNQFSLKLRSAT AADTAVYYC**ASISGALWD**WGQGTLVIVSS
16	Light chain variable domain TV1t2p4_D11	DIQMTQSPSSLSASVGDRVTITCRAS**QGISNS**LAWYQQTPGKAP KLLLY**AAST**LESGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC**Q QYYGMSRT**FGQGTKVEIK

In one embodiment, the antibody or antigen-binding fragment thereof comprises the combination of the heavy chain CDR1 to CDR3 and the light chain CDR1 to CDR3 amino acid sequence of one antibody selected from the group comprising TV1t4p2_H8 (having a CDR-H1 amino acid sequence of SEQ ID No. 45, a CDR-H2 amino acid sequence of SEQ ID No. 46, a CDR-H3 amino acid sequence of SEQ ID No. 47, a CDR-L1 amino acid sequence of SEQ ID No. 48, a CDR-L2 amino acid sequence of SEQ ID No. 49, a CDR-L3 amino acid sequence of SEQ ID No. 50), TV1t2p7_F11 (having a CDR-H1 amino acid sequence of SEQ ID No. 51, a CDR-H2 amino acid sequence of SEQ ID No. 52, a CDR-H3 amino acid sequence of SEQ ID No. 53, a CDR-L1 amino acid sequence of SEQ ID No. 54,

a CDR-L2 amino acid sequence of SEQ ID No. 55, a CDR-L3 amino acid sequence of SEQ ID No. 56), TV1t4p1_F7 (having a CDR-H1 amino acid sequence of SEQ ID No. 57, a CDR-H2 amino acid sequence of SEQ ID No. 58 a CDR-H3 amino acid sequence of SEQ ID No. 59 a CDR-L1 amino acid sequence of SEQ ID No. 60 a CDR-L2 amino acid sequence of SEQ ID No. 61, a CDR-L3 amino acid sequence of SEQ ID No. 62), and TV1t2p4_D11 (having a CDR-H1 amino acid sequence of SEQ ID No. 63, a CDR-H2 amino acid sequence of SEQ ID No. 64, a CDR-H3 amino acid sequence of SEQ ID No. 65, a CDR-L1 amino acid sequence of SEQ ID No. 66, a CDR-L2 amino acid sequence of SEQ ID No. 67, a CDR-L3 amino acid sequence of SEQ ID No. 68).

According to one embodiment, the CDR sequences of the light and heavy chain variable region sequences of the additional antibodies and antigen-binding fragments thereof described herein with the internal designations TV1t4p2_H8, TV1t2p7_F11, TV1t4p1_F7, and TV1t2p4_D11 are as follows:

Source	CDR1	SEQ ID CDR1	CDR2	SEQ ID CDR2	CDR3	SEQ ID CDR3
Heavy chain TV1t4p2_H8	EIIVSRNY	45	IYSGGSTF	46	ARDLMEFGGMDV	47
Light chain TV1t4p2_H8	QSVNNW	48	KASS	49	QLYNSYSST	50
Heavy chain TV1t2p7_F11	EIIVSRNY	51	IYSGGSTF	52	ARDLMEFGGMDV	53
Light chain TV1t2p7_F11	QSVNNW	54	KASS	55	QLYNSYSST	56
Heavy chain TV1t4p1_F7	EIIVSRNY	57	IYSGGSTF	58	ARDLMEFGGMDV	59
Light chain TV1t4p1_F7	QSINNW	60	KASS	61	QLYNSYSST	62
Heavy chain TV1t2p4_D11	GGSISSPNW	63	IHHGGSTQ	64	ASISGALWD	65
Light chain TV1t2p4_D11	QGISNS	66	AAST	67	QQYYGMSRT	68

According to one embodiment, the antibody or antigen-binding fragment thereof comprises a heavy chain variable region amino acid sequence of antibody TV1t4p2_H8 (SEQ ID No. 9), or a heavy chain

variable region amino acid sequence of antibody TV1t2p7_F11 (SEQ ID No. 11), or a heavy chain variable region amino acid sequence of antibody TV1t4p1_F7 (SEQ ID No. 13), or a heavy chain variable region amino acid sequence of antibody TV1t2p4_D11 (SEQ ID No. 15).

According to an embodiment, the antibody or antigen-binding fragment thereof comprises a light chain variable region amino acid sequence of antibody TV1t4p2_H8 (SEQ ID No. 10), or a light chain variable region amino acid sequence of antibody TV1t2p7_F11 (SEQ ID No. 12), or a light chain variable region amino acid sequence of antibody TV1t4p1_F7 (SEQ ID No. 14), or a light chain variable region amino acid sequence of antibody TV1t2p4_D11 (SEQ ID No. 16).

According to another embodiment, the antibody comprises a heavy chain variable region amino acid sequence of SEQ ID No. 9 and a light chain variable region amino acid sequence of SEQ ID No. 10, or the antibody comprises a heavy chain variable region amino acid sequence of SEQ ID No. 11 and a light chain variable region amino acid sequence of SEQ ID No. 12, or the antibody comprises a heavy chain variable region amino acid sequence of SEQ ID No. 13 and a light chain variable region amino acid sequence of SEQ ID No. 14, or the antibody comprises a heavy chain variable region amino acid sequence of SEQ ID No. 15 and a light chain variable region amino acid sequence of SEQ ID No. 16.

According to a specific embodiment, the antibody consists of two heavy chains of sequence SEQ ID NO. 9 and two light chains of sequence SEQ ID NO. 10, or the antibody consists of two heavy chains of sequence SEQ ID NO. 11 and two light chains of sequence SEQ ID NO. 12, or the antibody consists of two heavy chains of sequence SEQ ID NO. 13 and two light chains of sequence SEQ ID NO. 14, or the antibody consists of two heavy chains of sequence SEQ ID NO. 15 and two light chains of sequence SEQ ID NO. 16.

In another embodiment, the antibody used as a source for sequences comprised in the antibody of the invention is TV1t4p1_G7. This antibody is able to efficiently cross-neutralize the SARS-related coronavirus strain SARS-CoV-1 in addition to efficient neutralization of different variants of SARS-CoV-2.

In yet another embodiment of the present invention, the antibody used as a source for sequences comprised in the antibody of the invention is TV1t4p3_H5. This antibody is able to efficiently cross-neutralize the SARS-related coronavirus strain SARS-CoV-1 in addition to efficient neutralization different variants of SARS-CoV-2.

