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(57) Abstract: The present invention relates to antibodies capable of binding to the spike protein of coronavirus SARS-CoV-2, and methods and uses thereof in the prevention, treatment and/or diagnosis of coronavirus infections, and diseases and/or complications associated with coronavirus infections, including COVID-19.

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ANTIBODIES

Field of invention

The invention relates to antibodies useful for the prevention, treatment and/or diagnosis of coronavirus infections, and diseases and/or complications associated with coronavirus infections, including COVID-19.

Background of the invention

Since emerging in late 2019 severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is estimated to have led to 757 million infections and 6.9 million deaths. Effective vaccines and increasing herd immunity from natural infection have greatly reduced the mortality from SARS-CoV-2 infection but are less effective at preventing infection. SARS-CoV-2 therefore still causes significant mortality in high-risk groups such as the immunosuppressed or elderly who show reduced or absent responses to vaccination.

To date, two domains of the S1 region of spike, the N-terminal domain (NTD) and the receptor binding domain (RBD), have been described as binding sites for potent neutralizing mAbs. Most potent anti-RBD mAbs bind on or in close proximity to the receptor binding motif (Yuan, *et al. Science* **369**, 1119-1123 (2020)), a small 25 amino acid patch that lies at the tip of the RBD. mAbs binding here mediate neutralization by blocking binding of S to the SARS-CoV-2 cellular receptor angiotensin converting enzyme 2 (ACE-2). A second group of antibodies, exemplified by S309, bind on or around the N-linked glycan at residue N453, these do not block interaction with ACE2 and may function to destabilize the S-trimer. Potent anti-NTD mAbs bind to a so-called supersite on the NTD, do not block ACE2 interaction and their mechanism of action is not well understood. All commercially developed mAbs to date target the RBD (Westendorf *et al. Cell Rep* 39, 110812 (2022); Weinreich *et al. N Engl J Med* 384, 238-251 (2021); Dong, *et al. bioRxiv* (2021)), whilst anti-NTD mAbs are frequently SARS-CoV-2 variant specific because of the extensive mutation of the supersite between variants.

Both RBD and NTD are hot spots of mutation in SARS-CoV-2. RBD mutations can impart selective advantages to the virus, firstly some can increase the affinity to ACE2 and are believed to drive increased transmissibility, the N501Y mutation found in the Alpha variant is an example of this. Secondly, mutations in the RBD and NTD may also

lead to escape from neutralizing antibody responses. As herd immunity from vaccination and natural infection increases there is intense selective pressure to allow the virus to break through pre-existing immunity. Evolution of S has therefore been rapid with many mutations mapping closely to the sites of interaction of potent mAbs in the RBD and NTD. SARS-CoV-2, in a period of 3 years since its emergence, evolved variants that escape all mAbs that have been developed for clinical use. The arrival of Omicron in late 2021 caused often profound drops in neutralization titres in serum from vaccinees and from natural infection, leading Omicron to spread globally with a large wave of infection and become the dominant variant in a matter of weeks, since when it has dominated.

However, Omicron has continued to evolve rapidly, BA.1 was replaced by BA.1.1 and BA.2 which were in turn been replaced by BA.4/5, BA.4.6 and BF.7. Since late 2022, an increasing number of BA.2 sub-variants have begun to cocirculate, with convergent evolution leading to the acquisition of subsets of common mutations in related variants. Currently XBB.1.5 and CH.1.1 are the dominant strains, with frequently several strains cocirculating such as XBF, BQ.1.1, BF.7, showing large differences in frequency in different geographical locations.

Therefore, it is an object of the invention to identify further and improved antibodies useful for preventing, treating and/or diagnosing coronavirus infections, and diseases and/or complications associated with coronavirus infections (e.g. COVID-19), especially those caused by the Omicron variants of concern (VoCs) and variants having further mutations in the spike protein of SARS-CoV-2.

Summary of the invention

The inventors have identified 24 potent spike binding mAbs (IC50 < 50 ng/ml) from vaccinees who suffered vaccine break-through infections with Omicron sublineages BA.4/5. One mAb, BA.4/5-2, binds at the back of the left shoulder of the RBD in an area which is so far not in a mutational hot spot.

Accordingly, the invention provides an antibody capable of binding to the spike protein of coronavirus SARS-CoV-2, wherein the antibody comprises the six CDRs of antibody BA.4/5-2 described herein, or of any one of the antibodies in Tables 1 and 3 to 9 as described herein.

In a further embodiment, the invention provides an antibody capable of binding to the spike protein of coronavirus SARS-CoV-2, wherein the antibody comprises CDRH1, CDRH2 and CDRH3, from a first antibody in Table 1 and CDRL1, CDRL2 and CDRL3

from a second antibody in Table 1, with the proviso that the first antibody and the second antibody are different.

In a further embodiment, the invention provides one or more polynucleotides encoding the antibody, one or more vectors comprising said polynucleotides, or a host cell comprising said vectors.

In a further embodiment, the invention provides a method for producing an antibody that is capable of binding to the spike protein of coronavirus SARS-CoV-2, the method comprising culturing the host cell and isolating the antibody from said culture.

In a further embodiment, the invention provides a pharmaceutical composition comprising: (a) the antibody, and (b) at least one pharmaceutically acceptable diluent or carrier.

In a further embodiment, the invention provides the antibody or the pharmaceutical composition for use in a method for treatment of a human or animal by therapy, or for use in a method of treating or preventing coronavirus infection, or a disease or complication associated with coronavirus infection.

In a further embodiment, the invention provides a method of treating or preventing coronavirus infection, or a disease or complication associated with coronavirus infection in a subject, comprising administering a therapeutically effective amount of the antibody or the pharmaceutical composition to said subject.

In a further embodiment, the invention provides a method of identifying the presence of coronavirus, or a protein fragment thereof, in a sample, comprising: (i) contacting the sample with the antibody; and (ii) detecting the presence or absence of an antibody-antigen complex, wherein the presence of the antibody-antigen complex indicates the presence of coronavirus, or a fragment thereof, in the sample.

In a further embodiment, the invention provides a method of treating or preventing coronavirus infection, or a disease or complication associated therewith, in a subject, the method comprising identifying the presence of coronavirus according to the method above, and treating the subject with the antibody, an anti-viral drug or an anti-inflammatory agent.

In a further embodiment, the invention provides the use of the antibody or the pharmaceutical composition for preventing, treating and/or diagnosing coronavirus infection, or a disease or complication associated therewith.

In a further embodiment, the invention provides the use of the antibody or the pharmaceutical composition for the manufacture of a medicament for treating or preventing coronavirus infection, or a disease or complication associated therewith.

Brief description of the figures

Figure 1. Generation of BA.4/5 mAb. (A) Live virus neutralization FRNT50 titres against Victoria, an ancestral SARS-CoV-2 isolate, BA.2, BA.4 and BA.5 viruses using serum from vaccine breakthrough BA.4/5. (B) Sorting strategy for BA.4/5 specific B cells. (C) Heavy chain and light chain gene usage of potent BA.4/5 mAbs. (D) Number of somatic mutations found in BA.4/5 mAbs compared to sets previously isolated from early pandemic, Beta, BA.1 and BA.2 infection. (E) Blocking of ACE2-S interaction by potent BA.4/5 mAbs.

Figure 2. Heatmaps of antibody IC50 neutralisation titres and live virus neutralising activity of BA.4/5-2 and BA.4/5-5. (A) Heatmap of IC50s of potent BA.4/5 mAbs against pseudoviruses expressing variant S sequences. (B) Neutralisation curves and IC50s of BA.4/5-2 against 19 live virus variants. (C) Heatmap of IC50s of therapeutic monoclonal antibodies against pseudoviruses.

Figure 3. Structures of BA.4/5-1 and BA.4/5-2 complexes with RBD or spike. a, b, Binding mode of BA.4/5-1 and BA.4/5-2, respectively, as viewed from front (left) and back (right) of the RBD. RBD is drawn as grey surface representation with BA.4 mutation sites shown in magenta and further mutation sites found in Omicron sublineages in cyan. Only VhVl domains of the Fabs are shown as ribbons for clarity with HC in red LC in blue. **C-G**, Binding position of the CDRs and detailed interactions for BA.4/5-1/RBD, **H-L** for BA.4/5-2/RBD. Protein main chains are drawn as ribbons and coils, and side chains as sticks with Fab HC in red and LC in blue, RBD in grey. Hydrogen bonds are shown as yellow broken sticks.

Figure 4. Structures of RBD and Fab complexes and comparisons. a-c, Crystal structures of Delta-RBB/BA.4/5-1/EY6A, Delta-RBD/BA.4/5-2/Beta-49, and Delta-RBD/Omi-42/Beta-49, respectively. **d**, Cryo-EM structure of Delta-RBD/BA.2-07/SAR1-34/C1 complex. **e**, Binding of BA.4/5-5 stabilizes the nearby loops 620-640 from SD2 and 835-848 immediately after the fusion peptide from an adjacent chain. The start and end of each loop are marked by spheres. **f-h**, The binding mode of Omi-42 is compared with that of BA.4/5-2 by overlapping the RBD. Protein main chains are drawn as ribbons and coils, and side chains as sticks with Fab HC in red and LC in blue, SD1 in grey. Hydrogen bonds are shown as yellow broken sticks. Omi-42 HC and LC are in brown and pale blue, respectively.

Figure 5. ACE2 footprint, mutation sites of Omicron variants and Fab footprints on RBD. a, Surface representation of RBD with residues on the ACE2 footprint showing in green. **b**, RBD with the known mutation sites of Omicron variants in magenta. **c-f**, BA.4/5-1, BA.4/5-2, BA.2-07 and Omi-42 footprints shown in cyan, respectively, and ACE2 footprint marked by black outlines.

Figure 6. Mutations in RBD for variants shown in Fig. 2a. Indicated mutations are those additional mutations relative to the sequence of BA.2.

Figure 7. Data collection, structure determination and refinement statistics.

Detailed description of the invention

Antibodies of the invention

An antibody of the invention specifically binds to the spike protein of SAR-CoV-2. In particular, it specifically binds to the S1 subunit of the spike protein, such as the receptor binding domain (RBD) or the N-terminal domain (NTD).

An antibody of the invention may comprise all six CDRs of an antibody in Table 1. The antibody may comprise a heavy chain variable domain comprising or consisting of an amino acid sequence having at least 80% sequence identity, such as at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99% or 100% sequence identity, to the heavy chain variable domain of an antibody in Table 1. The antibody may comprise a light chain variable domain comprising or consisting of an amino acid sequence having at least 80% sequence identity, such as at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99% or 100% sequence identity, to the light chain variable domain of an antibody in Table 1. The antibody may comprise a heavy chain variable domain and a light chain variable domain comprising or consisting of an amino acid sequence having at least 80% sequence identity, such as at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99% or 100% sequence identity, to the heavy chain variable domain and light chain domain, respectively, of an antibody in Table 1. The antibody may comprise mutations in the framework regions of the variable domains compared to the antibody in Table 1. For example, the antibody may comprise a heavy chain variable domain comprising the CDRH1, CDRH2 and CDRH3 of an antibody in Table 1, and a light chain variable domain comprising the CDRL1, CDRL2 and CDRL3 of the antibody in Table 1, wherein the heavy chain variable domain and the light chain variable domain comprises or consists of an amino acid sequence having at least 80% sequence identity,

such as at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99% or 100% sequence identity, to the heavy chain variable domain and light chain variable domain, respectively of the antibody in Table 1. The antibody may be any one of the antibodies in Table 1.

Table 1 lists 24 individual antibodies that were identified from recovered BA.4/5 SARS-CoV-2 infected patients. Table 1 also lists the SEQ ID NOs for the heavy chain variable domain and light chain variable domain nucleotide and amino acid sequences, and the complementarity determining regions (CDRs) of the variable domains, of each of the antibodies. Typically, the CDRH3 is the CDRH3 provided in the penultimate column of Table 1, and/or the CDRL3 is the CDRL3 provided in the penultimate column of Table 1. In some cases, the CDRH3 is the CDRH3 AA Junction provided in the ultimate column of Table 1 and/or the CDRL3 is the CDRL3 AA Junction provided in the ultimate column of Table 1. The "AA Junction" CDR3 sequences are the CDR3 sequences defined by the IMGT numbering scheme plus an additional amino acid on the N-terminal and C-terminal sides of the CDR taken from the framework region.

The antibody in Table 1 may be selected from the group consisting of BA.4/5-2 and BA.4/5-1. These antibodies were surprisingly found to retain strong neutralisation of pseudoviral constructs of the SARS-CoV-2 variant strains Victoria, Alpha, Beta, Gamma, Delta, BA.1, BA.1.1, BA.2, BA.2.12.1, BA.4/BA.5, BA.4.6, BA.5.9, BA.2.75, BA.2.10.4, BJ.1, BA.2.75.2, BF.7, BS.1, BA.2.3.20, BN.1, BQ.1, BQ.1.1+A475V, BQ1.1, XBB, CA.3.1, XBB.1, CH.1.1, XBF, XBB.1.5 and DS.1. The antibody in Table 1 may be selected from the group consisting of BA.4/5-2, BA.4/5-1, BA.4/5-8, BA.4/5-9, BA.4/5-22, BA.4/5-28, BA.4/5-31 and BA.4/5-34. These antibodies were surprisingly found to retain strong neutralisation of pseudoviral constructs of the SARS-CoV-2 variant strains Victoria, Alpha, Beta, Gamma, Delta, BA.4/BA.5, BA.4.6, BA.5.9, BA.2.75, BA.2.10.4, BA.2.75.2, BF.7, BA.2.3.20, BQ.1, BQ1.1, XBB, CA.3.1, XBB.1, CH.1.1, XBF, XBB.1.5 and DS.1.

The neutralisation data presented herein were performed *in vitro* and may underestimate *in vivo* neutralization due to antibody dependent cell mediated cytotoxicity and complement activity.

In one embodiment, the antibody in Table 1 may be BA.4/5-2. BA.4/5-2 was found to neutralise the SARS-CoV-2 variant strains Victoria, Alpha, Beta, Gamma, Delta, BA.1, BA.1.1, BA.2, BA.2.12.1, BA.4/BA.5, BA.4.6, BA.5.9, BA.2.75, BA.2.10.4, BJ.1, BA.2.75.2, BF.7, BS.1, BA.2.3.20, BN.1, BQ.1, BQ.1.1+A475V, BQ1.1, XBB, CA.3.1, XBB.1, CH.1.1, XBF, XBB.1.5 and DS.1 with an IC50 of ≤ 0.02 µg/ml. BA.4/5-2 is

further advantageous as it binds at the back of the left shoulder of the receptor binding domain (RBD) in an area that has resisted mutational change to date. In one embodiment, an antibody of the invention may comprise a CDRH1, CDRH2 and CDRH3 having the amino acid sequences specified in SEQ ID NOs: 15, 16 and 17, respectively, and a CDRL1, CDRL2 and CDRL3 having the amino acid sequences specified in SEQ ID NOs: 21, 22 and 23, respectively. In one embodiment, an antibody of the invention may comprise a heavy chain variable domain comprising or consisting of an amino acid sequence having ≥80%, ≥90%, ≥95%, ≥96%, ≥97%, ≥98%, ≥99% or 100% sequence identity to the heavy chain variable domain of antibody BA.4/5-2 (i.e. SEQ ID NO: 14). In one embodiment, an antibody of the invention may comprise a light chain variable domain comprising or consisting of an amino acid sequence having ≥80%, ≥90%, ≥95%, ≥96%, ≥97%, ≥98%, ≥99% or 100% sequence identity to the light chain variable domain of antibody BA.4/5-2 (i.e. SEQ ID NO: 20). In one embodiment, an antibody of the invention may comprise a heavy chain variable domain and a light chain variable domain comprising or consisting of an amino acid sequence having ≥80%, ≥90%, ≥95%, ≥96%, ≥97%, ≥98%, ≥99% or 100% sequence identity to the heavy chain variable domain and light chain variable domain, respectively, of antibody BA.4/5-2 (i.e. SEQ ID NOs: 14 and 20, respectively). In one embodiment, an antibody of the invention may comprise a heavy chain variable domain comprising a CDRH1, CDRH2 and CDRH3 having the amino acid sequences specified in SEQ ID NOs: 15, 16 and 17, respectively, and a CDRL1, CDRL2 and CDRL3 having the amino acid sequences specified in SEQ ID NOs: 21, 22 and 23, respectively, wherein the heavy chain variable domain and the light chain variable domain comprises or consists of an amino acid sequence having ≥80%, ≥90%, ≥95%, ≥96%, ≥97%, ≥98%, ≥99% or 100% sequence identity to the heavy chain variable domain and light chain variable domain, respectively, of antibody BA.4/5-2 (i.e. SEQ ID NOs: 14 and 22, respectively). In one embodiment, the antibody may be a full-length antibody, for example, the antibody may comprise a heavy chain variable domain and a light chain variable domain as set out in SEQ ID NOs: 14 and 22, respectively, and a constant region, such as an IgA, IgD, IgE, IgG (IgG1, IgG2, IgG3 or IgG4) or IgM constant region.

The heavy chain domain of BA.4/5-2 is derived from a IGHV3-30 v-region, and the inventors have previously demonstrated that switching of the heavy chains and light chains between antibodies derived from the same v-region results in an antibody that is particularly useful with the invention (explained further below). Hence, an antibody of the invention may comprise the heavy chain of BA.4/5-2, and not the light chain of BA.4/5-2.

For example, the antibody may comprise a CDRH1, CDRH2 and CDRH3 having the amino acid sequences specified in SEQ ID NOs: 15, 16 and 17, respectively. The antibody may comprise a heavy chain variable domain comprising or consisting of an amino acid sequence having ≥80%, ≥90%, ≥95%, ≥96%, ≥97%, ≥98%, ≥99% or 100% sequence identity to the heavy chain variable domain of antibody BA.4/5-2 (i.e. SEQ ID NO: 14). The antibody may comprise a heavy chain variable domain comprising or consisting of SEQ ID NO: 14.