According to one preferred embodiment, the light and heavy chain variable region sequences of the antibodies TV1t4p1_G7 and TV1t4p3_H5 described herein are as follows (CDRs marked in bold):

SEQ ID NO	Source	Sequence
17	Heavy chain variable domain TV1t4p1_G7	QVQLQESGLGLVKPSGTLSLTCAVS**GASISRNNW**WSWVRQSPG KGLEWLGE**IHHSGSAH**YNPSLQSRVTMSVDESKNQFSLILRSVTA ADTAVYFC**ASISGAFWD**WGQGTLVAVSS
18	Light chain variable domain TV1t4p1_G7	DIQMTQSPSSLSASVGDRVTITCRAS**QDISNS**LAWYQQKPGKAP NLLLY**ASST**LESGVPSRFSGRGSGTDFTLTITSLQPEDFATYYC**Q QYYGSTRT**FGQGTKVDIK
19	Heavy chain variable domain TV1t4p3_H5	QVQLQESGPGLVKPSGTLSLTCAVS**GASISRNNW**WTWVRQSPG KGLEWLGE**IHHSGSTH**YNPSLKSRVTMSVDESKNQFSLKLRSVT AADTAVYYC**ASISGALWD**WGLGTLVTVSS
20	Light chain variable domain TV1t4p3_H5	DIQMTQSPSSLSASVGDRVTITCRAS**QDISNS**LAWYQQKPGKAP NLLLY**ASST**LESGVPSRFSGRGSGTDFTLTITSLQPEDFATYYC**Q QYYGSTRT**FGQGTKVDIK

According to one embodiment of the present disclosure, the antibody has a heavy chain variable region amino acid sequence of antibody TV1t4p1_G7 (SEQ ID No. 17), or a heavy chain variable region amino acid sequence of antibody TV1t4p3_H5 (SEQ ID No. 19). According to an embodiment of the present invention, the antibody has a light chain variable region amino acid sequence of antibody TV1t4p1_G7 (SEQ ID No. 18), or a light chain variable region amino acid sequence of antibody TV1t4p3_H5 (SEQ ID No. 20).

According to a further embodiment, the antibody comprises a heavy chain variable region amino acid sequence of SEQ ID No. 17 and a light chain variable region amino acid sequence of SEQ ID No. 18, or the antibody comprises a heavy chain variable region amino acid sequence of SEQ ID No. 19 and a light chain variable region amino acid sequence of SEQ ID No. 20.

According to another embodiment, the antibody consists of two heavy chains of sequence SEQ ID NO. 17 and two light chains of sequence SEQ ID NO. 18, or the antibody consists of two heavy chains of sequence SEQ ID NO. 19 and two light chains of sequence SEQ ID NO. 20.

According to an embodiment, the CDR sequences of the light and heavy chain variable region sequences of the antibodies TV1t4p1_G7 and TV1t4p3_H5 described herein are as follows:

Source	CDR1	SEQ ID CDR1	CDR2	SEQ ID CDR2	CDR3	SEQ ID CDR3
Heavy chain variable domain TV1t4p1_G7	GASISRNNW	69	IHHSGSAH	70	ASISGAFWD	71
Light chain variable domain TV1t4p1_G7	QDISNS	72	ASST	73	QQYYGSTRT	74
Heavy chain variable domain TV1t4p3_H5	GASISRNNW	75	IHHSGSTH	76	ASISGALWD	77
Light chain variable domain TV1t4p3_H5	QDISNS	78	ASST	79	QQYYGSTRT	80

In one embodiment, the antibody or antigen-binding fragment thereof comprises the combination of the heavy chain CDR1 to CDR3 and the light chain CDR1 to CDR3 amino acid sequence of one antibody selected from the group comprising TV1t4p1_G7 (having a CDR-H1 amino acid sequence of SEQ ID No. 69, a CDR-H2 amino acid sequence of SEQ ID No. 70, a CDR-H3 amino acid sequence of SEQ ID No. 71, a CDR-L1 amino acid sequence of SEQ ID No. 72, a CDR-L2 amino acid sequence of SEQ ID No. 73, a CDR-L3 amino acid sequence of SEQ ID No. 74), and TV1t4p3_H5 (having a CDR-H1 amino acid sequence of SEQ ID No. 75, a CDR-H2 amino acid sequence of SEQ ID No. 76, a CDR-H3 amino acid sequence of SEQ ID No. 77, a CDR-L1 amino acid sequence of SEQ ID No. 78, a CDR-L2 amino acid sequence of SEQ ID No. 79, a CDR-L3 amino acid sequence of SEQ ID No. 80).

In general, the antibodies or antigen-binding fragments thereof as described herein further encompass antibody amino acid sequences being at least 80% identical to the sequences as defined above as long as they are still directed against the spike (S) protein of SARS-CoV-2 as in SEQ ID NO. 81, preferably as long as they are still directed against the receptor-binding domain (RBD) of the spike (S) protein of SARS-CoV-2 as in SEQ ID NO. 82.

According to one other embodiment, the specific sequence of the spike (S) protein of SARS-CoV-2 or the receptor-binding domain thereof against which the antibodies or antigen-binding fragments thereof should be directed may be taken from one of the commonly known SARS-CoV-2 variants Wu01, Alpha, Beta, Delta, BA.1, BA.2, BA.2.12.1, BA.4/5, BA.2.75, BA.2.75.2, BQ.1.1, BA.4.6, XBB.1, XBB.1.5, and BF.7.

According to one embodiment of the present invention, the antibody or antigen-binding fragment thereof according to the present invention does not display autoreactivity defined as detectable binding when tested against permeabilized HEp-2 cells using an antinuclear antibody (ANA) testing kit (NOVA-Lite HEp-2 ANA kit; Inova Diagnostics) at concentrations of 100 µg/ml of the antibody or antigen-binding fragment thereof.

The sequence variations encompassed herein are meant to include sequences having trivial mutations, i.e., conservative mutations, of the antibody amino acid sequence which do not interfere with structural folds and the affinity of the antibody to the spike (S) protein. Preferably, the deviations in the amino acid sequence leading to an at least 80%, 85%, 90% or 95% overall identity to the individualized sequences explicitly disclosed herein are present exclusively outside the CDR regions of the antibodies according to the invention. In particular, the present invention encompasses antibody amino acid sequences having 1, 2, 3, 4, 5, or 6 mutations within the constant regions of the antibody.

The antibodies according to the present invention are preferably of human origin. Thus, at least the sequences outside the CDRs, such as framework and constant regions of the antibody, are preferably of human origin or can be attributed to human origin. Furthermore, the antibodies of the present invention are preferably monoclonal.

In one preferred embodiment, the antibody is a monoclonal antibody or a fragment thereof that retains binding specificity and ability to neutralize infectious pathogen. In one preferred embodiment, the antibody is an IgG1, IgG2, IgG3, or IgG4 antibody. For example, the antibody may be an antibody comprising an Fc domain of any human IgG isotype (e.g. IgG1, IgG2, IgG3, or IgG4).

Optionally, the antigen-binding compound consists of or comprises a Fab, Fab', Fab'-SH, F(ab)2, Fv, a diabody, single-chain antibody fragment, or a multispecific antibody comprising multiple different antibody fragments.

Within the present invention, an antibody or antigen-binding fragment directed against the spike (S) protein of SARS-CoV-2 means an antibody binding to the spike (S) protein of SARS-CoV-2 with an at least 10-fold, more preferably at least 50-fold, particularly preferably at least 100-fold increased affinity compared to unrelated epitopes, proteins or protein regions.

It is a trivial task for a skilled person to determine if an antibody which exhibits a certain degree of identity is directed against the spike (S) protein of SARS-CoV-2 based on the above or the common general knowledge.

The determination of percent identity between two sequences is accomplished according to the present invention by using the mathematical algorithm of Karlin and Altschul (Proc. Natl. Acad. Sci. USA (1993) 90: 5873-5877). Such an algorithm is the basis of the BLASTN and BLASTP programs of Altschul et al. (J. Mol. Biol. (1990) 215: 403-410). BLAST nucleotide searches are performed with the BLASTN program. To obtain gapped alignments for comparative purposes, Gapped BLAST is utilized as described by Altschul et al. (Nucleic Acids Res. (1997) 25: 3389-3402). When utilizing BLAST and Gapped BLAST programs, the default parameters of the respective programs are used.

According to a preferred embodiment of the present invention, antibody amino acid sequences form part of the invention which consist of or comprise a nucleic acid sequence being at least 85% identical to the sequences defined above and disclosed herein, more preferably at least 90% identical, even more preferred at least 95% identical.

According to a preferred embodiment of the present invention, the SARS-related coronavirus strain is severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which may alternatively be referred to as SARS-related coronavirus 2 in the art. According to another preferred embodiment of the present invention, the SARS-related coronavirus strains are severe acute respiratory syndrome coronavirus (SARS-CoV or SARS-CoV-1) or the Bat SARS-like coronavirus WIV-1, preferably the severe acute respiratory syndrome coronavirus (SARS-CoV or SARS-CoV-1).

According to another preferred embodiment of the invention, the antibody or antigen-binding fragment thereof is directed against the ectodomain of the spike (S) protein of SARS-CoV-2.

According to a more preferred embodiment of the present invention, the antibody or antigen-binding fragment thereof is directed against the Wu01 spike (S) homotrimer of SARS-CoV-2 as described in Hoffmann M. et al. (2020). Cell 181, 271–280 (EPI_ISL_406716. This virus isolate has been studied intensively and is best understood at the time of filing.

However, preferably, the antibody or antigen-binding fragment thereof should also be directed against equivalent sequences of other virus variants. According to one specific embodiment, the antibody or antigen-binding fragment thereof is directed against the receptor-binding domain (RBD) of the spike (S) protein of SARS-CoV-2 (SEQ ID NO. 82).

According to a preferred embodiment of the present invention, the antibody or antigen-binding fragment thereof does not display autoreactivity against human cells defined as a detectable binding pattern when tested against permeabilized HEp-2 cells using an antinuclear antibody (ANA) testing kit (NOVA-Lite HEp-2 ANA kit; Inova Diagnostics) at concentrations of 100 µg/ml of the antibody or antigen-binding fragment thereof. Alternatively, preferably, other assays known in the art may be used to determine or exclude autoreactivity of antibodies or antigen-binding fragments thereof.

In the description of the present application, antibody designations may be used. It is pointed out that the antibodies consist of heavy and light chains which also form part of the present description. If reference is made to an antibody by its designation or to a SEQ ID NO., it should be understood that these ways of reference are interchangeable.

The present invention further relates to a pharmaceutical composition comprising an antibody or antigen-binding fragment thereof according to the invention as defined and further described herein and at least one pharmaceutically acceptable excipient. In one aspect, the pharmaceutical composition is a vaccination composition for a human and/or animal subject. In another aspect, the pharmaceutical composition is capable of conferring passive immunity against SARS-CoV-2 to a subject, preferably a human subject.

The present invention also encompasses a kit comprising an antibody or antigen-binding fragment thereof according to the invention as defined and further described herein and a container.

In one aspect, the present invention is also directed to the antibody or antigen-binding fragment thereof according to the invention as defined and further described herein, the pharmaceutical composition as described herein and the kit for use as a medicament, preferably for use as a vaccine.

In another aspect, the antibody or antigen-binding fragment thereof according to the invention as defined and further described herein, the pharmaceutical composition as described herein and the kit as described herein are provided for use in conferring passive immunity to a subject and/or provided for use in the form of a composition capable of conferring passive immunity to a subject.

In another aspect, the present invention is also directed to the antibody or antigen-binding fragment thereof according to the invention as defined and further described herein, the pharmaceutical composition as described herein and the kit for use in the treatment or prevention of a disease caused by SARS-related coronavirus in human or animal subjects, preferably for use in the treatment or prevention of a disease caused by SARS-related coronavirus 2 (SARS-CoV-2) in human or animal subjects.

In one aspect, the present invention is directed to the antibody or antigen-binding fragment thereof according to the invention as defined and further described herein, the pharmaceutical composition as described herein and the kit for use in prevention of infection of a human and/or animal subject with SARS-related coronavirus, preferably of infection of a human and/or animal subject with SARS-related coronavirus 2 (SARS-CoV-2).

In another aspect, the present invention is directed to a method of treating or preventing a SARS-related coronavirus infection or reducing the severity of disease in a human and/or animal subject comprising administering a therapeutically effective amount of at least one antibody and/or antigen-binding fragment thereof as described herein to said subject, preferably wherein the SARS-related coronavirus is SARS-CoV-2.