Alternatively, in an embodiment of the invention, the antibody may comprise the light chain of BA.4/5-2, and not the heavy chain of BA.4/5-2. For example, the antibody may comprise a CDRL1, CDRL2 and CDRL3 having the amino acid sequences specified in SEQ ID NOs: 21, 22 and 23, respectively. The antibody may comprise a light chain variable domain comprising or consisting of an amino acid sequence having ≥80%, ≥90%, ≥95%, ≥96%, ≥97%, ≥98%, ≥99% or 100% sequence identity to the light chain variable domain of antibody BA.4/5-2 (i.e. SEQ ID NO: 20). The antibody may comprise a light chain variable domain comprising or consisting of SEQ ID NO: 20.

In one embodiment, the antibody in Table 1 may be BA.4/5-1. BA.4/5-1 was found to neutralise the SARS-CoV-2 variant strains Victoria, Alpha, Beta, Gamma, Delta, BA.1, BA.1.1, BA.2, BA.2.12.1, BA.4/BA.5, BA.4.6, BA.5.9, BA.2.75, BA.2.10.4, BJ.1, BA.2.75.2, BF.7, BS.1, BA.2.3.20, BN.1, BQ.1, BQ.1.1+A475V, BQ1.1, XBB, CA.3.1, XBB.1, CH.1.1, XBF, XBB.1.5 and DS.1 with an IC50 of ≤ 0.15 μg/ml, and the SARS-CoV-2 variant strains Victoria, Alpha, Beta, Gamma, Delta, BA.1, BA.1.1, BA.2, BA.2.12.1, BA.4/BA.5, BA.4.6, BA.5.9, BA.2.75, BA.2.10.4, BJ.1, BA.2.75.2, BF.7, BA.2.3.20, BN.1, BQ.1, BQ.1.1+A475V, BQ1.1, XBB, CA.3.1, XBB.1, CH.1.1, XBF, XBB.1.5 and DS.1 with an IC50 of ≤ 0.04 μg/ml. In one embodiment, an antibody of the invention may comprise a CDRH1, CDRH2 and CDRH3 having the amino acid sequences specified in SEQ ID NOs: 3, 4 and 5, respectively, and a CDRL1, CDRL2 and CDRL3 having the amino acid sequences specified in SEQ ID NOs: 9, 10 and 11, respectively. In one embodiment, an antibody of the invention may comprise a heavy chain variable domain comprising or consisting of an amino acid sequence having ≥80%, ≥90%, ≥95%, ≥96%, ≥97%, ≥98%, ≥99% or 100% sequence identity to the heavy chain variable domain of antibody BA.4/5-1 (i.e. SEQ ID NO: 2). In one embodiment, an antibody of the invention may comprise a light chain variable domain comprising or consisting of an amino acid sequence having ≥80%, ≥90%, ≥95%, ≥96%, ≥97%, ≥98%, ≥99% or 100% sequence identity to the light chain variable domain of antibody BA.4/5-1 (i.e. SEQ ID

NO: 8). In one embodiment, an antibody of the invention may comprise a heavy chain variable domain and a light chain variable domain comprising or consisting of an amino acid sequence having ≥80%, ≥90%, ≥95%, ≥96%, ≥97%, ≥98%, ≥99% or 100% sequence identity to the heavy chain variable domain and light chain variable domain, respectively, of antibody BA.4/5-1 (i.e. SEQ ID NOs: 2 and 8, respectively). In one embodiment, an antibody of the invention may comprise a heavy chain variable domain comprising a CDRH1, CDRH2 and CDRH3 having the amino acid sequences specified in SEQ ID NOs: 3, 4 and 5, respectively, and a CDRL1, CDRL2 and CDRL3 having the amino acid sequences specified in SEQ ID NOs: 9, 10 and 11, respectively, wherein the heavy chain variable domain and the light chain variable domain comprises or consists of an amino acid sequence having ≥80%, ≥90%, ≥95%, ≥96%, ≥97%, ≥98%, ≥99% or 100% sequence identity to the heavy chain variable domain and light chain variable domain, respectively, of antibody BA.4/5-1 (i.e. SEQ ID NOs: 2 and 8, respectively). In one embodiment, the antibody may be a full-length antibody, for example, the antibody may comprise a heavy chain variable domain and a light chain variable domain as set out in SEQ ID NOs: 2 and 8, respectively, and a constant region, such as an IgA, IgD, IgE, IgG (IgG1, IgG2, IgG3 or IgG4) or IgM constant region.

The heavy chain domain of BA.4/5-1 is derived from a IGHV4-39 v-region, and the inventors have previously demonstrated that switching of the heavy chains and light chains between antibodies derived from the same v-region results in an antibody that is particularly useful with the invention (explained further below). Hence, an antibody of the invention may comprise the heavy chain of BA.4/5-1, and not the light chain of BA.4/5-1. For example, the antibody may comprise a CDRH1, CDRH2 and CDRH3 having the amino acid sequences specified in SEQ ID NOs: 3, 4 and 5, respectively. The antibody may comprise a heavy chain variable domain comprising or consisting of an amino acid sequence having ≥80%, ≥90%, ≥95%, ≥96%, ≥97%, ≥98%, ≥99% or 100% sequence identity to the heavy chain variable domain of antibody BA.4/5-1 (i.e. SEQ ID NO: 2). The antibody may comprise a heavy chain variable domain comprising or consisting of SEQ ID NO: 2.

Alternatively, in an embodiment of the invention, the antibody may comprise the light chain of BA.4/5-1, and not the heavy chain of BA.4/5-1. For example, the antibody may comprise a CDRL1, CDRL2 and CDRL3 having the amino acid sequences specified in SEQ ID NOs: 9, 10 and 11, respectively. The antibody may comprise a light chain variable domain comprising or consisting of an amino acid sequence having ≥80%, ≥90%,

≥95%, ≥96%, ≥97%, ≥98%, ≥99% or 100% sequence identity to the light chain variable domain of antibody BA.4/5-1 (i.e. SEQ ID NO: 8). The antibody may comprise a light chain variable domain comprising or consisting of SEQ ID NO: 8.

In one embodiment, the antibody in Table 1 may be BA.4/5-8. BA.4/5-8 was found to neutralise the SARS-CoV-2 variant strains Victoria, Alpha, Beta, Gamma, Delta, BA.1, BA.1.1, BA.2, BA.2.12.1, BA.4/BA.5, BA.4.6, BA.5.9, BA.2.10.4, BJ.1, BA.2.75.2, BF.7, BS.1, BA.2.3.20, BQ.1, BQ1.1, XBB, CA.3.1, XBB.1, CH.1.1, XBF and XBB.1.5 with an IC50 of ≤ 0.1 μg/ml and inter alia the SARS-CoV-2 variant strains BQ.1.1, CH.1.1, BF.7, XBB, XBB.1 and XBB.1.5 with an IC50 of ≤ 0.05 μg/ml. In one embodiment, an antibody of the invention may comprise a CDRH1, CDRH2 and CDRH3 having the amino acid sequences specified in SEQ ID NOs: 51, 52 and 53, respectively, and a CDRL1, CDRL2 and CDRL3 having the amino acid sequences specified in SEQ ID NOs: 57, 58 and 59, respectively. In one embodiment, an antibody of the invention may comprise a heavy chain variable domain comprising or consisting of an amino acid sequence having ≥80%, ≥90%, ≥95%, ≥96%, ≥97%, ≥98%, ≥99% or 100% sequence identity to the heavy chain variable domain of antibody BA.4/5-8 (i.e. SEQ ID NO: 50). In one embodiment, an antibody of the invention may comprise a light chain variable domain comprising or consisting of an amino acid sequence having ≥80%, ≥90%, ≥95%, ≥96%, ≥97%, ≥98%, ≥99% or 100% sequence identity to the light chain variable domain of antibody BA.4/5-8 (i.e. SEQ ID NO: 56). In one embodiment, an antibody of the invention may comprise a heavy chain variable domain and a light chain variable domain comprising or consisting of an amino acid sequence having ≥80%, ≥90%, ≥95%, ≥96%, ≥97%, ≥98%, ≥99% or 100% sequence identity to the heavy chain variable domain and light chain variable domain, respectively, of antibody BA.4/5-8 (i.e. SEQ ID NOs: 50 and 56, respectively). In one embodiment, an antibody of the invention may comprise a heavy chain variable domain comprising a CDRH1, CDRH2 and CDRH3 having the amino acid sequences specified in SEQ ID NOs: 51, 52 and 53, respectively, and a CDRL1, CDRL2 and CDRL3 having the amino acid sequences specified in SEQ ID NOs: 57, 58 and 59, respectively, wherein the heavy chain variable domain and the light chain variable domain comprises or consists of an amino acid sequence having ≥80%, ≥90%, ≥95%, ≥96%, ≥97%, ≥98%, ≥99% or 100% sequence identity to the heavy chain variable domain and light chain variable domain, respectively, of antibody BA.4/5-8 (i.e. SEQ ID NOs: 50 and 56, respectively). In one embodiment, the antibody may be a full-length antibody, for example, the antibody may comprise a heavy chain variable domain and a light chain variable domain as set out in

SEQ ID NOs: 50 and 56, respectively, and a constant region, such as an IgA, IgD, IgE, IgG (IgG1, IgG2, IgG3 or IgG4) or IgM constant region.

The heavy chain domain of BA.4/5-8 is derived from a IGHV3-66 v-region, and the inventors have previously demonstrated that switching of the heavy chains and light chains between antibodies derived from the same v-region, and in the case of IGHV3-66 also derived from IGHV3-53, results in an antibody that is particularly useful with the invention (explained further below). Hence, an antibody of the invention may comprise the heavy chain of BA.4/5-8, and not the light chain of BA.4/5-8. For example, the antibody may comprise a CDRH1, CDRH2 and CDRH3 having the amino acid sequences specified in SEQ ID NOs: 51, 52 and 53, respectively. The antibody may comprise a heavy chain variable domain comprising or consisting of an amino acid sequence having ≥80%, ≥90%, ≥95%, ≥96%, ≥97%, ≥98%, ≥99% or 100% sequence identity to the heavy chain variable domain of antibody BA.4/5-8 (i.e. SEQ ID NO: 50). The antibody may comprise a heavy chain variable domain comprising or consisting of SEQ ID NO: 50.

Alternatively, in an embodiment of the invention, the antibody may comprise the light chain of BA.4/5-2, and not the heavy chain of BA.4/5-8. For example, the antibody may comprise a CDRL1, CDRL2 and CDRL3 having the amino acid sequences specified in SEQ ID NOs: 57, 58 and 59, respectively. The antibody may comprise a light chain variable domain comprising or consisting of an amino acid sequence having ≥80%, ≥90%, ≥95%, ≥96%, ≥97%, ≥98%, ≥99% or 100% sequence identity to the light chain variable domain of antibody BA.4/5-8 (i.e. SEQ ID NO: 56). The antibody may comprise a light chain variable domain comprising or consisting of SEQ ID NO: 56.

In one embodiment, the antibody in Table 1 may be BA.4/5-9. BA.4/5-9 was found to neutralise the SARS-CoV-2 variant strains Victoria, Alpha, Beta, Gamma, Delta, BA.4/BA.5, BA.4.6, BA.5.9, BA.2.75, BA.2.10.4, BA.2.75.2, BF.7, BA.2.3.20, BN.1, BQ.1, BQ.1.1+A475V, BQ1.1, XBB, CA.3.1, XBB.1, XBF, and DS.1 with an IC50 of ≤ 0.05 μg/ml. In one embodiment, an antibody of the invention may comprise a CDRH1, CDRH2 and CDRH3 having the amino acid sequences specified in SEQ ID NOs: 63, 64 and 65, respectively, and a CDRL1, CDRL2 and CDRL3 having the amino acid sequences specified in SEQ ID NOs: 69, 70 and 71, respectively. In one embodiment, an antibody of the invention may comprise a heavy chain variable domain comprising or consisting of an amino acid sequence having ≥80%, ≥90%, ≥95%, ≥96%, ≥97%, ≥98%, ≥99% or 100% sequence identity to the heavy chain variable domain of antibody BA.4/5-9 (i.e. SEQ ID NO: 62). In one embodiment, an antibody of the invention may comprise a light chain

variable domain comprising or consisting of an amino acid sequence having ≥80%, ≥90%, ≥95%, ≥96%, ≥97%, ≥98%, ≥99% or 100% sequence identity to the light chain variable domain of antibody BA.4/5-9 (i.e. SEQ ID NO: 68). In one embodiment, an antibody of the invention may comprise a heavy chain variable domain and a light chain variable domain comprising or consisting of an amino acid sequence having ≥80%, ≥90%, ≥95%, ≥96%, ≥97%, ≥98%, ≥99% or 100% sequence identity to the heavy chain variable domain and light chain variable domain, respectively, of antibody BA.4/5-9 (i.e. SEQ ID NOs: 62 and 68, respectively). In one embodiment, an antibody of the invention may comprise a heavy chain variable domain comprising a CDRH1, CDRH2 and CDRH3 having the amino acid sequences specified in SEQ ID NOs: 63, 64 and 65, respectively, and a CDRL1, CDRL2 and CDRL3 having the amino acid sequences specified in SEQ ID NOs: 69. 70 and 71, respectively, wherein the heavy chain variable domain and the light chain variable domain comprises or consists of an amino acid sequence having ≥80%, ≥90%, ≥95%, ≥96%, ≥97%, ≥98%, ≥99% or 100% sequence identity to the heavy chain variable domain and light chain variable domain, respectively, of antibody BA.4/5-9 (i.e. SEQ ID NOs: 62 and 68, respectively). In one embodiment, the antibody may be a full-length antibody, for example, the antibody may comprise a heavy chain variable domain and a light chain variable domain as set out in SEQ ID NOs: 62 and 68, respectively, and a constant region, such as an IgA, IgD, IgE, IgG (IgG1, IgG2, IgG3 or IgG4) or IgM constant region.

The heavy chain domain of BA.4/5-9 is derived from a IGHV1-46 v-region, and the inventors have previously demonstrated that switching of the heavy chains and light chains between antibodies derived from the same v-region results in an antibody that is particularly useful with the invention (explained further below). Hence, an antibody of the invention may comprise the heavy chain of BA.4/5-9, and not the light chain of BA.4/5-9. For example, the antibody may comprise a CDRH1, CDRH2 and CDRH3 having the amino acid sequences specified in SEQ ID NOs: 63, 64 and 65, respectively. The antibody may comprise a heavy chain variable domain comprising or consisting of an amino acid sequence having ≥80%, ≥90%, ≥95%, ≥96%, ≥97%, ≥98%, ≥99% or 100% sequence identity to the heavy chain variable domain of antibody BA.4/5-9 (i.e. SEQ ID NO: 62). The antibody may comprise a heavy chain variable domain comprising or consisting of SEQ ID NO: 62.

Alternatively, in an embodiment of the invention, the antibody may comprise the light chain of BA.4/5-9, and not the heavy chain of BA.4/5-9. For example, the antibody

may comprise a CDRL1, CDRL2 and CDRL3 having the amino acid sequences specified in SEQ ID NOs: 69, 70 and 71, respectively. The antibody may comprise a light chain variable domain comprising or consisting of an amino acid sequence having ≥80%, ≥90%, ≥95%, ≥96%, ≥97%, ≥98%, ≥99% or 100% sequence identity to the light chain variable domain of antibody BA.4/5-9 (i.e. SEQ ID NO: 68). The antibody may comprise a light chain variable domain comprising or consisting of SEQ ID NO: 68.

In one embodiment, the antibody in Table 1 may be BA.4/5-22. BA.4/5-22 was found to neutralise the SARS-CoV-2 variant strains Victoria, Alpha, Beta, Gamma, Delta, BA.4/BA.5, BA.4.6, BA.5.9, BA.2.75, BA.2.10.4, BA.2.75.2, BF.7, BA.2.3.20, BN.1, BQ.1, BQ.1.1+A475V, BQ1.1, XBB, CA.3.1, XBB.1, CH.1.1, XBF, XBB.1.5 and DS.1 with an IC50 of ≤ 0.025 μg/ml and inter alia the SARS-CoV-2 variant strains XBF, CH.1.1, BQ.1.1, BF.7, XBB, XBB.1 and XBB.1.5 with an IC50 of ≤ 0.02 μg/ml. In one embodiment, an antibody of the invention may comprise a CDRH1, CDRH2 and CDRH3 having the amino acid sequences specified in SEQ ID NOs: 183, 184 and 185, respectively, and a CDRL1, CDRL2 and CDRL3 having the amino acid sequences specified in SEQ ID NOs: 189, 190 and 191, respectively. In one embodiment, an antibody of the invention may comprise a heavy chain variable domain comprising or consisting of an amino acid sequence having ≥80%, ≥90%, ≥95%, ≥96%, ≥97%, ≥98%, ≥99% or 100% sequence identity to the heavy chain variable domain of antibody BA.4/5-22 (i.e. SEQ ID NO: 182). In one embodiment, an antibody of the invention may comprise a light chain variable domain comprising or consisting of an amino acid sequence having ≥80%, ≥90%, ≥95%, ≥96%, ≥97%, ≥98%, ≥99% or 100% sequence identity to the light chain variable domain of antibody BA.4/5-22 (i.e. SEQ ID NO: 188). In one embodiment, an antibody of the invention may comprise a heavy chain variable domain and a light chain variable domain comprising or consisting of an amino acid sequence having ≥80%, ≥90%, ≥95%, ≥96%, ≥97%, ≥98%, ≥99% or 100% sequence identity to the heavy chain variable domain and light chain variable domain, respectively, of antibody BA.4/5-22 (i.e. SEQ ID NOs: 182 and 188, respectively). In one embodiment, an antibody of the invention may comprise a heavy chain variable domain comprising a CDRH1, CDRH2 and CDRH3 having the amino acid sequences specified in SEQ ID NOs: 183, 184 and 185, respectively, and a CDRL1, CDRL2 and CDRL3 having the amino acid sequences specified in SEQ ID NOs: 189, 190 and 191, respectively, wherein the heavy chain variable domain and the light chain variable domain comprises or consists of an amino acid sequence having ≥80%, ≥90%, ≥95%, ≥96%, ≥97%, ≥98%, ≥99% or 100% sequence

identity to the heavy chain variable domain and light chain variable domain, respectively, of antibody BA.4/5-2 (i.e. SEQ ID NOs: 182 and 188, respectively). In one embodiment, the antibody may be a full-length antibody, for example, the antibody may comprise a heavy chain variable domain and a light chain variable domain as set out in SEQ ID NOs: 182 and 188, respectively, and a constant region, such as an IgA, IgD, IgE, IgG (IgG1, IgG2, IgG3 or IgG4) or IgM constant region.