In one aspect of the invention, an antibody and/or antigen-binding fragment thereof according to the invention is administered to a patient in need thereof by intravenous injection or infusion, subcutaneous injection, intramuscular injection, or inhalative application, preferably by intravenous injection.

In a preferred embodiment, the antibody or antigen-binding fragment thereof is administered by intravenous infusion at an absolute dose of up to 4000 mg, preferably up to 2000 mg, more preferably up to 1200 mg, even more preferably up to 600 mg, even more preferably up to 300 mg, particularly preferably up to 150 mg.

The dosage of an antibody or antigen-binding fragment thereof of the invention to be administered to a subject can further vary depending on such things as the severity of the symptoms exhibited as well as the age, sex, and health of the subject.

In another aspect of the invention, an antibody according to the invention is administered to a patient in need thereof by inhalative application. In a preferred embodiment, the antibody is administered by

inhalative application, wherein it is provided in a liquid pharmaceutical composition which is nebulized by a mesh nebulizer or a jet nebulizer prior to administration.

A pharmaceutical composition of the invention is formulated to be compatible with its intended route of administration. Examples of routes of administration include, but are not limited to, parenteral, e.g., intravenous, intradermal, subcutaneous, oral, intranasal (e.g., inhalation and inhaled through the mouth), transdermal (e.g., topical), transmucosal, and rectal administration.

In a specific embodiment, the composition is formulated in accordance with routine procedures as a pharmaceutical composition adapted for intravenous, subcutaneous, intramuscular, oral, intranasal, or topical administration to human beings. Typically, compositions for intravenous administration are solutions in sterile isotonic aqueous buffer. Where necessary, the composition may also include a solubilizing agent and a local anesthetic such as lignocaine to ease pain at the site of the injection.

The methods of the invention may comprise pulmonary administration, e.g., by use of an inhaler or nebulizer, of a composition formulated with an aerosolizing agent. See, e.g., U.S. Pat. Nos. 6,019,968, 5,985,320, 5,985,309, 5,934,272, 5,874,064, 5,855,913, 5,290,540, and 4,880,078; and PCT Publication Nos. WO 92/19244, WO 97/32572, WO 97/44013, WO 98/31346, and WO 99/66903, each of which is incorporated herein by reference their entireties.

The methods of the invention may also comprise administration of a composition formulated for parenteral administration by injection (e.g., by bolus injection or continuous infusion). The pharmaceutical formulation of the present invention may be provided in liquid form or may be provided in lyophilized form.

In one aspect, the present invention relates to a nucleic acid encoding an antibody or antigen-binding fragment thereof as described herein. In another aspect, the present invention relates to an expression vector comprising the nucleic acid as described herein in functional association with an expression control sequence.

In another aspect, the present invention relates to a host cell comprising a nucleic acid as described herein. In one aspect, the present invention relates to a host cell comprising an expression vector as described herein.

In another aspect, the present invention relates to a method of production of an antibody or antigen-binding fragment as described herein, comprising (a) cultivating a host cell as described herein under

conditions allowing expression of the antibody or antigen-binding fragment thereof, and (b) recovering the antibody or antigen-binding fragment thereof.

In another embodiment, the present invention relates to an antibody or antigen-binding fragment thereof against SARS-related coronavirus 2 (SARS-CoV-2) as described herein for use in medicine in combination with at least one further antibody directed against SARS-related coronavirus 2 (SARS-CoV-2), wherein said further antibody has a different binding specificity.

In another aspect, the present invention is also directed to the use of the antibody or antigen-binding fragment thereof according to the invention or a pharmaceutical composition of the invention in the manufacture of a medicament for treatment of a disease caused by SARS-related coronavirus in human or animal subjects, preferably for treatment or prevention of COVID-19 in human or animal subjects.

All embodiments of the present invention as described and/or claimed herein are deemed to be combinable within the present invention in any combination, unless the skilled person considers such a combination to not make any technical sense or to be excluded by contradiction.

Examples

Study subjects and sample collection

Samples were obtained under study protocols 16-054 and 20-1187 (approved by the Ethics Commission of the Medical Faculty of the University of Cologne). All participants provided written informed consent. 250 ml blood were drawn into heparin-filled syringes. Plasma and PBMCs were isolated by density gradient centrifugation (Histopaque, Sigma Aldrich) as advised in the manufacturer's instructions. Plasma aliquots were stored at -80°C and PBMCs at -150°C in 10% DMSO (Sigma-Aldrich) and 90% (v/v) FBS (Sigma-Aldrich).

Cell lines

FreeStyle Expression Medium (Thermo Fisher) containing 0.2% Penicillin-Streptomycin (Gibco) was used for maintenance of HEK-293-6E cells (National Research Council Canada, file 11565). Cells were incubated in a shaking incubator at 110 rpm, 37°C and 6% CO_2. HEK-293T-ACE2 cells were maintained in T75 tissue culture flasks (Sarstedt) with DMEM (Gibco) containing 10% FBS (Sigma

Aldrich), 1 mM L-Glutamine (Gibco), 1 mM Sodium pyruvate (Gibco) and 1% Penicillin-Streptomycin (Gibco) at 37°C and 5% CO_2.

B cell isolation

B cells were isolated from PBMCs through use of magnetic CD19 microbeads (Miltenyi Biotec) and subsequently stained with anti-CD20-Alexa700, anti-IgG-PE, DAPI, and labeled SARS-CoV-2 spike protein in FACS buffer (PBS with 2% FCS and 0.1% 0.5 M EDTA) for 20 min at 4°C in the dark. Spike binding was determined by a double-staining with Wu01 spike protein marked with DyLight 488 and DyLight 650 (DyLight Antibody Labeling Kit, Thermo Fisher) for time points 1 and 2. For time point 3 and 4, a double-staining with Wu01 (DyLight 480) and BA.1 and BA.2 (both DyLight 650) was used. Single cells were sorted using a FACSAria Fusion cell sorter (BD) into 96 well plates containing 4 µl of lysis buffer per well consisting of 0.5x PBS (Gibco), 0.5 U/µl RNAsin (Promega), 0.5 U/µl RNaseOUT (Thermo Fisher), and 10 mM DTT. Plates with sorted cells were stored at -80°C.