The heavy chain domain of BA.4/5-22 is derived from a IGHV1-69 v-region, and the inventors have previously demonstrated that switching of the heavy chains and light chains between antibodies derived from the same v-region results in an antibody that is particularly useful with the invention (explained further below). Hence, an antibody of the invention may comprise the heavy chain of BA.4/5-22, and not the light chain of BA.4/5-22. For example, the antibody may comprise a CDRH1, CDRH2 and CDRH3 having the amino acid sequences specified in SEQ ID NOs: 183, 184 and 185, respectively. The antibody may comprise a heavy chain variable domain comprising or consisting of an amino acid sequence having ≥80%, ≥90%, ≥95%, ≥96%, ≥97%, ≥98%, ≥99% or 100% sequence identity to the heavy chain variable domain of antibody BA.4/5-22 (i.e. SEQ ID NO: 182). The antibody may comprise a heavy chain variable domain comprising or consisting of SEQ ID NO: 182.

Alternatively, in an embodiment of the invention, the antibody may comprise the light chain of BA.4/5-22, and not the heavy chain of BA.4/5-22. For example, the antibody may comprise a CDRL1, CDRL2 and CDRL3 having the amino acid sequences specified in SEQ ID NOs: 189, 190 and 191, respectively. The antibody may comprise a light chain variable domain comprising or consisting of an amino acid sequence having ≥80%, ≥90%, ≥95%, ≥96%, ≥97%, ≥98%, ≥99% or 100% sequence identity to the light chain variable domain of antibody BA.4/5-22 (i.e. SEQ ID NO: 188). The antibody may comprise a light chain variable domain comprising or consisting of SEQ ID NO: 188.

In one embodiment, the antibody in Table 1 may be BA.4/5-28. BA.4/5-28 was found to neutralise the SARS-CoV-2 variant strains Victoria, Alpha, Beta, Gamma, Delta, BA.1, BA.1.1, BA.2, BA.2.12.1, BA.4/BA.5, BA.4.6, BA.5.9, BA.2.75, BA.2.10.4, BJ.1, BA.2.75.2, BF.7, BA.2.3.20, BN.1, BQ.1, BQ1.1, XBB, CA.3.1, XBB.1, CH.1.1, XBF, XBB.1.5 and DS.1 with an IC50 of ≤ 0.1 μg/ml. In one embodiment, an antibody of the invention may comprise a CDRH1, CDRH2 and CDRH3 having the amino acid sequences specified in SEQ ID NOs: 231, 232 and 233, respectively, and a CDRL1, CDRL2 and CDRL3 having the amino acid sequences specified in SEQ ID NOs: 237, 238 and 239,

respectively. In one embodiment, an antibody of the invention may comprise a heavy chain variable domain comprising or consisting of an amino acid sequence having ≥80%, ≥90%, ≥95%, ≥96%, ≥97%, ≥98%, ≥99% or 100% sequence identity to the heavy chain variable domain of antibody BA.4/5-28 (i.e. SEQ ID NO: 230). In one embodiment, an antibody of the invention may comprise a light chain variable domain comprising or consisting of an amino acid sequence having ≥80%, ≥90%, ≥95%, ≥96%, ≥97%, ≥98%, ≥99% or 100% sequence identity to the light chain variable domain of antibody BA.4/5-28 (i.e. SEQ ID NO: 236). In one embodiment, an antibody of the invention may comprise a heavy chain variable domain and a light chain variable domain comprising or consisting of an amino acid sequence having ≥80%, ≥90%, ≥95%, ≥96%, ≥97%, ≥98%, ≥99% or 100% sequence identity to the heavy chain variable domain and light chain variable domain, respectively, of antibody BA.4/5-28 (i.e. SEQ ID NOs: 230 and 236, respectively). In one embodiment, an antibody of the invention may comprise a heavy chain variable domain comprising a CDRH1, CDRH2 and CDRH3 having the amino acid sequences specified in SEQ ID NOs: 231, 232 and 233, respectively, and a CDRL1, CDRL2 and CDRL3 having the amino acid sequences specified in SEQ ID NOs: 237, 238 and 239, respectively, wherein the heavy chain variable domain and the light chain variable domain comprises or consists of an amino acid sequence having ≥80%, ≥90%, ≥95%, ≥96%, ≥97%, ≥98%, ≥99% or 100% sequence identity to the heavy chain variable domain and light chain variable domain, respectively, of antibody BA.4/5-28 (i.e. SEQ ID NOs: 230 and 236, respectively). In one embodiment, the antibody may be a full-length antibody, for example, the antibody may comprise a heavy chain variable domain and a light chain variable domain as set out in SEQ ID NOs: 230 and 236, respectively, and a constant region, such as an IgA, IgD, IgE, IgG (IgG1, IgG2, IgG3 or IgG4) or IgM constant region.

The heavy chain domain of BA.4/5-28 is derived from a IGHV3-66 v-region, and the inventors have previously demonstrated that switching of the heavy chains and light chains between antibodies derived from the same v-region, and in the case of IGHV3-66 also derived from IGHV3-53, results in an antibody that is particularly useful with the invention (explained further below). Hence, an antibody of the invention may comprise the heavy chain of BA.4/5-28, and not the light chain of BA.4/5-28. For example, the antibody may comprise a CDRH1, CDRH2 and CDRH3 having the amino acid sequences specified in SEQ ID NOs: 231, 232 and 233, respectively. The antibody may comprise a heavy chain variable domain comprising or consisting of an amino acid sequence having ≥80%, ≥90%, ≥95%, ≥96%, ≥97%, ≥98%, ≥99% or 100% sequence identity to the heavy

chain variable domain of antibody BA.4/5-28 (i.e. SEQ ID NO: 230). The antibody may comprise a heavy chain variable domain comprising or consisting of SEQ ID NO: 230.

Alternatively, in an embodiment of the invention, the antibody may comprise the light chain of BA.4/5-28, and not the heavy chain of BA.4/5-28. For example, the antibody may comprise a CDRL1, CDRL2 and CDRL3 having the amino acid sequences specified in SEQ ID NOs: 237, 238 and 239, respectively. The antibody may comprise a light chain variable domain comprising or consisting of an amino acid sequence having ≥80%, ≥90%, ≥95%, ≥96%, ≥97%, ≥98%, ≥99% or 100% sequence identity to the light chain variable domain of antibody BA.4/5-28 (i.e. SEQ ID NO: 236). The antibody may comprise a light chain variable domain comprising or consisting of SEQ ID NO: 236.

In one embodiment, the antibody in Table 1 may be BA.4/5-31. BA.4/5-31 was found to neutralise the SARS-CoV-2 variant strains Victoria, Alpha, Beta, Gamma, Delta, BA.1, BA.1.1, BA.2, BA.2.12.1, BA.4/BA.5, BA.4.6, BA.5.9, BA.2.75, BA.2.10.4, BJ.1, BA.2.75.2, BF.7, BA.2.3.20, BN.1, BQ.1, BQ.1.1+A475V, BQ1.1, XBB, CA.3.1, XBB.1, CH.1.1, XBF, XBB.1.5 and DS.1 with an IC50 of ≤ 0.2 μg/ml and the SARS-CoV-2 variant strains XBF, CH.1.1, BQ.1.1, BF.7, XBB, XBB.1 and XBB.1.5 with an IC50 of ≤ 0.03 μg/ml. In one embodiment, an antibody of the invention may comprise a CDRH1, CDRH2 and CDRH3 having the amino acid sequences specified in SEQ ID NOs: 243, 244 and 245, respectively, and a CDRL1, CDRL2 and CDRL3 having the amino acid sequences specified in SEQ ID NOs: 249, 250 and 251, respectively. In one embodiment, an antibody of the invention may comprise a heavy chain variable domain comprising or consisting of an amino acid sequence having ≥80%, ≥90%, ≥95%, ≥96%, ≥97%, ≥98%, ≥99% or 100% sequence identity to the heavy chain variable domain of antibody BA.4/5-31 (i.e. SEQ ID NO: 242). In one embodiment, an antibody of the invention may comprise a light chain variable domain comprising or consisting of an amino acid sequence having ≥80%, ≥90%, ≥95%, ≥96%, ≥97%, ≥98%, ≥99% or 100% sequence identity to the light chain variable domain of antibody BA.4/5-31 (i.e. SEQ ID NO: 248). In one embodiment, an antibody of the invention may comprise a heavy chain variable domain and a light chain variable domain comprising or consisting of an amino acid sequence having ≥80%, ≥90%, ≥95%, ≥96%, ≥97%, ≥98%, ≥99% or 100% sequence identity to the heavy chain variable domain and light chain variable domain, respectively, of antibody BA.4/5-31 (i.e. SEQ ID NOs: 242 and 248, respectively). In one embodiment, an antibody of the invention may comprise a heavy chain variable domain comprising a CDRH1, CDRH2 and CDRH3 having the amino acid sequences specified in SEQ ID NOs: 243, 244 and 245,

respectively, and a CDRL1, CDRL2 and CDRL3 having the amino acid sequences specified in SEQ ID NOs: 249, 250 and 251, respectively, wherein the heavy chain variable domain and the light chain variable domain comprises or consists of an amino acid sequence having ≥80%, ≥90%, ≥95%, ≥96%, ≥97%, ≥98%, ≥99% or 100% sequence identity to the heavy chain variable domain and light chain variable domain, respectively, of antibody BA.4/5-31 (i.e. SEQ ID NOs: 242 and 248, respectively). In one embodiment, the antibody may be a full-length antibody, for example, the antibody may comprise a heavy chain variable domain and a light chain variable domain as set out in SEQ ID NOs: 242 and 248, respectively, and a constant region, such as an IgA, IgD, IgE, IgG (IgG1, IgG2, IgG3 or IgG4) or IgM constant region.

The heavy chain domain of BA.4/5-31 is derived from a IGHV4-39 v-region, and the inventors have previously demonstrated that switching of the heavy chains and light chains between antibodies derived from the same v-region results in an antibody that is particularly useful with the invention (explained further below). Hence, an antibody of the invention may comprise the heavy chain of BA.4/5-31, and not the light chain of BA.4/5-31. For example, the antibody may comprise a CDRH1, CDRH2 and CDRH3 having the amino acid sequences specified in SEQ ID NOs: 243, 244 and 245, respectively. The antibody may comprise a heavy chain variable domain comprising or consisting of an amino acid sequence having ≥80%, ≥90%, ≥95%, ≥96%, ≥97%, ≥98%, ≥99% or 100% sequence identity to the heavy chain variable domain of antibody BA.4/5-31 (i.e. SEQ ID NO: 242). The antibody may comprise a heavy chain variable domain comprising or consisting of SEQ ID NO: 242.

Alternatively, in an embodiment of the invention, the antibody may comprise the light chain of BA.4/5-31, and not the heavy chain of BA.4/5-31. For example, the antibody may comprise a CDRL1, CDRL2 and CDRL3 having the amino acid sequences specified in SEQ ID NOs: 249, 250 and 251, respectively. The antibody may comprise a light chain variable domain comprising or consisting of an amino acid sequence having ≥80%, ≥90%, ≥95%, ≥96%, ≥97%, ≥98%, ≥99% or 100% sequence identity to the light chain variable domain of antibody BA.4/5-31 (i.e. SEQ ID NO: 248). The antibody may comprise a light chain variable domain comprising or consisting of SEQ ID NO: 248.

In one embodiment, the antibody in Table 1 may be BA.4/5-34. BA.4/5-34 was found to neutralise the SARS-CoV-2 variant strains Victoria, Alpha, Beta, Gamma, Delta, BA.4/BA.5, BA.4.6, BA.5.9, BA.2.75, BA.2.10.4, BA.2.75.2, BF.7, BA.2.3.20, BN.1, BQ.1, BQ.1.1+A475V, BQ1.1, XBB, CA.3.1, XBB.1, CH.1.1, XBF, XBB.1.5 and DS.1

with an IC50 of ≤ 0.1 μg/ml and the SARS-CoV-2 variant strains XBF, CH.1.1, BQ.1.1, BF.7, XBB, XBB.1 and XBB.1.5 with an IC50 of ≤ 0.05 μg/ml. In one embodiment, an antibody of the invention may comprise a CDRH1, CDRH2 and CDRH3 having the amino acid sequences specified in SEQ ID NOs: 279, 280 and 281, respectively, and a CDRL1, CDRL2 and CDRL3 having the amino acid sequences specified in SEQ ID NOs: 285, 286 and 287, respectively. In one embodiment, an antibody of the invention may comprise a heavy chain variable domain comprising or consisting of an amino acid sequence having ≥80%, ≥90%, ≥95%, ≥96%, ≥97%, ≥98%, ≥99% or 100% sequence identity to the heavy chain variable domain of antibody BA.4/5-34 (i.e. SEQ ID NO: 278). In one embodiment, an antibody of the invention may comprise a light chain variable domain comprising or consisting of an amino acid sequence having ≥80%, ≥90%, ≥95%, ≥96%, ≥97%, ≥98%, ≥99% or 100% sequence identity to the light chain variable domain of antibody BA.4/5-34 (i.e. SEQ ID NO: 284). In one embodiment, an antibody of the invention may comprise a heavy chain variable domain and a light chain variable domain comprising or consisting of an amino acid sequence having ≥80%, ≥90%, ≥95%, ≥96%, ≥97%, ≥98%, ≥99% or 100% sequence identity to the heavy chain variable domain and light chain variable domain, respectively, of antibody BA.4/5-34 (i.e. SEQ ID NOs: 278 and 284, respectively). In one embodiment, an antibody of the invention may comprise a heavy chain variable domain comprising a CDRH1, CDRH2 and CDRH3 having the amino acid sequences specified in SEQ ID NOs: 279, 280 and 281, respectively, and a CDRL1, CDRL2 and CDRL3 having the amino acid sequences specified in SEQ ID NOs: 285, 286 and 287, respectively, wherein the heavy chain variable domain and the light chain variable domain comprises or consists of an amino acid sequence having ≥80%, ≥90%, ≥95%, ≥96%, ≥97%, ≥98%, ≥99% or 100% sequence identity to the heavy chain variable domain and light chain variable domain, respectively, of antibody BA.4/5-34 (i.e. SEQ ID NOs: 278 and 284, respectively). In one embodiment, the antibody may be a full-length antibody, for example, the antibody may comprise a heavy chain variable domain and a light chain variable domain as set out in SEQ ID NOs: 278 and 284, respectively, and a constant region, such as an IgA, IgD, IgE, IgG (IgG1, IgG2, IgG3 or IgG4) or IgM constant region.

The heavy chain domain of BA.4/5-34 is derived from a IGHV1-69 v-region, and the inventors have previously demonstrated that switching of the heavy chains and light chains between antibodies derived from the same v-region results in an antibody that is particularly useful with the invention (explained further below). Hence, an antibody of the invention may comprise the heavy chain of BA.4/5-34, and not the light chain of BA.4/5-

34. For example, the antibody may comprise a CDRH1, CDRH2 and CDRH3 having the amino acid sequences specified in SEQ ID NOs: 279, 280 and 281, respectively. The antibody may comprise a heavy chain variable domain comprising or consisting of an amino acid sequence having ≥80%, ≥90%, ≥95%, ≥96%, ≥97%, ≥98%, ≥99% or 100% sequence identity to the heavy chain variable domain of antibody BA.4/5-34 (i.e. SEQ ID NO: 278). The antibody may comprise a heavy chain variable domain comprising or consisting of SEQ ID NO: 278.

Alternatively, in an embodiment of the invention, the antibody may comprise the light chain of BA.4/5-34, and not the heavy chain of BA.4/5-34. For example, the antibody may comprise a CDRL1, CDRL2 and CDRL3 having the amino acid sequences specified in SEQ ID NOs: 285, 286 and 287, respectively. The antibody may comprise a light chain variable domain comprising or consisting of an amino acid sequence having ≥80%, ≥90%, ≥95%, ≥96%, ≥97%, ≥98%, ≥99% or 100% sequence identity to the light chain variable domain of antibody BA.4/5-34 (i.e. SEQ ID NO: 284). The antibody may comprise a light chain variable domain comprising or consisting of SEQ ID NO: 284.

Mixed chain antibodies of the invention

An antibody of the invention may comprise a light chain variable domain comprising CDRL1, CDRL2 and CDRL3 from a first antibody in Table 1 and a heavy chain variable domain comprising CDRH1, CDRH2 and CDRH3 from a second antibody in Table 1, with the proviso that the first and second antibodies are different. Such antibodies are referred to as mixed chain antibodies herein.

Examples of the mixed chain antibodies useful with the invention are provided in Tables 3 to 9. Table 3 shows examples of mixed chain antibodies generated from antibodies in Table 1 that are derived from the same germline heavy chain IGHV 4-39. Table 4 shows examples of mixed chain antibodies generated from antibodies in Table 1 that are derived from the same germline heavy chain IGHV3-30. Table 5 shows examples of mixed chain antibodies generated from antibodies in Table 1 that are derived from the same germline heavy chain IGHV3-53. Table 6 shows examples of mixed chain antibodies generated from antibodies in Table 1 that are derived from the same germline heavy chain IGHV3-66. Table 7 shows examples of mixed chain antibodies generated from antibodies in Table 1 that are derived from the same germline heavy chain IGHV3-53 and IGHV3-66. Table 8 shows examples of mixed chain antibodies generated from antibodies in Table 1 that are derived from the same germline heavy chain IGHV1-69.

Table 9 shows examples of mixed chain antibodies generated from antibodies in Table 1 that are derived from the same germline heavy chain IGHV3-9. Examples of mixed chain antibodies that are derived from the same germline heavy chain IGHV1-69 are BA.4/5-22H+BA.4/5-34L and BA.4/5-34H+BA.4/5-22L.

Hence, in one embodiment, an antibody of the invention comprises a heavy chain variable domain comprising CDRH1, CDRH2 and CDRH3 from a first antibody in Table 1 and a light chain variable domain comprising CDRL1, CDRL2 and CDRL3 from a second antibody in Table 1, with the proviso that the first and second antibodies are different. The antibody may comprise a heavy chain variable domain amino acid sequence having at least 80% sequence identity to the heavy chain variable domain from a first antibody in Table 1, and a light chain variable domain amino acid sequence having at least 80% sequence identity to the light chain variable domain from a second antibody in Table 1, with the proviso that the first and second antibodies are different. For example, the antibody may comprise a heavy chain variable domain comprising or consisting of an amino acid sequence having ≥80%, ≥90%, ≥95%, ≥96%, ≥97%, ≥98%, ≥99% or 100% sequence identity to the heavy chain variable domain of an antibody in Table 1, and a light chain variable domain comprising or consisting of an amino acid sequence having ≥80%, ≥90%, ≥95%, ≥96%, ≥97%, ≥98%, ≥99% or 100% sequence identity to the light chain variable domain of an antibody in Table 1, with the proviso that the first and second antibodies are different. In some embodiments, an antibody of the invention comprises a heavy chain variable domain comprising CDRH1, CDRH2 and CDRH3 from a first antibody in Table 1 and a light chain variable domain comprising CDRL1, CDRL2 and CDRL3 from a second antibody in Table 1, and comprise a heavy chain variable domain comprising or consisting of an amino acid sequence having ≥80%, ≥90%, ≥95%, ≥96%, ≥97%, ≥98%, ≥99% or 100% sequence identity to the heavy chain variable domain of the first antibody in Table 1, and a light chain variable domain comprising or consisting of an amino acid sequence having ≥80%, ≥90%, ≥95%, ≥96%, ≥97%, ≥98%, ≥99% or 100% sequence identity to the light chain variable domain of the second antibody in Table 1, with the proviso that the first and second antibodies are different.

The antibody in Table 1 may be selected from the group consisting of: BA.4/5-2, BA.4/5-1, BA.4/5-8, BA.4/5-22, BA.4/5-28, BA.4/5-31 and BA.4/5-34.

In one embodiment, the first antibody and the second antibody are both selected from the group consisting of: BA.4/5-1 and BA.4/5-31. The heavy chain variable domain of these antibodies are derived from IGHV 4-39. The resulting mixed chain antibodies are

set out in Table 3. Hence, the antibody of the invention may comprise all six CDRs (CDRH1-3 and CDRL1-3), and/or a heavy chain variable domain and a light chain variable domain, each comprising or consisting of an amino acid sequence having at least 80% (e.g. ≥80%, ≥90%, ≥95%, ≥96%, ≥97%, ≥98%, ≥99% or 100%) sequence identity to the corresponding variable domain of any one of the mixed chain antibodies as set out in Table 3.

In one embodiment, the first antibody and the second antibody are both selected from the group consisting of: BA.4/5-2 and BA.4/5-12. The heavy chain variable domain of these antibodies are derived from IGHV 3-30. The resulting mixed chain antibodies are set out in Table 4. Hence, the antibody of the invention may comprise all six CDRs (CDRH1-3 and CDRL1-3), and/or a heavy chain variable domain and a light chain variable domain, each comprising or consisting of an amino acid sequence having at least 80% (e.g. ≥80%, ≥90%, ≥95%, ≥96%, ≥97%, ≥98%, ≥99% or 100%) sequence identity to the corresponding variable domain of any one of the mixed chain antibodies as set out in Table 4.

In one embodiment, the first antibody and the second antibody are both selected from the group consisting of: BA.4/5-6, BA.4/5-7, BA.4/5-17 and BA.4/5-23. The heavy chain variable domain of these antibodies are derived from IGHV3-53. The resulting mixed chain antibodies are set out in Table 5. Hence, the antibody of the invention may comprise all six CDRs (CDRH1-3 and CDRL1-3), and/or a heavy chain variable domain and a light chain variable domain, each comprising or consisting of an amino acid sequence having at least 80% sequence identity to the corresponding variable domain of any one of the mixed chain antibodies as set out in Table 5.

In one embodiment, the first antibody and the second antibody are both selected from the group consisting of: BA.4/5-8, BA.4/5-10, BA.4/5-28 and BA.4/5-32. The heavy chain variable domain of these antibodies are derived from IGHV3-66. The resulting mixed chain antibodies are set out in Table 6. Hence, the antibody of the invention may comprise all six CDRs (CDRH1-3 and CDRL1-3), and/or a heavy chain variable domain and a light chain variable domain, each comprising or consisting of an amino acid sequence having at least 80% sequence identity to the corresponding variable domain of any one of the mixed chain antibodies as set out in Table 6.

Antibodies derived from IGHV3-53 may be used to produce mixed-chain antibodies with antibodies from IGHV3-66 (see, e.g. Dejnirattisai, Wanwisa, et al. "The antigenic anatomy of SARS-CoV-2 receptor binding domain." Cell 184(8) (2021): 2183-

2200; Supasa, Piyada, et al. "Reduced neutralization of SARS-CoV-2 B.1.1.7 variant by convalescent and vaccine sera." Cell 184(8) (2021): 2201-2211; Zhou, Daming, et al. "Evidence of escape of SARS-CoV-2 variant B.1.351 from natural and vaccine-induced sera." Cell 184(9) (2021): 2348-2361; Dejnirattisai, Wanwisa, et al. "Antibody evasion by the P.1 strain of SARS-CoV-2." Cell 184(11) (2021): 2939-2954; Liu, Chang, et al. "Reduced neutralization of SARS-CoV-2 B.1.617 by vaccine and convalescent serum." Cell 184(16) (2021): 4220-4236)). Accordingly, in one embodiment, the first antibody is selected from the group consisting of BA.4/5-6, BA.4/5-7, BA.4/5-17 and BA.4/5-23, and the second antibody is selected from the group consisting of BA.4/5-8, BA.4/5-10, BA.4/5-28 and BA.4/5-32. In an alternative embodiment, the first antibody is selected from the group consisting of BA.4/5-8, BA.4/5-10, BA.4/5-28 and BA.4/5-32, and the second antibody is selected from the group consisting of BA.4/5-6, BA.4/5-7, BA.4/5-17 and BA.4/5-23. The heavy chain variable domain of these antibodies are derived from IGHV3-53 and IGVH3-66. Examples of the resulting mixed chain antibodies are set out in Table 7. Hence, the antibody of the invention may comprise all six CDRs (CDRH1-3 and CDRL1-3), and/or a heavy chain variable domain and a light chain variable domain, each comprising or consisting of an amino acid sequence having at least 80% sequence identity to the corresponding variable domain of any one of the mixed chain antibodies as set out in Table 7.

In one embodiment, the first antibody and the second antibody are both selected from the group consisting of: BA.4/5-13, BA.4/5-18, BA.4/5-22, BA.4/5-25 and BA.4/5-34. The heavy chain variable domain of these antibodies are derived from IGHV1-69. The resulting mixed chain antibodies are set out in Table 8. Hence, the antibody of the invention may comprise all six CDRs (CDRH1-3 and CDRL1-3), and/or a heavy chain variable domain and a light chain variable domain, each comprising or consisting of an amino acid sequence having at least 80% (e.g. ≥80%, ≥90%, ≥95%, ≥96%, ≥97%, ≥98%, ≥99% or 100%)sequence identity to the corresponding variable domain of any one of the mixed chain antibodies as set out in Table 8.

In one embodiment, the first antibody and the second antibody are both selected from the group consisting of: BA.4/5-15, BA.4/5-20, BA.4/5-21 and BA.4/5-24. The heavy chain variable domain of these antibodies are derived from IGHV3-9. The resulting mixed chain antibodies are set out in Table 9. Hence, the antibody of the invention may comprise all six CDRs (CDRH1-3 and CDRL1-3), and/or a heavy chain variable domain

and a light chain variable domain, each comprising or consisting of an amino acid sequence having at least 80% (e.g. ≥80%, ≥90%, ≥95%, ≥96%, ≥97%, ≥98%, ≥99% or 100%) sequence identity to the corresponding variable domain of any one of the mixed chain antibodies as set out in Table 9.

The constant region domains of an antibody molecule of the invention, if present, may be selected having regard to the proposed function of the antibody molecule, and in particular the effector functions which may be required. For example, the constant region domains may be human IgA, IgD, IgE, IgG or IgM domains. Typically, the constant regions are of human origin. In particular, human IgG (i.e. IgG1, IgG2, IgG3 or IgG4) constant region domains may be used. Typically, the constant region is a human IgG1 constant region.

Properties of the antibodies of the invention

An antibody of the invention may be or may comprise a modification from the amino acid sequence of an antibody in Tables 1 and 3 to 9, whilst maintaining the activity and/or function of the antibody. The modification may a substitution, deletion and/or addition. For example, the modification may comprise 1, 2, 3, 4, 5, up to 10, up to 20, up to 30 or more amino acid substitutions and/or deletions from the amino acid sequence of an antibody in Tables 1 and 3 to 9. For example, the modification may comprise an amino acid substituted with an alternative amino acid having similar properties. Some properties of the 20 main amino acids, which can be used to select suitable substituents, are as follows:

Ala	aliphatic, hydrophobic, neutral	Met	hydrophobic, neutral
Cys	polar, hydrophobic, neutral	Asn	polar, hydrophilic, neutral
Asp	polar, hydrophilic, charged (-)	Pro	hydrophobic, neutral
Glu	polar, hydrophilic, charged (-)	Gln	polar, hydrophilic, neutral
Phe	aromatic, hydrophobic, neutral	Arg	polar, hydrophilic, charged (+)
Gly	aliphatic, neutral	Ser	polar, hydrophilic, neutral
His	aromatic, polar, hydrophilic, charged (+)	Thr	polar, hydrophilic, neutral
Ile	aliphatic, hydrophobic, neutral	Val	aliphatic, hydrophobic, neutral
Lys	polar, hydrophilic, charged (+)	Trp	aromatic, hydrophobic, neutral
Leu	aliphatic, hydrophobic, neutral	Tyr	aromatic, polar, hydrophobic

The modification may comprise a derivatised amino acid, e.g. a labelled or non-natural amino acid, providing the function of the antibody is not significantly adversely affected.

Modification of antibodies of the invention as described above may be prepared during synthesis of the antibody or by post-production modification, or when the antibody is in recombinant form using the known techniques of site-directed mutagenesis, random mutagenesis, or enzymatic cleavage and/or ligation of nucleic acids.

Antibodies of the invention may be modified (e.g. as described above) to improve the potency of said antibodies or to adapt said antibodies to new SARS-CoV-2 variants. The modifications may be amino acid substitutions to adapt the antibody to substitutions in a virus variant. For example, the known mode of binding of an antibody to the spike protein (e.g. by crystal structure determination, or modelling) may be used to identify the amino acids of the antibody that interact with the substitution in the virus variant. This information can then be used to identify possible substitutions of the antibody that will compensate for the change in the epitope characteristics. For example, a substitution of a hydrophobic amino acid in the spike protein to a negatively changes amino acid may be compensated by substituting the amino acid from the antibody that interacts with said amino acid in the spike protein to a positively charged amino acid. Methods for identifying residues of an antibody that may be substituted are encompassed by the present disclosure, for example, by determining the structure of antibody-antigen complexes as described herein.

The antibodies of the invention may contain one or more modifications to increase their cross-lineage neutralisation property. For example, E484 of the spike protein, which is a key residue that mediates the interaction with ACE2, is mutated in almost all currently circulating SARS-CoV-2 strains (see e.g. Figure 6, demonstrating that the Victoria, Delta and Gamma strains comprise E484 and that all remaining strains shown comprise an E484K, E484A or E484R mutation) resulting in differing neutralisation effects of the antibodies. Thus, antibodies that bind to E484 can be modified to compensate for the changes in E484 of the spike protein. For example, E484 is mutated from a negatively charged amino acid in the Victoria strain to a positively charged amino acid in the BA.2.3.20 SARs-CoV-2 strain. The amino acid residues of antibodies that bind to or near E484 may be mutated to compensate for the change in charge.

Antibodies of the invention may be isolated antibodies. A composition consisting of an isolated antibody is substantially free of other antibodies having different antigenic specificities.

The term 'antibody' as used herein may relate to whole antibodies (i.e. comprising the elements of two heavy chains and two light chains inter-connected by disulphide

bonds) as well as antigen-binding fragments thereof. Antibodies typically comprise immunologically active portions of immunoglobulin (Ig) molecules, i.e., molecules that contain an antigen binding site that specifically binds (immunoreacts with) an antigen. By "specifically binds" or "immunoreacts with", it is meant that the antibody reacts with one or more antigenic determinants of the desired antigen and does not react with other polypeptides. Each heavy chain is comprised of a heavy chain variable region (abbreviated herein as HCVR or VH) and at least one heavy chain constant region. Each light chain is comprised of a light chain variable region (abbreviated herein as LCVR or VL) and a light chain constant region. The variable regions of the heavy and light chains contain a binding domain that interacts with an antigen. The VH and VL regions can be further subdivided into regions of hypervariability, termed complementarity determining regions (CDR), interspersed with regions that are more conserved, termed framework regions (FR). Antibodies may include, but are not limited to, polyclonal, monoclonal, chimeric, dAb (domain antibody), single chain, Fab, Fab' and F(ab')2 fragments, scFvs, and Fab expression libraries

An antibody of the invention may be a monoclonal antibody. Monoclonal antibodies (mAbs) of the invention may be produced by a variety of techniques, including conventional monoclonal antibody methodology, for example those disclosed in "Monoclonal Antibodies: a manual of techniques" (Zola H, 1987, CRC Press) and in "Monoclonal Hybridoma Antibodies: techniques and applications" (Hurrell JGR, 1982 CRC Press).

An antibody of the invention may be multispecific, such as bispecific. A bispecific antibody of the invention binds two different epitopes. The epitopes may be in the same protein (e.g. two epitopes in spike protein of SARS-CoV-2) or different proteins (e.g. one epitope in spike protein and one epitope in another protein (such as coat protein) of SARS-CoV-2).

In one embodiment, a bispecific antibody of the invention may bind to two separate epitopes on the spike protein of SARS-CoV-2. The bispecific antibody may bind to the NTD of the spike protein and to the RBD of the spike protein. The bispecific antibody may bind to two different epitopes in the RBD of the spike protein.

One or more (e.g. two) antibodies of the invention can be coupled to form a multispecific (e.g. bispecific) antibody. Methods to prepare multispecific, e.g. bispecific, antibodies are well known in the art.

An antibody may be selected from the group consisting of single chain antibodies, single chain variable fragments (scFvs), variable fragments (Fvs), fragment antigen-binding regions (Fabs), recombinant antibodies, monoclonal antibodies, fusion proteins comprising the antigen-binding domain of a native antibody or an aptamer, single-domain antibodies (sdAbs), also known as VHH antibodies, nanobodies (Camelid-derived single-domain antibodies), shark IgNAR-derived single-domain antibody fragments called VNAR, diabodies, triabodies, Anticalins, aptamers (DNA or RNA) and active components or fragments thereof.

The constant region domains of an antibody molecule of the invention, if present, may be selected having regard to the proposed function of the antibody molecule, and in particular the effector functions which may be required. For example, the constant region domains may be human IgA, IgD, IgE, IgG or IgM domains. Typically, the constant regions are of human origin. In particular, human IgG (i.e. IgG1, IgG2, IgG3 or IgG4) constant region domains may be used. Typically, the constant region is a human IgG1 constant region.

The light chain constant region may be either lambda or kappa.

Antibodies of the invention may be mono-specific or multi-specific (e.g. bi-specific). A multi-specific antibody comprises at least two different variable domains, wherein each variable domain is capable of binding to a separate antigen or to a different epitope on the same antigen.

An antibody of the invention may be a chimeric antibody, a CDR-grafted antibody, a nanobody, a human or humanised antibody. Typically, the antibody is a human antibody. Fully human antibodies are those antibodies in which the variable regions and the constant regions (where present) of both the heavy and the light chains are all of human origin, or substantially identical to sequences of human origin, but not necessarily from the same antibody.

The antibody of the invention may be a full-length antibody. For example, the antibody may comprise a heavy chain variable domain of an antibody in Table 1 or 3 to 9, a light chain variable domain of an antibody in Table 1 or 3 to 9, and a constant region, such as an IgA, IgD, IgE, IgG (IgG1, IgG2, IgG3 or IgG4) or IgM constant region.

The antibody of the invention may be an antigen-binding fragment. An antigen-binding fragment of the invention binds to the same epitope of the parent antibody, i.e. the antibody from which the antigen-binding fragment is derived. An antigen-binding fragment of the invention typically retains the parts of the parent antibody that interact with

the epitope. The antigen-binding fragment typically comprise the complementarity-determining regions (CDRs) that interact with the antigen, such as one, two, three, four, five or six CDRs. In some embodiments, the antigen-binding fragment further comprises the structural scaffold surrounding the CDRs of the parent antibody, such as the variable region domains of the heavy and/or light chains. Typically, the antigen-binding fragment retains the same or similar binding affinity to the antigen as the parent antibody.

An antigen-binding fragment does not necessarily have an identical sequence to the parent antibody. In one embodiment, the antigen-binding fragment may have ≥70%, ≥80%, ≥90%, ≥95%, ≥96%, ≥97%, ≥98%, ≥99% or 100% sequence identity with the respective CDRs of the parent antibody. In one embodiment, the antigen-binding fragment may have ≥70%, ≥80%, ≥90%, ≥95%, ≥96%, ≥97%, ≥98%, ≥99% or 100% sequence identity with the respective variable region domains of the parent antibody. Typically, the non-identical amino acids of a variable region are not in the CDRs.

The antigen-binding fragments of antibodies of the invention retain the ability to selectively bind to an antigen. Antigen-binding fragments of antibodies include single chain antibodies (i.e. a full-length heavy chain and light chain); Fab, modified Fab, Fab', modified Fab', F(ab')2, Fv, Fab-Fv, Fab-dsFv, single domain antibodies (e.g. VH or VL or VHH), scFv.

An antigen-binding function of an antibody can be performed by fragments of a full-length antibody. The methods for creating and manufacturing these antibody fragments are well known in the art (see for example Verma R *et al.*, 1998, J. Immunol. Methods, 216, 165-181).

Methods for screening antibodies of the invention that do not share 100% amino acid sequence identity with one of the antibodies disclosed herein, that possess the desired specificity, affinity and functional activity include the methods described herein, e.g. enzyme linked immunosorbent assays, biacore, focus reduction neutralisation assay (FRNT), and other techniques known within the art.