Antibody heavy and light chain gene amplification and sequence analysis

Heavy and light chain genes of sorted B cells were amplified using a single-cell PCR protocol previously described. Following cell lysis, Superscript IV reverse transcriptase (Thermo Fisher), random hexamer primers (Invitrogen), RNasin (Promega), and RNaseOUT (Thermo Fisher) were used to create cDNA from RNA. The cDNA formed the template for following heavy and light chain amplification through semi-nested PCR with PlatinumTaq HotStart DNA polymerase (Thermo Fisher), V gene-specific forward primer mixes, reverse primers, and KB extender. Quality check of PCR products was ensured with gel electrophoresis. Afterwards, Sanger sequencing was performed and quality control passing sequences (chromatograms with mean Phred scores of at least 28 and length of at least 240 nucleotides) were annotated with IgBLAST. Sequences were trimmed to variable gene section (FWR1 to end of J gene). Sequences containing variable domains with more than 15 base calls with Phred scores below 16, frame shift mutations, or stop codons were excluded. Clonal groups were identified by identical V, D, and J gene usage and at least 75% amino acid identity within the CDRH3 region as described previously.

Cloning for production of monoclonal antibodies

Sequences of the single-cell PCR products were used to order double-stranded DNA fragments (eBlocks, IDT DNA) for antibody production. Expression vector overhangs were added to the DNA fragments to enable sequence- and ligation-independent cloning (SLIC). DNA fragments were

inserted into human antibody expression vectors (IgG1 heavy-, kappa-, or lambda chain) as previously published. 25 ng eBlock DNA fragment was added to 80 ng cut vector for heavy, kappa, or lambda chain and 0.2 µl T4 DNA polymerase (3,000 units/ml) in NEBuffer 2.1. This mix was incubated for 2:30 min at 24 °C and then for at least 10 min on ice. The product of the SLIC reaction was used to transform DH5α competent bacteria.

Production of monoclonal antibodies (24 well format)

Monoclonal antibodies were produced in a 24 well format and transfection supernatant used for further assays without purification. 1.25 µg of each heavy and light chain plasmid were mixed with branched polyethylenimine (PEI, Sigma Aldrich) to transfect 2.5 ml HEK-293-6E cells (cell density 0,8x10/ml) in a 24 well plate (Sarstedt). HEK-293-6E cells were cultured in FreeStyle 293 Expression Medium (Gibco) containing 0.2% Penicillin + Streptomycin (Gibco). After 7 days in New Brunswick S41i incubator shaking at 250 rpm (37°C and 6% CO_2), plates were centrifuged for 5 min at 400 g (4°C) and transfection supernatant was harvested.

Quantification of IgG in transfection supernatants by ELISA

96 well ELISA plates (Greiner) were coated with 2.5 µg/ml anti-IgG (Jackson Immunoresearch, AffiniPure Goat Anti-Human IgG) in PBS at 4°C over night. All following steps were performed at RT. Plates were washed with PBS (Gibco) containing 0.05% Tween (Carl Roth) before blocking with PBS 5% milk (Panreac AppliChem, nonfat dried milk powder) for one hour. After another washing step, transfection supernatant was added with a 1:20 dilution as the highest concentration and subsequent 1:3 dilutions in PBS 5% milk. IgG1 kappa from human myeloma plasma (Sigma-Aldrich) was used as a standard with a starting concentration of 4 µg/ml. After incubation for 1.5 h, plates were washed. Goat Anti-Human IgG-HRP (Southern Biotech) was added as a secondary antibody in a 1:2500 dilution in PBS 5% milk. One hour later, plates were washed again and ABTS Solution (Life Technologies) was used as a substrate for readout at 415 nm with reference at 695 nm with a TECAN Microplate Reader (Software XFlour4). IgG concentrations in transfection supernatants were calculated relating the measured OD values of sample and standard.

Detection of spike-binding IgG by ELISA

Greiner flat bottom 96 well plates were coated with 2 µg/ml SARS-CoV-2 trimeric spike protein (Wu01 and BA.1 HexaPro protein as described below). After incubation at 4°C over night, plates were washed with PBS (Gibco) containing 0.05% Tween (Carl Roth) before blocking with PBS 5% milk

(Panreac AppliChem, nonfat dried milk powder) for one hour at RT. All following steps were performed at RT. Plates were washed and transfection supernatants adjusted to a starting concentration of 10 µg/ml were added in a 1:5 dilution series. An antibody with known spike reactivity was used as a positive control. As a negative control, an HIV-reactive antibody was used. After 1.5 h incubation, plates were washed and 1:2500 Goat Anti-Human IgG-HRP (Southern Biotech) in 5% milk was added for one hour. After washing, ABTS Single Solution (Life Technologies) was added as a substrate and the signal was measured at 415 nm with reference at 695 nm using a TECAN Microplate Reader (Software XFlour4).

Detection of spike RBD-binding IgG by chemiluminescent microparticle immunoassay (CMIA)

IgG targeting the receptor binding domain (RBD) of the spike protein was quantified by the chemiluminescent microparticle immunoassay (CMIA) SARS-CoV-2 IgG II Quant (Abbott) on the automated system Alinity i (Abbott). Anti-RBD IgG titers were reported in binding antibody unit per milliliter (BAU/mL), according to the World Health Organization (WHO) international standard.

Production of monoclonal antibodies (50 ml format) and purification

A 50 ml transfection format was applied for antibodies presenting good Omicron neutralization activity in screening with 24 well transfection supernatant. 25 µg heavy chain and 25 µg light chain plasmids were combined with 2.25 ml DPBS (Gibco). 170 µl polyethylenimine (PEI, Sigma Aldrich) were added. Vortexing the mix was followed by 10 min incubation at RT. The transfection solution was added dropwise to 50 ml HEK-293-6E cells (density 0.8x10/ml) in culture flasks. After 7 days shaking at 37°C and 6% CO_2, plates were centrifuged at 4000 rpm at 4°C for 25 min. The supernatant was incubated with Protein G Sepharose (GE Life Sciences) at 4°C over night rotating. Then, antibodies bound to Sepharose beads were isolated using chromatography columns (Bio-Rad). Elution was done with 4.5 ml 0.1 M Glycin pH 3 into 0.5 ml 1M Tris HCl pH 8. Antibody enrichment and buffer exchange to PBS was performed using 30 kD Amicon membranes (Millipore).