With regards to function, an antibody of the invention may be able to neutralise at least one biological activity of SAR-CoV-2 (a neutralising antibody), particularly to neutralise virus infectivity.

Neutralisation may also be determined using IC_{50} or IC_{90} values. For example, the antibody may have an IC_{50} value of ≤0.1μg/ml, ≤0.05μg/ml, ≤0.01μg/ml ≤0.005μg/ml or ≤0.002μg/ml. In some instances an antibody of the invention may have an IC_{50} value of

between 0.0001 μg/ml and 0.1 μg/ml, sometimes between 0.0001μg/ml and 0.05 μg/ml or even between 0.0001 μg/ml and 0.001 μg/ml.

For example, the IC_{50} values of some of the antibodies of Table 1 are provided in Figure 2A and Figure 2B.

The ability of an antibody to neutralise virus infectivity may be measured using an appropriate assay, particularly using a cell-based neutralisation assay, as is known in the art. For example, the neutralisation ability may be measured in a focus reduction neutralisation assay (FRNT) where the reduction in the number of cells (e.g. human cells) infected with the virus (e.g. for 2 hours at 37 °C) in the presence of the antibody is compared to a negative control in which no antibodies were added.

An antibody of the invention may block the interaction between the spike protein of SAR-CoV-2 with the cell surface receptor, angiotensin-converting enzyme 2 (ACE2), of the target cell, e.g. by direct blocking or by disrupting the pre-fusion conformation of the spike protein.

Blocking of the interaction between spike and ACE2 can be total or partial. For example, an antibody of the invention may reduce spike-ACE2 formation by ≥50%, ≥60%, ≥70%, ≥80%, ≥90%, ≥95%, ≥99% or 100%. Blocking of spike-ACE2 formation can be measured by any suitable means known in the art, for example, by ELISA.

Most antibodies showing neutralisation also showed blocking of the interaction between the spike protein and ACE2. Furthermore, a number of non-neutralising antibodies are good ACE2 blockers.

In terms of binding kinetics, an antibody of the invention may have an affinity constant (K_D) value for the spike protein of SARS-CoV-2 of ≤5nM, ≤4nM, ≤3nM, ≤2nM, ≤1nM, ≤0.5nM, ≤0.4nM, ≤0.3nM, ≤0.2nM or ≤0.1nM.

The KD value can be measured by any suitable means known in the art, for example, by ELISA or Surface Plasmon Resonance (Biacore) at 25 °C.

Binding affinity (K_D) may be quantified by determining the dissociation constant (K_d) and association constant (K_a) for an antibody and its target. For example, the antibody may have an association constant (K_a) of ≥ 10000 $M^{-1}s^{-1}$, ≥ 50000 $M^{-1}s^{-1}$, ≥ 100000 $M^{-1}s^{-1}$, ≥ 200000 $M^{-1}s^{-1}$ or ≥ 500000 $M^{-1}s^{-1}$, and/or a dissociation constant (K_d) of ≤ 0.001 s^{-1}, ≤ 0.0005 s^{-1}, ≤ 0.004 s^{-1}, ≤ 0.003 s^{-1}, ≤ 0.002 s^{-1} or ≤ 0.0001 s^{-1}.

An antibody of the invention is preferably able to provide *in vivo* protection in coronavirus (e.g. SARS-CoV-2) infected animals. For example, administration of an antibody of the invention to coronavirus (e.g. SARS-CoV-2) infected animals may result in

a survival rate of ≥30%, ≥40%, ≥50%, ≥60%, ≥70%, ≥80%, ≥90%, ≥95% or 100%. Survival rates may be determined using routine methods.

Antibodies of the invention may have any combination of one or more of the above properties.

Antibodies of the invention may bind to the same epitope as, or compete for binding to SARS-CoV-2 spike protein with, any one of the antibodies described herein (i.e. in particular with antibodies with the heavy and light chain variable regions described above). Methods for identifying antibodies binding to the same epitope, or cross-competing with one another, are used in the Examples and discussed further below.

Fc regions

An antibody of the invention may or may not comprise an Fc domain.

The antibodies of the invention may be modified in the Fc region in order to improve their stability. Such modifications are known in the art. Modifications may improve the stability of the antibody during storage of the antibody. The *in vivo* half-life of the antibody may be improved by modifications of the Fc-region.

For example, cysteine residue(s) can be introduced into the Fc region, thereby allowing interchain disulphide bond formation in this region. The homodimeric antibody thus generated can have improved internalization capability and/or increased complement-mediated cell killing and antibody-dependent cellular cytotoxicity (ADCC). (See Caron et al., J. Exp Med., 176: 1191-1195 (1992) and Shopes, J. Immunol., 148: 2918-2922 (1992)). Alternatively, an antibody can be engineered that has dual Fc regions and can thereby have enhanced complement lysis and ADCC capabilities. (See Stevenson et al., Anti-Cancer Drug Design, 3: 219-230 (1989)).

For example, an antibody of the invention may be modified to promote the interaction of the Fc domain with FcRn. The Fc domain may be modified to improve the stability of the antibody by affecting Fc and FcRn interaction at low pH, such as in the endosome. The M252Y/S254T/T256E (YTE) mutation may be used to improve the half-life of an IgG1 antibody.

The antibody may be modified to affect the interaction of the antibody with other receptors, such as FcγRI, FcγRIIA, FcγRIIB, FcγRIII, and FcαR. Such modifications may be used to affect the effector functions of the antibody.

In one embodiment, an antibody of the invention comprises an altered Fc domain as described herein below. In another preferred embodiment an antibody of the invention

comprises an Fc domain, but the sequence of the Fc domain has been altered to modify one or more Fc effector functions.

In one embodiment, an antibody of the invention comprises a "silenced" Fc region. For example, in one embodiment an antibody of the invention does not display the effector function or functions associated with a normal Fc region. An Fc region of an antibody of the invention does not bind to one or more Fc receptors.

In one embodiment, an antibody of the invention does not comprise a CH_2 domain. In one embodiment, an antibody of the invention does not comprise a CH_3 domain. In one embodiment, an antibody of the invention comprises additional CH_2 and/or CH_3 domains.

In one embodiment, an antibody of the invention does not bind Fc receptors. In one embodiment, an antibody of the invention does not bind complement. In an alternative embodiment, an antibody of the invention does not bind FcγR, but does bind complement.

In one embodiment, an antibody of the invention in general may comprise modifications that alter serum half-life of the antibody. Hence, in another embodiment, an antibody of the invention has Fc region modification(s) that alter the half-life of the antibody. Such modifications may be present as well as those that alter Fc functions. In one preferred embodiment, an antibody of the invention has modification(s) that alter the serum half-life of the antibody.

In one embodiment, an antibody of the invention may comprise a human constant region, for instance IgA, IgD, IgE, IgG or IgM domains. In particular, human IgG constant region domains may be used, especially of the IgG1 and IgG3 isotypes when the antibody molecule is intended for therapeutic uses where antibody effector functions are required. Alternatively, IgG2 and IgG4 isotypes may be used when the antibody molecule is intended for therapeutic purposes and antibody effector functions are not required.

In one embodiment, the antibody heavy chain comprises a CH_1 domain and the antibody light chain comprises a CL domain, either kappa or lambda. In one embodiment, the antibody heavy chain comprises a CH_1 domain, a CH_2 domain and a CH_3 domain and the antibody light chain comprises a CL domain, either kappa or lambda.

The four human IgG isotypes bind the activating Fcγ receptors (FcγRI, FcγRIIa, FcγRIIc, FcγRIIIa), the inhibitory FcγRIIb receptor, and the first component of complement (C1q) with different affinities, yielding very different effector functions (Bruhns P. *et al.*, 2009. Specificity and affinity of human Fcγ receptors and their polymorphic variants for human IgG subclasses. Blood. 113(16):3716-25), see also Jeffrey B. Stavenhagen, et al. *Cancer Research* 2007 Sep 15; 67(18):8882-90. In one

embodiment, an antibody of the invention does not bind to Fc receptors. In another embodiment of the invention, the antibody does bind to one or more type of Fc receptors.

In one embodiment the Fc region employed is mutated, in particular a mutation described herein. In one embodiment the Fc mutation is selected from the group comprising a mutation to remove or enhance binding of the Fc region to an Fc receptor, a mutation to increase or remove an effector function, a mutation to increase or decrease half-life of the antibody and a combination of the same. In one embodiment, where reference is made to the impact of a modification it may be demonstrated by comparison to the equivalent antibody but lacking the modification.

Some antibodies that selectively bind FcRn at pH 6.0, but not pH 7.4, exhibit a higher half-life in a variety of animal models. Several mutations located at the interface between the CH_2 and CH_3 domains, such as T250Q/M428L (Hinton PR. *et al.*, 2004. Engineered human IgG antibodies with longer serum half-lives in primates. J Biol Chem. 279(8):6213-6) and M252Y/S254T/T256E + H433K/N434F (Vaccaro C. *et al.*, 2005. Engineering the Fc region of immunoglobulin G to modulate *in vivo* antibody levels. Nat Biotechnol. 23(10):1283-8), have been shown to increase the binding affinity to FcRn and the half-life of IgG1 *in vivo*. Hence, modifications may be present at M252/S254/T256 + H44/N434 that alter serum half-life and in particular M252Y/S254T/T256E + H433K/N434F may be present. In one embodiment, it is desired to increase half-life. In another embodiment, it may be actually desired to decrease serum half-life of the antibody and so modifications may be present that decrease serum half-life.

Numerous mutations have been made in the CH_2 domain of human IgG1 and their effect on ADCC and CDC tested *in vitro* (Idusogie EE. *et al.*, 2001. Engineered antibodies with increased activity to recruit complement. J Immunol. 166(4):2571-5). Notably, alanine substitution at position 333 was reported to increase both ADCC and CDC. Hence, in one embodiment a modification at position 333 may be present, and in particular one that alters ability to recruit complement. Lazar *et al.* described a triple mutant (S239D/I332E/A330L) with a higher affinity for FcγRIIIa and a lower affinity for FcγRIIb resulting in enhanced ADCC (Lazar GA. et al., 2006). Hence, modifications at S239/I332/A330 may be present, particularly those that alter affinity for Fc receptors and in particular S239D/I332E/A330L . Engineered antibody Fc variants with enhanced effector function. PNAS 103(11): 4005–4010). The same mutations were used to generate an antibody with increased ADCC (Ryan MC. *et al.*, 2007. Antibody targeting of B-cell maturation antigen on malignant plasma cells. Mol. Cancer Ther., 6: 3009 – 3018).

Richards *et al.* studied a slightly different triple mutant (S239D/I332E/G236A) with improved FcγRIIIa affinity and FcγRIIa/FcγRIIb ratio that mediates enhanced phagocytosis of target cells by macrophages (Richards JO *et al* 2008. Optimization of antibody binding to Fcgamma RIIa enhances macrophage phagocytosis of tumor cells. Mol Cancer Ther. 7(8):2517-27). In one embodiment, S239D/I332E/G236A modifications may be therefore present.

In another embodiment, an antibody of the invention may have a modified hinge region and/or CH1 region. Alternatively, the isotype employed may be chosen as it has a particular hinge regions.

Major public V regions

Public V-regions, also described as public V-genes herein, are the V regions of the germline heavy chain and light chain regions that are found in a large proportion of the antibody responses to SARS-CoV-2 found within the population. In this application, the V regions are specific responses to the original BA.4/5 SARS-CoV-2 variant. That is to say, many individuals utilise the same v-regions from their germline v-region repertoire when generating an immune response to SARS-CoV-2 variants.

As used herein, an antibody "derived" from a specific v-region refers to antibodies that were generated by V(D)J recombination using that germline v-region sequence. For example, the germline IGHV1-69 v-region sequence may undergo somatic recombination and somatic mutation to arrive at an antibody that specifically binds to the spike protein of SARS-CoV-2. The nucleotide sequence encoding the antibody does not comprise a sequence identical to the IGHV1-69 germline sequence, nevertheless, the antibody is still derived from this v-region. An antibody of the invention typically comprises no more than 20 non-silent mutations in the v-region, when compared to the germline sequence, such as no more than 17 non-silent mutations. An antibody of the invention typically comprises between 5-20 non-silent mutations in the v-region, when compared to the germline sequence, such as between 6-18, 7-17 and 8-15 non-silent mutations. An antibody of the invention typically comprises between 5-15 amino acid changes in the v-region, when compared to the amino acid sequence encoded by the germline sequence, such as between 6-14 and 7-12 amino acid changes. Germline v-region sequences are well known in the art, and methods of identifying whether a certain region of an antibody is derived from a particular germline v-region sequence are also well known in the art.

In one embodiment, an antibody of the invention derives from a v-region selected from IGHV4-39, IGHV3-30, IGHV3-53, IGHV3-66, IGHV1-46, IGHV3-33, IGHV3-9, IGHV1-69 or IGHV3-23. The inventors found that the potent neutralising antibodies identified herein comprised non-silent mutations in the CDRs of these v-regions, as set out in Table 2. Thus, in one embodiment, an antibody of the invention is encoded by a v-region selected from IGHV4-39, IGHV3-30, IGHV3-53, IGHV3-66, IGHV1-46, IGHV3-33, IGHV3-9, IGHV1-69 or IGHV3-23 and having 5-20 non-silent nucleotide mutations, such as 6-18, 7-17 and 8-15 non-silent mutations, when compared to the naturally occurring germline sequence. In one embodiment, an antibody of the invention is encoded by a v-region selected from IGHV1-69 and having 10-20 non-silent nucleotide mutations, when compared to the naturally occurring germline sequence. In one embodiment, an antibody of the invention is encoded by a v-region selected from IGHV3-66 and having 2-15 non-silent nucleotide mutations, when compared to the naturally occurring germline sequence. In one embodiment, an antibody of the invention is encoded by a v-region selected from IGHV3-53 and having 8-18 non-silent nucleotide mutations, when compared to the naturally occurring germline sequence. In one embodiment, an antibody of the invention is encoded by a v-region selected from IGHV3-9 and having 7-13 non-silent nucleotide mutations, when compared to the naturally occurring germline sequence. In one embodiment, an antibody of the invention is encoded by a v-region selected from IGHV3-30 and having 10-16 non-silent nucleotide mutations, when compared to the naturally occurring germline sequence. In one embodiment, an antibody of the invention is encoded by a v-region selected from IGHV4-39 and having 5-6 non-silent nucleotide mutations, when compared to the naturally occurring germline sequence.

A silent mutation is defined herein is a change in the nucleotide sequence without a change in the amino acid sequence for which the nucleotide sequence encodes. A non-silent mutation is therefore a mutation that leads to a change in the amino acid sequence encoded by the nucleotide sequence.

The inventors have surprisingly found that the light chain variable region of two antibodies having the same heavy chain v-region may be exchanged to produce a mixed-chain antibody comprising the heavy chain variable region of a first antibody and the light chain variable region of a second antibody. For example, the two antibodies may both comprise a heavy chain variable region derived from IGHV3-53. Preferably, both antibodies also comprise a light chain variable region derived from the same light chain v-region, although this is not essential because, for example, the light chain of some

antibodies having a heavy chain variable region derived from IGHV3-53 may be matched with any heavy chain variable region derived from IGHV3-53 and lead to a potent neutralising antibody. As described above, the two antibodies may comprise a heavy chain variable region derived from IGHV3-53 and/or IGHV3-66.

In one embodiment, an antibody of the invention comprises the CDRs of an heavy chain variable domain of an antibody derived from a major public v-region selected from IGHV1-69, IGHV3-9, IGHV3-53/3-66, IGHV3-30 and IGHV4-39, such as antibodies BA.4/5-1 and BA.4/5-31 for IGHV4-39, antibodies BA.4/5-2 and BA.4/5-12 for IGHV3-30, antibodies BA.4/5-6, BA.4/5-7, BA.4/5-17, BA.4/5-23, BA.4/5-8, BA.4/5-10, BA.4/5-28 and BA.4/5-32 for IGHV3-53/3-66, antibodies BA.4/5-13, BA.4/5-18, BA.4/5-22, BA.4/5-25 and BA.4/5-34 for IGHV1-69, or antibodies BA.4/5-15, BA.4/5-20, BA.4/5-21 and BA.4/5-24 for IGHV3-9. The SEQ ID NOs corresponding to the CDRs of each of these antibodies are shown in Table 1.

In one embodiment, an antibody of the invention comprises the heavy chain variable domain of an antibody derived from a major public v-region selected from IGHV1-69, IGHV3-9, IGHV3-53/3-66, IGHV3-30 and IGHV4-39, such as antibodies BA.4/5-1 and BA.4/5-31 for IGHV4-39, antibodies BA.4/5-2 and BA.4/5-12 for IGHV3-30, antibodies BA.4/5-6, BA.4/5-7, BA.4/5-17, BA.4/5-23, BA.4/5-8, BA.4/5-10, BA.4/5-28 and BA.4/5-32 for IGHV3-53/3-66, antibodies BA.4/5-13, BA.4/5-18, BA.4/5-22, BA.4/5-25 and BA.4/5-34 for IGHV1-69, or antibodies BA.4/5-15, BA.4/5-20, BA.4/5-21 and BA.4/5-24 for IGHV3-9. The SEQ ID NOs corresponding to the CDRs of each of these antibodies are shown in Table 1.

In one embodiment, the invention provides a method of generating an antibody that binds specifically to the spike protein of SARS-CoV-2 (e.g. a SARS-CoV-2 strain of the Victoria, Alpha, Beta, Gamma, Delta, BA.1, BA.1.1, BA.2, BA.10.4, BA.2.12.1, BA.2.30.2, BA.2.75, BA.2.75.2, BA.4/5, BA.4.6, BQ.1, BQ.1.1, BJ.1, BS.1, BF.7, BN.1, XBB, XBB.1 and/or XBB.1.5), the method comprising identifying two or more antibodies derived from the same light chain and/or heavy chain v-regions, replacing the light chain of a first antibody with the light chain of a second antibody, to thereby generate a mixed-chain antibody comprising the heavy chain of the first antibody and the light chain of the second antibody. In one embodiment, the method further comprises determining the affinity for and/or neutralisation of SARS-CoV-2 of the mixed-chain antibody. The method may further comprise comparing the affinity of the mixed-chain antibody with that

of the first and/or second antibodies. The method may further comprise selecting a mixed chain antibody that has the same or greater affinity than the first and/or second antibodies.

In another embodiment, the invention provides an antibody that specifically binds to the BA.4/5 variant of SARS-CoV-2, wherein the antibody has a v-region derived from IGHV1-69, IGHV3-9, IGHV3-53 or IGHV3-66. It has been surprisingly discovered that antibody responses to infection with the BA.4/5 variant of SARS-CoV-2 is biased towards antibodies with a heavy chain variable region derived from IGHV1-69, IGHV3-9, IGHV3-53 or IGHV3-66. In one embodiment, wherein the antibody heavy chain is derived from IGHV1-69, the antibody of the invention comprises the CDRH1, CDRH2 and CDRH3 from BA.4/5-13, BA.4/5-18, BA.4/5-22, BA.4/5-25 or BA.4/5-34. In one embodiment, wherein the antibody heavy chain is derived from IGHV3-9, the antibody of the invention comprises the CDRH1, CDRH2 and CDRH3 from BA.4/5-15, BA.4/5-20, BA.4/5-21 or BA.4/5-24. In one embodiment, wherein the antibody heavy chain is derived from IGHV3-53, the antibody of the invention comprises the CDRH1, CDRH2 and CDRH3 from BA.4/5-6, BA.4/5-7, BA.4/5-17 or BA.4/5-23. In one embodiment, wherein the antibody heavy chain is derived from IGHV3-66, the antibody of the invention comprises the CDRH1, CDRH2 and CDRH3 from BA.4/5-8, BA.4/5-10, BA.4/5-28 or BA.4/5-32.

Antibody conjugates

The invention also pertains to immunoconjugates comprising an antibody conjugated to a cytotoxic agent such as a toxin (e.g., an enzymatically active toxin of bacterial, fungal, plant, or animal origin, or fragments thereof), or a radioactive isotope (i.e., a radioconjugate). Conjugates of the antibody and cytotoxic agent may be made using a variety of bifunctional protein-coupling agents known in the art.

An antibody, of the invention may be conjugated to a molecule that modulates or alters serum half-life. An antibody, of the invention may bind to albumin, for example in order to modulate the serum half-life. In one embodiment, an antibody of the invention will also include a binding region specific for albumin. In another embodiment, an antibody of the invention may include a peptide linker which is an albumin binding peptide. Examples of albumin binding peptides are included in WO2015/197772 and WO2007/106120 the entirety of which are incorporated by reference.

Polynucleotides, vectors and host cells

The invention also provides one or more isolated polynucleotides (e.g. DNA) encoding the antibody of the invention. In one embodiment, the polynucleotide sequence is collectively present on more than one polynucleotide, but collectively together they are able to encode an antibody of the invention. For example, the polynucleotides may encode the heavy and/or light chain variable regions(s) of an antibody of the invention. The polynucleotides may encode the full heavy and/or light chain of an antibody of the invention. Typically, one polynucleotide would encode each of the heavy and light chains. Hence, the invention provides a first polynucleotide encoding the heavy chain variable domain of an antibody of the invention and a second polynucleotide encoding the light chain variable domain of said antibody. The invention also provides a polynucleotide encoding the heavy chain variable domain and the light chain variable domain of an antibody according to the invention.

Polynucleotides which encode an antibody of the invention can be obtained by methods well known to those skilled in the art. For example, DNA sequences coding for part or all of the antibody heavy and light chains may be synthesised as desired from the corresponding amino acid sequences.

General methods by which the vectors may be constructed, transfection methods and culture methods are well known to those skilled in the art. In this respect, reference is made to "Current Protocols in Molecular Biology", 1999, F. M. Ausubel (ed), Wiley Interscience, New York and the Maniatis Manual produced by Cold Spring Harbor Publishing.

A polynucleotide of the invention may be provided in the form of an expression cassette, which includes control sequences operably linked to the inserted sequence, thus allowing for expression of the antibody of the invention *in vivo*. Hence, the invention also provides one or more expression cassettes encoding the one or more polynucleotides that encoding an antibody of the invention. These expression cassettes, in turn, are typically provided within vectors (e.g. plasmids or recombinant viral vectors). Hence, in one embodiment, the invention provides a vector encoding an antibody of the invention. In another embodiment, the invention provides vectors which collectively encode an antibody of the invention. The vectors may be cloning vectors or expression vectors. A suitable vector may be any vector which is capable of carrying a sufficient amount of genetic information, and allowing expression of a polypeptide of the invention.

The polynucleotides, expression cassettes or vectors of the invention are introduced into a host cell, e.g. by transfection. Hence, the invention also provides a host cell comprising the one or more polynucleotides, expression cassettes or vectors of the invention. The polynucleotides, expression cassettes or vectors of the invention may be introduced transiently or permanently into the host cell, allowing expression of an antibody from the one or more polynucleotides, expression cassettes or vectors. Such host cells include transient, or preferably stable higher eukaryotic cell lines, such as mammalian cells or insect cells, lower eukaryotic cells, such as yeast, or prokaryotic cells, such as bacteria cells. Particular examples of cells include mammalian HEK293, such as HEK293F, HEK293T, HEK293S or HEK Expi293F, CHO, HeLa, NS0 and COS cells, or any other cell line used herein, such as the ones used in the Examples. Preferably the cell line selected will be one which is not only stable, but also allows for mature glycosylation.

The invention also provides a process for the production of an antibody of the invention, comprising culturing a host cell containing one or more vectors of the invention under conditions suitable for the expression of the antibody from the one or more polynucleotides of the invention, and isolating the antibody from said culture.

Combination of antibodies

Certain Table 1 antibodies may be particularly effective when used in combination, e.g. to minimise loss of activity due to SARS-CoV-2 variants, maximise therapeutic effects and/or increase diagnostic power. Useful combinations include antibodies that do not cross-compete with one another and/or bind to non-overlapping epitopes.

Thus, the invention provides a combination of the antibodies of the invention, wherein each antibody is capable of binding to the spike protein of coronavirus SARS-CoV-2, wherein at least one antibody comprises all six CDRs of an antibody in Table 1.

The invention also provides a combination of antibodies, comprising a first antibody which is an antibody according to the invention, in combination with at least one further antibody that does not compete with the first antibody for binding to the spike protein of coronavirus SARS-CoV-2. The first and the at least one further antibodies may bind to different epitopes in the same domain, or may bind to epitopes in different domains in the spike protein. For example, the first antibody may bind to the RBD domain and the at least one further antibody may bind to the NTD of the spike protein. Alternatively, the first antibody may bind to the NTD domain and the at least one further antibody may bind to the RBD of the spike protein.

A combination of the antibodies of the invention may be useful as a therapeutic cocktail. Hence, the invention also provides a pharmaceutical composition comprising a combination of the antibodies of the invention. This is because a new SARS-CoV-2 variant may circulate that is not neutralised by a first of the antibodies in the cocktail but is neutralised by a second antibody in the cocktail, whilst the converse may be true for a further SARS-CoV-2 variant that circulates. Thus, a cocktail of antibodies of the invention may provide a more robust treatment for SARS-CoV-2 than a single antibody of the invention alone.

A combination of the antibodies of the invention may be useful for diagnosis. Hence, the invention also provides a diagnostic kit comprising a combination of the antibodies of the invention. Also provided herein are methods of diagnosing a disease or complication associated with coronavirus infections in a subject, as explained further below.

A fully cross-neutralising antibody, e.g. BA.4/5-2, may be used as a reference to confirm the presence and/or amount of any variants of concern (VoC) SARS-CoV-2 in the sample. An antibody that binds to a limited number of VoCs may be used to confirm the presence and/or amount of that VoC in the sample. For example, if BA.4/5-2 exhibits binding to the sample but BA.4/5-8 does not exhibit binding to the sample of SARS-CoV-2, then the spike protein may be the spike protein of the BN.1 VoC. This may be determined by any method known to the skilled person, such as via an immunoassay, e.g. an ELISA or an immunochromatographic assay. Reduced binding may be determined by comparison and/or normalisation to the reference, and/or by comparison to positive/negative control samples or data.

Pharmaceutical composition

The invention provides a pharmaceutical composition comprising an antibody of the invention. The composition may comprise a combination (such as two, three or four) of the antibodies of the invention. The pharmaceutical composition may also comprise a pharmaceutically acceptable carrier.

The composition of the invention may include one or more pharmaceutically acceptable salts. A "pharmaceutically acceptable salt" refers to a salt that retains the desired biological activity of the parent compound and does not impart any undesired toxicological effects. Examples of such salts include acid addition salts and base addition salts.

Suitable pharmaceutically acceptable carriers comprise aqueous carriers or diluents. Examples of suitable aqueous carriers include water, buffered water and saline.

Other suitable pharmaceutically acceptable carriers include ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils, such as olive oil, and injectable organic esters, such as ethyl oleate. In many cases, it will be desirable to include isotonic agents, for example, sugars, polyalcohols such as mannitol, sorbitol, or sodium chloride in the composition.

Therapeutic compositions typically must be sterile and stable under the conditions of manufacture and storage. The composition can be formulated as a solution, microemulsion, liposome, or other ordered structure suitable to high drug concentration.

Pharmaceutical compositions of the invention may comprise additional therapeutic agents, for example an anti-viral agent. The anti-viral agent may bind to coronavirus and inhibit viral activity. Alternatively, the anti-viral agent may not bind directly to coronavirus but still affect viral activity/infectivity. The anti-viral agent could be a further anti-coronavirus antibody, which binds somewhere on SARS-CoV-2 other than the spike protein. Examples of an anti-viral agent useful with the invention include Remdesivir, Lopinavir, ritonavir, APN01, and Favilavir.

The additional therapeutic agent may be an anti-inflammatory agent, such as a corticosteroid (e.g. Dexamethasone) or a non-steroidal anti-inflammatory drug (e.g. Tocilizumab).

The additional therapeutic agent may be an anti-coronavirus vaccine.

The pharmaceutical composition may be administered subcutaneously, intravenously, intradermally, intramuscularly, intranasally or orally.

Also within the scope of the invention are kits comprising antibodies or other compositions of the invention and instructions for use. The kit may further contain one or more additional reagents, such as an additional therapeutic or prophylactic agent as discussed herein.

Methods and uses of the invention

The invention further relates to the use of the antibodies and the pharmaceutical compositions, described herein, e.g. in a method for treatment of the human or animal body by therapy, or in a diagnostic method. The method of treatment may be therapeutic or prophylactic.

For example, the invention relates to methods of treating coronavirus (e.g. SARS-CoV-2) infections, a disease or complication associated therewith, e.g. COVID-19. The method may comprise administering a therapeutically effective amount of an antibody, a combination of antibodies, or a pharmaceutical composition of the invention. The method may further comprise identifying the presence of coronavirus, or fragments thereof, in a sample, e.g. SARS-CoV-2, from the subject. The invention also relates to an antibody, a combination of antibodies, or a pharmaceutical composition according to the invention for use in a method of treating coronavirus (e.g. SARS-CoV-2) infections, a disease or complication associated therewith, e.g. COVID-19.

The invention also relates to a method of formulating a composition for treating coronavirus (e.g. SARS-CoV-2) infections, a disease or complication associated therewith, e.g. COVID-19, wherein said method comprises mixing an antibody, a combination of antibodies, or a pharmaceutical composition according to the invention with an acceptable carrier to prepare said composition.

The invention also relates to the use of an antibody, a combination of antibodies, or a pharmaceutical composition according to the invention for treating coronavirus (e.g. SARS-CoV-2) infections or a disease or complication associated therewith, e.g. COVID-19.

The invention also relates to the use of an antibody, a combination of antibodies, or a pharmaceutical composition according to the invention for the manufacture of a medicament for treating or preventing coronavirus (e.g. SARS-CoV-2) infections or a disease or complication associated therewith, e.g. COVID-19.

The invention also relates to preventing, treating or diagnosing coronavirus infection caused by any SARS-CoV-2 strain. The coronavirus infection may be caused by any SARS-CoV-2 strain.

The SARS-CoV-2 strain may be the earliest identified Wuhan strain (hCoV-19/Wuhan/WIV04/2019 (WIV04); GISAID accession no. EPI_ISL_402124), and variants thereof. For example, the SARS-CoV-2 strain may be a member of lineage Victoria, Alpha, Beta, Gamma, Delta, BA.1, BA.1.1, BA.2, BA.2.10.4, BA.2.12.1, BA.2.3.20, BA.2.75, BA.2.75.2, BA.4/5, BA.4.6, BQ.1, BQ.1.1, BJ.1, BS.1, BF.7, BN.1, XBB, XBB.1, or XBB1.5. The strain may be an as-yet-unidentified strain of SARS-CoV-2 comprising mutations in the RBD and/or NTD already identified in the existing strains, as shown in Figure 6.

The SARS-CoV-2 strain may comprise one or more mutations, e.g. in the spike protein, relative to the hCoV-19/Wuhan/WIV04/2019 (WIV04) (GISAID accession no. EPI_ISL_402124). In other words, the SARS-CoV-2 strain may be a modified hCoV-19/Wuhan/WIV04/2019 (WIV04) strain comprising one or more modifications, e.g. in the spike protein.

The mutation may be the mutations (e.g. substitutions) observed in the BA.4/5 strain of SARS-CoV-2. The mutation may be the mutations (e.g. substitutions) observed in the Victoria, Alpha, Beta, Gamma, Delta, BA.1, BA.1.1, BA.2, BA.2.10.4, BA.2.12.1, BA.2.3.20, BA.2.75, BA.2.75.2, BA.4/5, BA.4.6, BQ.1, BQ.1.1, BJ.1, BS.1, BF.7, BN.1, XBB, XBB.1, or XBB1.5 strains of SARS-CoV-2.

All of the antibodies provided in Table 1 are effective in neutralising the BA.4/5 SARS-Cov-2 strain (see Figure 2A). Hence, the invention may relate to these antibodies for use in treating, prevent, treating or diagnosing coronavirus infection caused by a SARS-Cov-2 strain.

The methods and uses of the invention may comprise inhibiting the disease state (such as COVID-19), *e.g.* arresting its development; and/or relieving the disease state (such as COVID-19), *e.g.* causing regression of the disease state until a desired endpoint is reached.

The methods and uses of the invention may comprise the amelioration or the reduction of the severity, duration or frequency of a symptom of the disease state (such as COVID-19) (*e.g.* lessen the pain or discomfort), and such amelioration may or may not be directly affecting the disease. The symptoms or complications may be fever, headache, fatigue, loss of appetite, myalgia, diarrhoea, vomiting, abdominal pain, dehydration, respiratory tract infections, cytokine storm, acute respiratory distress syndrome (ARDS) sepsis, and/or organ failure (e.g. heart, kidneys, liver, GI, lungs).

The methods and uses of the invention may lead to a decrease in the viral load of coronavirus (e.g. SARS-CoV-2), e.g. by ≥10%, ≥20%, ≥30%, ≥40%, ≥50%, ≥60%, ≥70%, ≥80%, ≥90%, or 100% compared to pre-treatment. Methods of determining viral load are well known in the art, e.g. infection assays.

The methods and uses of the invention may comprise preventing the coronavirus infection from occurring in a subject (*e.g.* humans), in particular, when such subject is predisposed to complications associated with coronavirus infection.

The invention also relates to identifying subjects that have a coronavirus infection, such as by SARS-CoV-2. For example, the methods and uses of the invention may involve

identifying the presence of coronavirus (e.g. SARS-CoV-2), or a protein or a fragment thereof, in a sample. The detection may be carried out *in vitro* or *in vivo*. In certain embodiments, the invention relates to population screening.

The invention relates to identifying any SARS-CoV-2 strain, as described herein.

The invention may also relate to a method of identifying escape mutants of SARS-CoV-2, comprising contacting a sample with a combination of antibodies of the invention and identifying if each antibody binds to the virus. The term "escape mutants" refers to variants of SARS-CoV-2 comprising non-silent mutations that may affect the efficacy of existing treatments of SARS-CoV-2 infection. Typically, the non-silent mutations is on an epitope recognised by a prior art antibody and/or antibodies described herein that specifically binds to an epitope of SARS-CoV-2, e.g. on the spike protein of SARS-CoV-2. If the antibody does not bind to the target, it may indicate that the target comprises a mutation that may alter the efficacy of existing SARS-CoV-2 treatments.

The methods and uses of the invention may include contacting a sample with an antibody or a combination of the antibodies of the invention, and detecting the presence or absence of an antibody-antigen complex, wherein the presence of the antibody-antigen complex indicates that the subject is infected with SARS-CoV-2.

Methods of determining the presence of an antibody-antigen complex are known in the art. For example, in vitro detection techniques include enzyme linked immunosorbent assays (ELISAs), Western blots, immunoprecipitations, and immunofluorescence. In vivo techniques include introducing into a subject a labelled anti-analyte protein antibody. For example, the antibody can be labelled with a radioactive marker whose presence and location in a subject can be detected by standard imaging techniques. The detection techniques may provide a qualitative or a quantitative readout depending on the assay employed.

Typically, the invention relates to methods and uses for a human subject in need thereof. However, non-human animals such as rats, rabbits, sheep, pigs, cows, cats, or dogs is also contemplated.

The subject may be at risk of exposure to coronavirus infection, such as a healthcare worker or a person who has come into contact with an infected individual. A subject may have visited or be planning to visit a country known or suspected of having a coronavirus outbreak. A subject may also be at greater risk, such as an immunocompromised individual, for example an individual receiving immunosuppressive

therapy or an individual suffering from human immunodeficiency syndrome (HIV) or acquired immune deficiency syndrome (AIDS).

The subject may be asymptomatic or pre-symptomatic.

The subject may be early, middle or late phase of the disease.

The subject may be in hospital or in the community at first presentation, and/or later times in hospital.

The subject may be male or female. In certain embodiments, the subject is typically male.

The subject may not have been infected with coronavirus, such as SARS-CoV-2.

The subject may have a predisposition to the more severe symptoms or complications associated with coronavirus infections. The method or use of the invention may comprise a step of identifying whether or not a patient is at risk of developing the more severe symptoms or complications associated with coronavirus.

In embodiments of the invention relating to prevention or treatment, the subject may or may not have been diagnosed to be infected with coronavirus, such as SARS-CoV-2.