Production of SARS-CoV pseudovirus particles

Pseudovirus particles were produced by cell transfection with plasmids coding for HIV-1 Tat, HIV-1 Gag/Pol, HIV-1 Rev, luciferase followed by an IRES and ZsGreen, and the SARS-CoV-2 spike protein as previously described. After transfection of HEK-293T cells with the pseudovirus encoding plasmids using FUGENE 6 Transfection Reagent (Promega) and incubation for 48 h and 72 h at 37°C and 5% CO_2, supernatant was harvested and stored at -80°C. The virus batches were titrated and used for

infection of HEK-293T-ACE2 cells. Luciferase activity was measured after incubation for 48 h at 37°C and 5% CO_2 by addition of luciferin/lysis buffer (10 mM MgCl2, 0.3 mM ATP, 0.5 mM Coenzyme A, 17 mM IGEPAL (all Sigma-Aldrich), and 1 mM D-Luciferin (GoldBio) in Tris-HCL) and read-out in a microplate reader (Berthold Technologies, Tristar 2). Batches showing around 1000-fold higher RLUs in contrast to non-infected cells were accepted for further use in assays.

Pseudovirus assay to determine IgG and plasma SARS-CoV-2 neutralizing activity

Pseudovirus neutralization assays were done as previously published. Transfection supernatants containing monoclonal antibodies were directly used in this assay without prior purification. Plasma was heat-inactivated for 45 min at 56°C. For one hour (37°C and 5% CO_2), a dilution series of each sample was incubated with the pseudovirus supernatants from the HEK-293T transfection in DMEM high glucose medium (Gibco, with 10% FBS, 1 mM L-Glutamine, 1 mM Sodium pyruvate, 1% Penicillin-Streptomycin) in 96 well plates. Afterwards, 1.25x10HEK-293T-ACE2 cells were added to each well and plates were incubated for 48 h, 37°C, 5% CO_2. Luciferase activity was measured after addition of luciferin-containing lysis buffer (10 mM MgCl2, 0.3 mM ATP, 0.5 mM Coenzyme A, 17 mM IGEPAL (all Sigma-Aldrich), and 1 mM D-Luciferin (GoldBio) in Tris-HCL) in relative luminescence units (RLUs) using a Tristar 2 reader (Berthold Technologies). Untreated virus control wells (without antibodies) were used on every plate to show the range of RLUs, same as negative controls (virus only and cells only). The mean value of these negative controls was determined as background activity and subtracted from sample values to calculate IC_{50} values (IgG concentration leading to 50% RLU reduction) and ID_{50} values (plasma dilution that achieves 50% RLU reduction) via dose response curves using GraphPad Prism 7.0. A summary of the results obtained with the antibodies of the invention is shown in Figure 4.

Cloning of SARS-CoV-2 spike variants for protein production

The different spike versions were amplified by PCR from synthetic gene plasmids and cloned into our modified Sleeping Beauty transposon expression vector. SARS-CoV-2 HexaPro spike trimer: MN908947, A.A. 16-1208, RRAR to GSAS, F817P, A892P, A899P, A942P, K986P, V987P, N-terminal BM40 signal peptide, C-terminal T4 foldon followed by a Twin strep tag, 139 kDa; SARS-CoV-2 HexaPro BA.1 spike trimer: MN908947, A.A. 16-1208, furin site: RRAR to GSAS, A76V, delta69-70, T95I, G142D, delta143-145, N211I, delta212, 215EPEins, G339D, S371L, S373P, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493R, G496S, Q498R, N501Y, Y505H, T547K, D614G, H655Y, N679K, P681H, N764K, D796Y, N856K, Q954H, N969K, L981F, including the stabilizing mutations: F817P, A892P, A899P, A942P, K986P, V987P, N-terminal BM40 signal

peptide, C-terminal T4 foldon followed by a Twin strep tag, 139 kDa; SARS-CoV-2 HexaPro BA.2 spike trimer: MN908947, A.A. 16-1208, furin site: RRAR to GSAS, T19I, L24S, 25PPAins, G142D, V213G, G339D, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, S477N, T478K, E484A, Q493R, Q498R, N501Y, Y505H, D614G, H655Y, N679K, P681H, N764K, D796Y, Q954H, N969K, including the stabilizing mutations: F817P, A892P, A899P, A942P, K986P, V987P, N-terminal BM40 signal peptide, C-terminal T4 foldon followed by a Twin strep tag, 139 kDa. For recombinant protein production, stable HEK293 EBNA cell lines were generated employing the sleeping beauty transposon system.

The expression constructs (2 µg) were co-transfected with the transposase plasmid (10:1) into HEK293 EBNA cells, and after stringent puromycin selection (3 mg/mL; Sigma), cells were transferred into triple flasks and protein production was induced by the addition of doxycycline (0.5 mg/mL, Sigma). Supernatants of confluent cultures were harvested every 3 days, filtered and the different spike proteins purified by applying it to Strep-TactinXT (IBA Lifescience, Goettingen, Germany) resin. Proteins, after intensive high salt washes, were eluted with biotin-containing TBS-buffer (IBA Lifescience, Goettingen, Germany), dialyzed against TBS-buffer, and analyzed on an SDS-gel by Coomassie brilliant blue staining. The spike proteins were stored as aliquots at -80°C.

Quantification and statistical analysis

Flow cytometry analysis and quantifications were done with FlowJo10. Statistical analyses were done with GraphPad Prism (v10), Microsoft Excel for Mac (v16), and Python (v3).

Claims

1. Antibody or antigen-binding fragment thereof directed against SARS-related coronavirus, wherein the antibody or antigen-binding fragment thereof comprises the combination of the heavy chain CDR1 to CDR3 and the light chain CDR1 to CDR3 amino acid sequence of one antibody selected from the group comprising:

TV1t4p2_A5 (having a CDR-H1 amino acid sequence of SEQ ID No. 27, a CDR-H2 amino acid sequence of SEQ ID No. 28, a CDR-H3 amino acid sequence of SEQ ID No. 29, a CDR-L1 amino acid sequence of SEQ ID No. 30, a CDR-L2 amino acid sequence of SEQ ID No. 31, a CDR-L3 amino acid sequence of SEQ ID No. 32),

TV1t2p6_D3 (having a CDR-H1 amino acid sequence of SEQ ID No. 33, a CDR-H2 amino acid sequence of SEQ ID No. 34 a CDR-H3 amino acid sequence of SEQ ID No. 35 a CDR-L1 amino acid sequence of SEQ ID No. 36 a CDR-L2 amino acid sequence of SEQ ID No. 37, a CDR-L3 amino acid sequence of SEQ ID No. 38),

TV1t4p3_E8 (having a CDR-H1 amino acid sequence of SEQ ID No. 21, a CDR-H2 amino acid sequence of SEQ ID No. 22, a CDR-H3 amino acid sequence of SEQ ID No. 23, a CDR-L1 amino acid sequence of SEQ ID No. 24, a CDR-L2 amino acid sequence of SEQ ID No. 25, a CDR-L3 amino acid sequence of SEQ ID No. 26), and

TV1t3p4_E1 (having a CDR-H1 amino acid sequence of SEQ ID No. 39, a CDR-H2 amino acid sequence of SEQ ID No. 40, a CDR-H3 amino acid sequence of SEQ ID No. 41, a CDR-L1 amino acid sequence of SEQ ID No. 42, a CDR-L2 amino acid sequence of SEQ ID No. 43, a CDR-L3 amino acid sequence of SEQ ID No. 44).