The invention relates to analysing samples from subjects. The sample may be tissues, cells and biological fluids isolated from a subject, as well as tissues, cells and fluids present within a subject. The sample may be blood and a fraction or component of blood including blood serum, blood plasma, or lymph. Typically, the sample is from a throat swab, nasal swab, or saliva.

The antibody-antigen complex detection assays may be performed *in situ*, in which case the sample is a tissue section (fixed and/or frozen) of the tissue obtained from biopsies or resections from a subject.

In the embodiments of the invention where the antibodies pharmaceutical compositions and combinations are administered, they may be administered subcutaneously, intravenously, intradermally, orally, intranasally, intramuscularly or intracranially. Typically, the antibodies pharmaceutical compositions and combinations are administered intravenously or subcutaneously.

The dose of an antibody may vary depending on the age and size of a subject, as well as on the disease, conditions and route of administration. Antibodies may be administered at a dose of about 0.1 mg/kg body weight to a dose of about 100 mg/kg body weight, such as at a dose of about 5 mg/kg to about 10 mg/kg. Antibodies may also be administered at a dose of about 50 mg/kg, 10 mg/kg or about 5 mg/kg body weight.

A combination of the invention may for example be administered at a dose of about 5 mg/kg to about 10 mg/kg for each antibody, or at a dose of about 10 mg/kg or about 5 mg/kg for each antibody. Alternatively, a combination may be administered at a dose of about 5 mg/kg total (e.g. a dose of 1.67 mg/kg of each antibody in a three antibody combination).

The antibody or combination of antibodies of the invention may be administered in a multiple dosage regimen. For example, the initial dose may be followed by administration of a second or plurality of subsequent doses. The second and subsequent doses may be separated by an appropriate time.

As discussed above, the antibodies of the invention are typically used in a single pharmaceutical composition/combination (co-formulated). However, the invention also generally includes the combined use of antibodies of the invention in separate preparations/compositions. The invention also includes combined use of the antibodies with additional therapeutic agents, as described above.

Combined administration of the two or more agents and/or antibodies may be achieved in a number of different ways. In one embodiment, all the components may be administered together in a single composition. In another embodiment, each component may be administered separately as part of a combined therapy.

For example, the antibody of the invention may be administered before, after or concurrently with another antibody, or binding fragment thereof, of the invention. The particularly useful combinations are described above for example.

For example, the antibody of the invention may be administered before, after or concurrently with an anti-viral agent or an anti-inflammatory agent.

In embodiments where the invention relates to detecting the presence of coronavirus, e.g. SARS-CoV-2, or a protein or a fragment thereof, in a sample, the antibody contains a detectable label. Methods of attaching a label to an antibody are known in the art, e.g. by direct labelling of the antibody by coupling (i.e., physically linking) a detectable substance to the antibody. Alternatively, the antibody may be indirect labelled, e.g. by reactivity with another reagent that is directly labelled. Examples of indirect labelling include detection of a primary antibody using a fluorescently-labelled secondary antibody and end-labelling of a DNA probe with biotin such that it can be detected with fluorescently-labelled streptavidin.

The detection may further comprise: (i) an agent known to be useful for detecting the presence of coronavirus, , e.g. SARS-CoV-2, or a protein or a fragment thereof, e.g. an

antibody against other epitopes of the spike protein, or other proteins of the coronavirus, such as an anti-nucleocapsid antibody; and/or (ii) an agent known to not be capable of detecting the presence of coronavirus, , e.g. SARS-CoV-2, or a fragment thereof, i.e. providing a negative control.

In certain embodiments, the antibody is modified to have increased stability. Suitable modifications are explained above.

The invention also encompasses kits for detecting the presence of coronavirus, e.g. SARS-CoV-2, in a sample. For example, the kit may comprise: a labelled antibody or a combination of labelled antibodies of the invention; means for determining the amount of coronavirus, e.g. SARS-CoV-2, in a sample; and means for comparing the amount of coronavirus, e.g. SARS-CoV-2, in the sample with a standard. The labelled antibody or the combination of labelled antibodies can be packaged in a suitable container. The kit can further comprise instructions for using the kit to detect coronavirus, e.g. SARS-CoV-2, in a sample. The kit may further comprise other agents known to be useful for detecting the presence of coronavirus, as discussed above.

For example, the antibodies or combinations of antibodies of the invention are used in a lateral flow test. Typically, the lateral flow test kit is a hand-held device with an absorbent pad, which based on a series of capillary beds, such as pieces of porous paper, microstructured polymer, or sintered polymer. The test runs the liquid sample along the surface of the pad with reactive molecules that show a visual positive or negative result. The test may further comprise using other agents known to be useful for detecting the presence of coronavirus, e.g. SARS-CoV-2, or a fragment thereof, as discussed above, such as anti- an anti-nucleocapsid antibody.

Other

It is to be understood that different applications of the disclosed antibodies combinations, or pharmaceutical compositions of the invention may be tailored to the specific needs in the art. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments of the invention only, and is not intended to be limiting.

In addition as used in this specification and the appended claims, the singular forms “a”, “an”, and “the” include plural references unless the content clearly dictates otherwise. Thus, for example, reference to “an antibody” includes two or more “antibodies”.

Furthermore, when referring to "$\geq x$" herein, this means equal to or greater than x. When referred to "$\leq x$" herein, this means less than or equal to x.

For the purpose of this invention, in order to determine the percent identity of two sequences (such as two polynucleotide or two polypeptide sequences), the sequences are aligned for optimal comparison purposes (e.g. gaps can be introduced in a first sequence for optimal alignment with a second sequence). The nucleotide or amino acid residues at each position are then compared. When a position in the first sequence is occupied by the same nucleotide or amino acid as the corresponding position in the second sequence, then the nucleotides or amino acids are identical at that position. The percent identity between the two sequences is a function of the number of identical positions shared by the sequences (i.e., % identity = number of identical positions /total number of positions in the reference sequence × 100).

Typically the sequence comparison is carried out over the length of the reference sequence. For example, if the user wished to determine whether a given ("test") sequence is 95% identical to SEQ ID NO: 3, SEQ ID NO: 3 would be the reference sequence. To assess whether a sequence is at least 95% identical to SEQ ID NO: 3 (an example of a reference sequence), the skilled person would carry out an alignment over the length of SEQ ID NO: 3, and identify how many positions in the test sequence were identical to those of SEQ ID NO: 3. If at least 95% of the positions are identical, the test sequence is at least 95% identical to SEQ ID NO: 3. If the sequence is shorter than SEQ ID NO: 3, the gaps or missing positions should be considered to be non-identical positions.

The skilled person is aware of different computer programs that are available to determine the homology or identity between two sequences. For instance, a comparison of sequences and determination of percent identity between two sequences can be accomplished using a mathematical algorithm. In an embodiment, the percent identity between two amino acid or nucleic acid sequences is determined using the Needleman and Wunsch (1970) algorithm which has been incorporated into the GAP program in the Accelrys GCG software package (available at http://www.accelrys.com/products/gcg/), using either a Blosum 62 matrix or a PAM250 matrix, and a gap weight of 16, 14, 12, 10, 8, 6, or 4 and a length weight of 1, 2, 3, 4, 5, or 6.

The CDRs of the heavy chain (CDRH) and light chain variable domain (CDRL) are located at residues 27-38 (CDR1), residues 56-65 (CDR2) and residues 105-117 (CDR3) of each chain according to the IMGT numbering system (http://www.imgt.org; Lefranc

MP, 1997, J, Immunol. Today, 18, 509). This numbering system is used in the present specification except where otherwise indicated.

All publications, patents and patent applications cited herein, whether supra or infra, are hereby incorporated by reference in their entirety.

The following examples illustrate the invention.

Examples

Example 1. Generation of mAbs from BA.4/5 infection samples

Blood was taken from 11 triple vaccinated volunteers >23 days (median 38) after PCR test confirmed SARS-CoV-2 BA.4 infection (n=3) or BA.5 infection (n=8). Focus reduction neutralisation tests (FRNT) were performed on Victoria (an early pandemic strain), together with BA.2, BA.4 and BA.5 live virus, to select the highest titre samples for antibody production **(Fig. 1A)**. Seven samples with the highest titres against BA.4 or BA.5 were used for mAb production.

PBMCs were stained with BA.4/5 S trimer (the S sequence is the same for BA.4 and BA.5) and single IgG positive memory B cells were sorted (**Fig. 1B**), meanwhile, 4 samples were stained with an S trimer termed BA.4+all, that was constructed to harbour additional mutations seen in recent sub-lineages (G339H, R346T, L368I, K444R, V445P, G446S, N450D, L452M, N460K, V483A, E484R, F486S, F490V and S494P) in a BA.4/5 background. From the selected cells, a degenerate PCR reaction was used to amplify heavy and light chains, which were assembled into an expression vector using Gibson assembly and the products expressed by transient transfection. Supernatants were tested for binding to full length BA.4/5 or BA.4+all S trimer, BA.4/5 or BA.4+all RBD and BA.4/5 NTD. From 861 sorted cells 414 antibodies were recovered leading to the selection of 29 potent mAbs (BA.4/5-34 was derived from the BA.4+all sort) showing FRNT 50% of BA.5 virus at <100 ng/ml. Heavy chain gene usage is evenly distributed on IGHV1-69 (5/29), IGHV3-9 (4/29), and public gene family IGHV3-53 (4/29) and IGHV3-66 (5/29) (**Fig. 1C, Table 2** (some antibodies not shown)**)**. Somatic mutation was comparable to a previous set of antibodies we developed following BA.1 infection, significantly greater than seen in early pandemic mAbs **(Fig. 1D)**. A number of mAbs showed little or no ACE2 blocking ability (e.g. BA.4/5-12, 15, 20 and 33) **(Fig. 1E)**.

Pseudo-typed virus neutralisation assays (Nie *et al. Emerg Microbes Infect* **9**, 680-686 (2020)) were used to test the antibodies against 30 variants seen throughout the pandemic with particular emphasis on Omicron sub-lineages **(Fig. 2A)**. All potent BA.4/5 mAbs shown, except BA.4/5-33, cross-neutralize early pandemic pseudovirus Victoria (IC50<100 ng/ml) and may have been selected from B cell clones originally generated following vaccination (**Fig. 2A**). Neutralization assays were performed using wild-type viruses **(Fig. 2B)**. BA.4/5-33 was the only anti-NTD antibody isolated, which was specific to BA.2 derived variants, although failed to neutralize Delta.

Many BA.4/5 mAbs showed >5-fold reduction of neutralization titre on at least one Omicron sub-lineage, compared to BA.4/5 **(Fig. 2A)** with activity completely knocked out for many antibodies for the most frequent variants, BA.2.75.2, BQ.1.1, BN.1, XBB.1.5 and CH.1.1.

Cross reactivity between different viral variants was mixed, BA.4/5-2 was broadly and potently neutralizing of all the variants tested (**Fig. 2A and 2B)** whilst BA.4/5-1 and 31, had a single vulnerability to BS.1. BS.1 contains a number of mutations in the RBD shared with other variants (**Figure 6**), but uniquely expresses G476S at the back of the left shoulder, which is likely responsible for the reduction in activity of BA.4/5-1 and 31 on BS.1. The R346T mutation, which exists in a number of variants including BA.4.6, BA.2.75.2, BQ.1.1, BJ.1, BS.1, BF.7, BN.1, XBB, CA.3.1, CH.1.1, XBB.1, XBF, XBB.1.5 and DS.1, disrupts the binding of many potent BA.4/5 mAbs, (BA.4/5-11, 12, 13, 15, 18, 20, 21 and 25, when comparing BA.4 with BA.4.6).

Finally, the activity of mAbs developed for clinical use were tested against newly emerging Omicron variants (**Fig. 2C**). Activity was knocked out for most mAbs tested and notably activity of S309 was knocked out against BN.1 and DS.1, likely due to mutation K356T.

Example 2. Structures of anti-BA.4/5 mAbs

To elucidate the binding mode and detailed interactions of the cross-reactive mAbs, structures of complexes of Delta-RBD with BA.4/5-1 and EY6A, and Delta-RBD with BA.4/5-2 and Beta-49, were determined by crystallography, as well as structures of BA.4 spike with BA.4/5-5, BA.2.12.1 spike with BA.2-07, and Delta-RBD with SARS1-31 (an antibody generated from a Delta infected case selected by single cell sorting with SARS1 S protein), where the early pandemic mAbs, EY6A, Beta-49 and SARS1-34 are used as chaperones for structure determination. Delta RBD was used since it yields better crystals.

In addition, the high resolution crystal structure of Delta-RBD with Omi-42 and Beta-49 was also determined, complementing the previously reported lower resolution cryo-EM structure of the spike/Omi-42 complex (Tuekprakhon *et al. Cell* **185**, 2422-2433 e2413 (2022)) to facilitate structure analysis and comparison (**Figs 3 to 5**).

BA.4/5-2 (IGHV3-30), the second ultra cross-reactive mAb, binds the RBD with the heavy chain (HC) at the back of the left shoulder and light chain at the back of the neck. The HC makes the majority of contacts with the RBD with a footprint of 650 $Å^2$, compared to 305 $Å^2$ for the LC (**Fig. 3B, 4B, 5D**). Of the 27 residues within this footprint, 12 overlap with the footprint of ACE2. CDR-H3 makes extensive interactions with RBD residues 416-417, 420-421, 455-460, 473 and 489. In contrast, CDR-L3 makes only weak contact to T415 of the RBD. CDR-H1 contacts residues 475-477 and 486-487 (**Fig. 3H-L**). Residues 405, 408, 417, 460, 476-477 and 505, which are mutated in VoC (**Fig. 6**), have direct contacts with BA.4/5-2, despite this, BA.4/5-2 retains the ability to broadly neutralize all of the variants tested (**Fig. 2A**).

BA.4/5-1 (IGHV4-39) is another RBD binding antibody that approaches the binding site from the back of the RBD, the HC binds at the top of the neck and LC at the back of the left shoulder making a large footprint of 1310 $Å^2$ (HC 670 $Å^2$ and LC 640 $Å^2$) (**Fig. 3A, 3C-G. 4A and 5C**). This antibody also heavily overlaps the ACE2 binding site; of the 35 RBD residues in the BA.4/5-1 footprint, 20 overlap with the ACE2 footprint. However, in this case a large number of mutation sites in the Omicron variants have either direct contact with, or are on the footprint of BA.4/5-1, including 405, 408, 417, 476, 477, 484, 486, 490, 493-494, 498, 501 and 505, but interestingly most of these mutations have little or no effect on the neutralization potency of BA.4/5-1, which maintains broad cross-reactivity (**Fig. 2A**). RBD residues L455, F456, Y489 and Q493 make extensive hydrophobic interactions ($\leq$ 4 Å) with CDR-H3, while F486, G476 and S477 contact CDR-L3 of BA.4/5-1. F486 also makes ring stacking contacts with Y35 and Y60 from the framework regions of the HC (**Fig. 3C-J**). Residue F486 undergoes a number of mutations in recently identified SARS CoV-2 variants: F486V in BA.4/5 and BQ.1, F486S in BA.2.75.2 and XBB and F486P in BA.2.10.4 and XBB.1.5 (**Figure 6**). It appears that despite showing close interaction with residue 486, BA.4/5-1 can tolerate mutations of F486 showing only modest reduction in titres to some of the newly described variants compared to BA.4/5 (**Fig. 2A**). Neutralization titres to BS.1 (a rarely described variant, which has failed to achieve a major break-through) were reduced 32-fold compared to BA.4/5 or BA.2.12.1. BS.1 contains the unique mutation G476S (**Figure 6**) compared to

the other variants tested in **Fig. 2A**, G476 has close contact with Y92 of CDR-L3 and the change to Ser likely disrupts this interaction (**Fig. 3G**).

The continued evolution of SARS CoV-2 is expected, prompted by vaccination and multiple rounds of natural infection, placing the virus under extreme selective pressure. **Fig. 6** shows that in response, 16% of the residues of the RBD have mutated, corresponding to 26% of the accessible surface of the RBD, however over half (56%) of the area of the ACE footprint has been mutated in the drive to escape ACE-blocking antibodies and optimise ACE2 binding. All monoclonal antibodies selected for prophylactic or therapeutic use bind to the RBD, some were derived from mAb isolated following SARS-CoV-1 infection (S309 and ADG20), whilst others were isolated from cases infected with SARS-CoV2 during the early pandemic. These first generation SARS-CoV-2 mAbs bind to areas of the RBD that were hotspots for neutralising antibody binding and therefore also hotspots for mutational escape. It is therefore unsurprising that the evolution of SARS-CoV-2 has led to the steady attrition of the available prophylactic and therapeutic mAbs, such that in many countries most are now recommended

Encouragingly for the prospects of second generation COVID-19 therapeutics we have identified here potent mAbs which show extreme breadth, being able to neutralize all variants tested. BA.4/5-2 binds the RBD at the back of the left shoulder, in an area that has been relatively resistant to mutational change to date (**Fig. 3 and 5D**).

Example 3. Materials and Methods

Bacterial Strains and Cell Culture

Vero (ATCC CCL-81) and VeroE6/TMPRSS2 cells were cultured in Dulbecco's Modified Eagle medium (DMEM) high glucose (Sigma-Aldrich) supplemented with 10% fetal bovine serum (FBS), 2 mM GlutaMAX (Gibco, 35050061) and 100 U/ml of penicillin–streptomycin at 37 °C. Human mAbs were expressed in HEK293T cells cultured in FreeStyle™ 293 Expression Medium (Cat# 12338018, Gibco™) at 37 °C with 5% CO_2. HEK293T (ATCC CRL-11268) cells were cultured in DMEM high glucose (Sigma-Aldrich) supplemented with 10% FBS, 1% 100X Mem Neaa (Gibco) and 1% 100X L-Glutamine (Gibco) at 37 °C with 5% CO_2. To express RBD, RBD variants and ACE2, HEK293T cells were cultured in DMEM high glucose (Sigma) supplemented with 2% FBS, 1% 100X Mem Neaa and 1% 100X L-Glutamine at 37 °C for transfection. BA.5 RBD were expressed in HEK293T (ATCC CRL-11268) cells cultured in FreeStyle™ 293 Expression Medium (Cat# 12338018, Gibco™) at 37 °C with 5% CO_2.