2. Antibody or antigen-binding fragment thereof according to claim 1, wherein the antibody or antigen-binding fragment thereof comprises the combination of the heavy chain variable region amino acid sequence and of the light chain variable region amino acid sequence of one antibody selected from the group comprising:

TV1t4p2_A5 (having the heavy chain variable region amino acid sequence of SEQ ID No. 3 and the light chain variable region amino acid sequence of SEQ ID No. 4),

TV1t2p6_D3 (having the heavy chain variable region amino acid sequence of SEQ ID No. 5 and the light chain variable region amino acid sequence of SEQ ID No. 6),

TV1t4p3_E8 (having the heavy chain variable region amino acid sequence of SEQ ID No. 1 and the light chain variable region amino acid sequence of SEQ ID No. 2), and

TV1t3p4_E1 (having the heavy chain variable region amino acid sequence of SEQ ID No. 7 and the light chain variable region amino acid sequence of SEQ ID No. 8).

3. Antibody or antigen-binding fragment thereof according to claim 1 or 2, wherein the amino acid sequences comprised are of one antibody selected from the group comprising TV1t4p2_A5, TV1t2p6_D3, and TV1t4p3_E8, preferably of one antibody from the group comprising TV1t4p2_A5 and TV1t2p6_D3, more preferably of antibody TV1t4p2_A5.

4. Antibody or antigen-binding fragment thereof according to any one of claims 1 to 3, wherein the amino acid sequences comprised are of the antibody TV1t4p2_A5.

5. Antibody or antigen-binding fragment thereof according to any one of claims 1 to 3, wherein the amino acid sequences comprised are of the antibody TV1t4p3_E8.

6. Antibody or antigen-binding fragment thereof according to any one of claims 1 to 5, wherein the SARS-related coronavirus strain is severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

7. Antibody or antigen-binding fragment thereof according to any one of claims 1 to 6, wherein the amino acid sequences of the variable regions or of the CDRs comprised therein are from an antibody which is able to neutralize each of the SARS-CoV-2 lineages Wu01, Alpha, Beta, Delta, BA.1, BA.2, BA.2.12.1, BA.4/5, BA.2.75, BA.2.75.2, BQ.1.1, BA.4.6, XBB.1, XBB.1.5, and BF.7 in a pseudovirus neutralization assay as described in the description with an IC_{50} of at most 0.07 µg/ml, preferably at most 0.06 µg/ml, more preferably at most 0.05 µg/ml, even more preferably at most 0.04 µg/ml, even more preferably at most 0.03 µg/ml, particularly preferably at most 0.025 µg/ml.

8. Pharmaceutical composition comprising an antibody or antigen-binding fragment thereof according to any one of claims 1 to 7 and at least one pharmaceutically acceptable excipient, preferably wherein the pharmaceutical composition is a vaccination composition for a human subject.

9 Kit comprising an antibody or antigen-binding fragment thereof according to any one of claims 1 to 7 and a container.

10 Antibody or antigen-binding fragment thereof according to any one of claims 1 to 7, pharmaceutical composition according to claim 8, or kit according to claim 9 for use as a medicament.

11. Antibody or antigen-binding fragment thereof according to any one of claims 1 to 7, pharmaceutical composition according to claim 8, or kit according to claim 9 for use as a vaccine.

12, Antibody or antigen-binding fragment thereof according to any one of claims 1 to 7, pharmaceutical composition according to claim 8, or kit according to claim 9 for use in the treatment or prevention of a disease caused by SARS-related coronavirus in human subjects, preferably for use in the treatment or prevention of a disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in human subjects.

13. Antibody or antigen-binding fragment thereof according to any one of claims 1 to 7, pharmaceutical composition according to claim 8, or kit according to claim 9 for use in prevention of infection of a human subject with SARS-related coronavirus, preferably of infection of a human subject with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

14 Antibody or antigen-binding fragment thereof for use according to any one of claims 10 to 13, wherein the antibody or antigen-binding fragment thereof is administered by intravenous infusion, by inhalative application, by subcutaneous injection or intramuscular injection, preferably wherein the antibody or antigen-binding fragment thereof is administered at an absolute dose of up to 4000 mg, preferably up to 2400 mg, more preferably up to 1200 mg, even more preferably up to 600 mg, even more preferably up to 300 mg, particularly preferably up to 150 mg.

15. Nucleic acid encoding an antibody or antigen-binding fragment thereof according to any of claims 1 to 7.

16 An expression vector comprising the nucleic acid of claim 15 in functional association with an expression control sequence.

17. Host cell comprising a nucleic acid according to claim 15 or the expression vector according to claim 16.

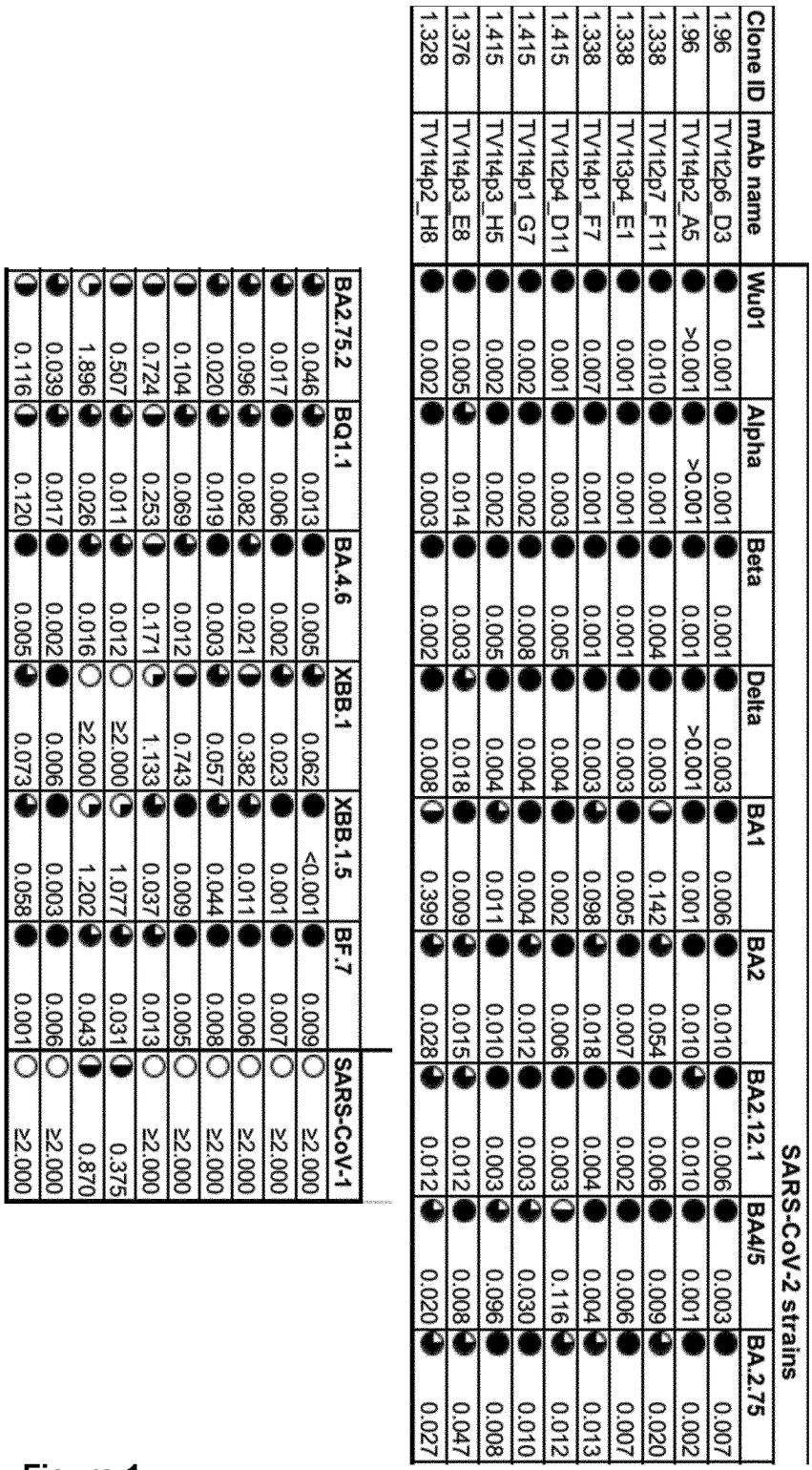
18. Method of production of an antibody or antigen-binding fragment thereof according to any one of claims 1 to 7, comprising

(a) cultivating the host cell of claim 17 under conditions allowing expression of the antibody or antigen-binding fragment thereof, and

(b) recovering the antibody or antigen-binding fragment thereof.

19. The antibody of any of claims 1 to 7 for use in medicine in combination with at least one further antibody directed against SARS-related coronavirus 2 (SARS-CoV-2), wherein said further antibody has a different binding specificity.

Figures



Clone ID	mAb name	SARS-CoV-2 strains										
		Wu01	Alpha	Beta	Delta	BA1	BA2	BA2.12.1	BA4/5	BA.2.75	BA2.75.2	BQ1.1	BA.4.6	XBB.1	XBB.1.5	BF.7	SARS-CoV-1
1.96	TV1t2p6_D3	0.001	0.001	0.001	0.003	0.006	0.010	0.006	0.003	0.007	0.046	0.013	0.005	0.062	<0.001	0.009	≥2.000
1.96	TV1t4p2_A5	>0.001	>0.001	0.001	>0.001	0.001	0.010	0.010	0.001	0.002	0.017	0.006	0.002	0.023	0.001	0.007	≥2.000
1.338	TV1t2p7_F11	0.010	0.001	0.004	0.003	0.142	0.054	0.006	0.009	0.020	0.096	0.082	0.021	0.382	0.011	0.006	≥2.000
1.338	TV1t3p4_E1	0.001	0.001	0.001	0.003	0.005	0.007	0.002	0.006	0.007	0.020	0.019	0.003	0.057	0.044	0.008	≥2.000
1.338	TV1t4p1_F7	0.007	0.001	0.001	0.003	0.098	0.018	0.004	0.004	0.013	0.104	0.069	0.012	0.743	0.009	0.005	≥2.000
1.415	TV1t2p4_D11	0.001	0.003	0.005	0.004	0.002	0.006	0.003	0.116	0.012	0.724	0.253	0.171	1.133	0.037	0.013	≥2.000
1.415	TV1t4p1_G7	0.002	0.002	0.008	0.004	0.004	0.012	0.003	0.030	0.010	0.507	0.011	0.012	≥2.000	1.077	0.031	0.375
1.415	TV1t4p3_H5	0.002	0.002	0.005	0.004	0.011	0.010	0.003	0.096	0.008	1.896	0.026	0.016	≥2.000	1.202	0.043	0.870
1.376	TV1t4p3_E8	0.005	0.014	0.003	0.018	0.009	0.015	0.012	0.008	0.047	0.039	0.017	0.002	0.006	0.003	0.006	≥2.000
1.328	TV1t4p2_H8	0.002	0.003	0.002	0.008	0.399	0.028	0.012	0.020	0.027	0.116	0.120	0.005	0.073	0.058	0.001	≥2.000

Figure 1

mAb name	SARS-CoV-2 strains										
	Wu01	Alpha	Beta	Delta	BA.1	BA.2	BA.2.12.1	BA.4/5	BA.2.75	BA.2.75.2	BQ1.1	BA.4.6	XBB.1	XBB.1.5	BF.7
SP1-77	0,013	0,029	0,006	0,031	0,005	0,014	0,006	0,016	0,009	2,000	2,000	2,000	2,000	2,000	2,000
TV1t4p2_A5	0,001	0,002	0,002	0,003	0,003	0,003	0,002	0,008	0,001	0,002	0,020	0,002	0,095	0,003	0,002
TV1t4p3_E8	0,008	0,009	0,009	0,014	0,005	0,007	0,005	0,013	0,013	0,023	0,029	0,005	0,027	0,004	0,007

Figure 2