E.coli DH5α bacteria were used for transformation and large-scale preparation of plasmids. A single colony was picked and cultured in LB broth at 37 °C at 200 rpm in a shaker overnight. To produce pseudo-typed lentivirus, HEK293T/17 cell was cultured in Dulbecco's Modified Eagle medium (DMEM) high glucose (Sigma-Aldrich) supplemented with 10% fetal bovine serum (FBS), 2 mM GlutaMAX (Gibco, 35050061) and 100 U/ml of penicillin–streptomycin at 37 °C.

Sera and PBMC from BA.4/5 infected cases, study subjects

Following informed consent, individuals with omicron BA.4 or BA.5 were co-enrolled into one or more of the following three studies: the ISARIC/WHO Clinical Characterisation Protocol for Severe Emerging Infections [Oxford REC C, reference 13/SC/0149], the "Innate and adaptive immunity against SARS-CoV-2 in healthcare worker family and household members" protocol (approved by the University of Oxford Central University Research Ethics Committee), or the Gastro-intestinal illness in Oxford: COVID sub study [Sheffield REC, reference: 16/YH/0247]. Diagnosis was confirmed through reporting of symptoms consistent with COVID-19, hospital presentation, and a test positive for SARS-CoV-2 using reverse transcriptase polymerase chain reaction (RT-PCR) from an upper respiratory tract (nose/throat) swab tested in accredited laboratories and lineage sequence confirmed through national reference laboratories in the United Kingdom. A blood sample was taken following consent at least 14 days after PCR test confirmation. Clinical information including severity of disease (mild, severe or critical infection according to recommendations from the World Health Organisation) and times between symptom onset and sampling and age of participant was captured for all individuals at the time of sampling.

Isolation of BA.4/5 S-specific single B cells by FACS

BA.4/5 S-specific single B cell sorting was performed. Briefly, PBMC were stained with LIVE/DEAD Fixable Aqua dye (Invitrogen) followed by recombinant trimeric S-twin-Strep of BA.4/5. Cells were then incubated with CD3-FITC, CD14-FITC, CD16-FITC, CD56-FITC, IgM-FITC, IgA-FITC, IgD-FITC, IgG-BV786 and CD19-BUV395, along with Strep-MAB-DY549 to stain the twin strep tag of the S protein. IgG+ memory B cells were gated as CD19+, IgG+, CD3-, CD14-, CD56-, CD16-, IgM-, IgA- and IgD-, and S+ was further selected and single cells were sorted into 96-well PCR plates with 10 µl of catching buffer (Tris, Nuclease free-H2O and RNase inhibitor). Plates were briefly centrifuged at 2000×g for 1 min and left on dry ice before being stored at -80 °C.

Cloning and expression of BA.4/5 S-specific human mAbs

BA.4/5 S-specific human mAbs were cloned and expressed. Briefly, genes for Ig IGHV, Ig Vκ and Ig Vλ were recovered from positive wells by RT-PCR. Genes encoding Ig IGHV, Ig Vκ and Ig Vλ were then amplified using Nested-PCR by a cocktail of primers specific to human IgG. PCR products of HCs and LCs were ligated into the expression vectors of human IgG1 or immunoglobulin κ-chain or λ-chain by Gibson assembly. For mAb expression, plasmids encoding HCs and LCs were co-transfected by PEI-transfection into a HEK293T cell line, and supernatants containing mAbs were collected and filtered 4-5 days after transfection, and the supernatants were further characterized or purified.

ACE2 binding inhibition assay by ELISA

MAXISORP immunoplates were coated with 5 μg/ml of purified ACE2-His protein overnight at 4 °C and then blocked by 2% BSA in PBS. Meanwhile, mAbs were serially diluted and mixed with 2.5 μg/ml of recombinant BA.4/5 trimeric S-twin-Strep. Antibody-S protein mixtures were incubated at 37°C for 1 hr. After incubation, the mixtures were transferred into the ACE2-coated plates and incubated for 1 hr at 37 °C. After washing, StrepMAB-Classic (2-1507-001, iba) was diluted at 0.2 μg/ml by 2% BSA and used as primary antibody followed by Goat anti-mouse IgG-AP (A9316, Sigma-Aldrich) at 1:10,000 dilution. The reaction was developed by adding PNPP substrate and stopped with NaOH. The absorbance was measured at 405nm. The ACE2/S binding inhibition was calculated by comparing to the antibody-free control well. IC50 was determined using the Probit program from the SPSS package.

Pseudovirus plasmid construction and lentiviral particles production

Pseudotyped lentivirus expressing SARS-CoV-2 S proteins from ancestral strain (Victoria, S247R), BA.2, BA.4/5, BA.2.75, BA.2.75.2, BA.2.3.20, BA.2.10.4, BJ.1, BN.1, and BA.4.6 were constructed and described in the art. The same method to construct BQ.1, BQ.1.1, BS.1, and BF.7 was employed, by adding more mutations into the BA.4 construct. BA.5.9 was created by adding R346I mutation into BA.4/5 backbone. To generate BQ.1, K444T and N460K were added into BA.4/5 backbone, and then R346T was introduced into BQ.1 to create BQ.1.1. A475V was added into BQ.1.1 to create BQ.1.1+A475V. To construct BS.1, R346T, L452R, N460K and G476S was added into BA.2 backbone. XBB was constructed by adding the following mutations into BA.2 backbone: V83A, H146Q, Q183E, R346T, L368I, V445P, G446S, N460K, F486S, F490S, and R493Q. To construct XBB.1, G252V was introduced into XBB, and F486P was added into XBB.1 to make XBB.1.5. XBF was constructed by adding F486P into BN.1, and then reverse mutated 356T in BN.1 to 356K in the original strain. To create BF.7, R346T was

introduced in BA.4 backbone. CH.1.1 was created by adding K444T and L452R into BA.2.12.1, and changed T444 in CH.1.1 to M444 to construct CA.3.1. To create DS.1, R403K and F486S were added into BN.1 template. The resulting pcDNA3.1 plasmid carrying S gene was used for generating pseudoviral particles together with the lentiviral packaging vector and transfer vector encoding luciferase reporter. All the constructs were Sanger sequence confirmed.

Pseudoviral neutralization test

The pseudoviral neutralization test has been described previously. Briefly, the neutralizing activity of potent monoclonal antibodies generated from donors who had recovered from BA.4 and BA.5 infections were tested against Victoria, Alpha, Beta, Gamma, Delta, BA.1, BA.1.1, BA.2, BA.2.12.1, BA.2.75, BA.2.75.2, BA.2.3.20, BA.2.10.4, BJ.1, BA.4/5, BA.4.6, BA.5.9, BQ.1, BQ.1.1, BQ.1.1+A475V, BS.1, BF.7, BN.1, XBB, XBB.1, XBB.1.5, XBF, CH.1.1, CA.3.1 and DS.1. Four-fold serial diluted mAbs were incubated with pseudoviral particles at 37 °C with 5% CO_2 for 1 hr. Stable HEK293T/17 cells expressing human ACE2 were then added to the mixture at 1.5×10^4 cells/well. 48 hr post infection, culture supernatants were removed and 50 µL of 1:2 Bright-Glo TM Luciferase assay system (Promega, USA) in 1 × PBS was added to each well. The reaction was incubated at room temperature for 5 mins and firefly luciferase activity was measured using CLARIOstar® (BMG Labtech, Ortenberg, Germany). The percentage neutralization was calculated relative to the control. Probit analysis was used to estimate the dilution that inhibited half maximum pseudotyped lentivirus infection (PVNT50).

Focus Reduction Neutralization Assay (FRNT)

The neutralization potential of Ab was measured using a Focus Reduction Neutralization Test (FRNT), where the reduction in the number of the infected foci is compared to a negative control well without antibodies. Briefly, serially diluted Ab or plasma was mixed with SARS-CoV-2 strains and incubated for 1 hr at 37 °C. The mixtures were then transferred to microplates containing confluent Vero cell monolayers in duplicate and incubated for a further 2 hrs followed by the addition of 1.5% semi-solid carboxymethyl cellulose (CMC) overlay medium to each well to limit virus diffusion. A focus forming assay was then performed by staining Vero cells with human anti-NP mAb (mAb206) followed by peroxidase-conjugated goat anti-human IgG (A0170; Sigma). Finally, the foci (infected cells) approximately 100 per well in the absence of antibodies, were visualized by adding TrueBlue Peroxidase Substrate. Virus-infected cell foci were

counted on the classic AID EliSpot reader using AID ELISpot software. The percentage of focus reduction was calculated and IC_{50} was determined using the probit program from the SPSS package.

Cloning of spike, RBD and NTD

Expression plasmids encoding BA.4 spike and RBD were constructed with human codon-optimized sequence from BA.4 spike. Mutations of G339H, R346T, L368I, K444R, V445P, G446S, N450D, L452M, N460K, V483A, A484R, V486S, F490S and S494P were introduced into BA.4 spike and RBD expression plasmids to create BA.4+all spike and BA.4+all RBD. The constructs were verified by Sanger sequencing.

Protein production

Twin-strep tagged BA.4 and BA.4+all spikes were transiently expressed in HEK293T cells and purified with Strep-Tactin XT resin (IBA lifesciences). Plasmids encoding BA.4 and BA.4+all RBD were transiently expressed in Expi293F™ Cells (ThermoFisher), cultured in FreeStyle™ 293 Expression Medium (ThermoFisher) at 30°C with 8% CO_2 for 4 days. The harvested medium was concentrated using a QuixStand benchtop system. His-tagged RBDs were purified with a 5 mL HisTrap nickel column (GE Healthcare), followed by a Superdex 75 10/300 GL gel filtration column (GE Healthcare).

IgG mAbs and Fabs production

AstraZeneca and Regeneron antibodies were provided by AstraZeneca, Vir, Lilly and Adagio antibodies were provided by Adagio, LY-CoV1404 was provided by LifeArc. For the in-house antibodies, heavy and light chains of the indicated antibodies were transiently transfected into 293T cells and antibody purified from supernatant on protein A as previously described [24]. Fabs were digested from purified IgGs with papain using a Pierce Fab Preparation Kit (Thermo Fisher), following the manufacturer's protocol.

Crystallization, X-ray data collection and structure determination

Purified Delta RBD was deglycosylated with Endoglycosidase H1. Fabs BA.4/5-1 and EY6A, BA.4/5-2 and Beta-49, and Omi-42 and Beta-49 were mixed with Delta RBD separately in a 1:1:1 molar ratio, with a final concentration of 7.0 mg ml^{-1}. Initial screening of crystals was set up in Crystalquick 96-well X plates (Greiner Bio-One) with a Cartesian Robot using the nanoliter sitting-drop vapor-diffusion method, with 100 nL of protein plus 100 nL of reservoir in each drop. Crystals of Delta-RBD/BA.4/5-1/EY6A and Delta-RBD/Omi-42/Beta-49 were formed in Hampton Research PEGRx condition 1-17, containing 0.1 M sodium citrate tribasic dihydrate pH 5.5 and 22% (w/v) PEG 1000.

Crystals of Delta-RBD/BA.4/5-2/Beta-49 were formed in Hampton Research PEGRx condition 1-46, containing 0.1 M sodium citrate tribasic dihydrate pH 5.0 and 18% (w/v) PEG 20000. Crystals of Delta-RBD/BA.4/5-35 were grown in condition containing 0.1 M Sodium citrate tribasic dihydrate pH 5.5, 18% (w/v) PEG 3,350.

Crystals were mounted in loops and dipped in solution containing 25% glycerol and 75% mother liquor for a second before frozen in liquid nitrogen. Diffraction data of Delta RBD/EY6A/BA.4/5-1 and Delta RBD/Beta-49/BA.4/5-2 were collected at beamline i04, and Delta-RBD/BA.4/5-35 and Delta RBD/Beta-49/Omi-42 at i03 of Diamond Light Source, UK, using the automated queue system that allows unattended automated data collection. 3600 diffraction images of 0.1° each were collected at 100 K from a single crystal for each data set. Data integration, scaling and reduction were automatically done with Xia2-dials The structures were determined using molecular replacement with Phaser, model rebuilding is done with COOT and refinement with Phenix. Structural comparisons used SHP and figures were prepared with PyMOL (The PyMOL Molecular Graphics System, Version 1.2r3pre, Schrödinger, LLC).

Delta RBD/mAb BA2.07/nbC1/mAb 1-34

For Delta-RBD/mAbBA.2-07/nbC1/mAb1-34, nanobody C1 and fab 1-34 were incubated with delta RBD at a 1.1 molar excess of each on ice for ca. 30 minutes prior to plunge freezing. Grids were prepared using a 3 μL aliquot of this complex mixture and plasma-cleaned (35 s, high with a Plasma Cleaner PDC-002-CE, Harrick Plasma) Quantifoil 2/1 300 mesh grids using a Vitrobot Mark IV (Thermo Fisher). Excess liquid was removed by blotting for 5 s with a force of -1 using vitrobot filter paper (grade 595, Ted Pella Inc.) in a chamber set to 4.5 °C, 100 % reported humidity before plunge freezing into liquid ethane.

Movies, in eer format, 13,121 in total, were collected at 165 kX magnification on a 300 kV Titan Krios equipped with a Falcon-IV Selectris, corresponding to a calibrated pixel size of 0.7303 $Å^2$ with a total dose of 50 $e^-/Å^2$ using EPU software (ThermoFisher scientific, defocus range of 0.8-2.6 μm).

Data were 4x binned and pre-processed on-the-fly in the cryoSPARC live interface v3.3.2 patch motion and ctf tools, and particles picked using the blob picker. Initially picked particles, 867189, were then subjected to two rounds of classification into 250 then 150 classes in cryoSPARC v3.3.2 'static' version with a circular mask diameter of 155 Å, 23 online iterations and 300 batch size per class. Heterogeneous refinement was then performed on the filtered particle set comprising 154,454, separating data into three classes

(initial references generated during on-the-fly processing ab initio model generation from a subset of 100,000 particles). The predominant class, with 89,552, was selected for further refinement. Curiously, one of the other classes, with 39,987 particles, appeared to have RBDs in a trimeric arrangement was observed, but the resulting map was too anisotropic for clear interpretation and thus excluded from further refinement. The final class appeared to be 'junk'. This subset of 89,552 particles were then non-uniform refined before unbinning and further refinement, resulting in a final reconstruction to 3.2 Å reported resolution (-103.3 reported global b-factor) with clear side-chain density could be seen at the RBD/immunobody interfaces.

For model generation, a previously published C1 VHH structure, 7oap and our model of delta-RBD with antibody 1-34 were rigid body-fitted into this final map using ChimeraX[37] before cycles of refinement/model building in coot/Phenix.

BA.2.12.1-Spike/BA.2-07

For the two Spike complexes, C-flat R2/1 grids glow discharged for 20 s using Plasma Cleaner PDC-002-CE, Harrick Plasma. Fabs and Spike were mixed at a molar ratio of 6:1 such that there was a two-fold molar excess of fab to sites, and fab/antigen complexes prepared < 5 minutes prior to application to the freshly glow discharged grid and excess liquid was removed by blotting for 5 s with a force of -1 using vitrobot filter paper (grade 595, Ted Pella Inc.) at 4.5 °C, 100 % reported humidity before plunge freezing into liquid ethane using a Vitrobot Mark IV (Thermo Fisher).

Movies, see Table 1 for totals, were collected on a Titan Krios operating at 300 kV equipped with a Falcon-IV Selectris at 165 kX magnification, corresponding to a calibrated pixel size of 0.7303 $Å^2$ with a total dose of 50 $e^-/Å^2$ for both Spike complexes, using EPU software (ThermoFisher scientific) and defocus range of 0.8-2.6 μm in EER format.

Data were binned four times pre-processed in the cryoSPARC live interface, with down-stream processing performed using cryoSPARC.

For BA2.12.1-S/BA.2-07, on-the-fly template-based picking using a template of a side-view of Spike was employed, and the resulting set of 1,467,174 particles were 2D classified into 150 classes. To generate an initial model for 3D refinement, from this classification, one class, with a projection image seemingly of a side view spike decorated with three fabs (2283 particles) was used for ab-initio model generation, split to two classes, with the predominant class, of 1785 particles, used as a template for classification. This ab initio volume already appeared to be S decorated with three fabs in a C3-symmetrical fashion (note that no symmetry had been imposed at this stage). In parallel,

109,708 particles were selected from the 2D classification job and used in a heterogeneous refinement job using the two ab-initio models (good predominant class, and smaller 'rubbish' class volume as templates, with C3 symmetry. Particles in the 'good' class, 62,197 in total, were then used in a non-uniform refinement job [39] before re-extraction to un-bin and further non-uniform refinement to 3.1 Å b-factor -67.3 reported resolution (gold-standard FSC in cryoSPARC = 0.146). Global CTF refinement and local ctf refinement followed by further non-uniform environment with the un-binned dataset resulting in a final map to 2.96 Å reported resolution (again gold-standard FSC in cryoSPARC = 0.146, b-factor -65.6).

Tables

Table 1 –Antibodies

Antibody	Heavy Chain						Light Chain						
	Nt Sequence (SEQ ID NO)	AA Sequence (SEQ ID NO)	CDR1-IMGT (SEQ ID NO)	CDR2-IMGT (SEQ ID NO)	CDR3-IMGT (SEQ ID NO)	CDR3 AA Junction (SEQ ID NO)	Nt Sequence (SEQ ID NO)	AA Sequence (SEQ ID NO)	CDR1-IMGT (SEQ ID NO)	CDR2-IMGT (SEQ ID NO)		CDR3-IMGT (SEQ ID NO)	CDR3 AA Junction (SEQ ID NO)
BA.4/5-1	1	2	3	4	5	6	7	8	9	10	TAS	11	12
BA.4/5-2	13	14	15	16	17	18	19	20	21	22	EAS	23	24
BA.4/5-6	25	26	27	28	29	30	31	32	33	34	DAS	35	36
BA.4/5-7	37	38	39	40	41	42	43	44	45	46	GAS	47	48
BA.4/5-8	49	50	51	52	53	54	55	56	57	58	DAS	59	60
BA.4/5-9	61	62	63	64	65	66	67	68	69	70	NAS	71	72
BA.4/5-10	73	74	75	76	77	78	79	80	81	82	AAS	83	84
BA.4/5-11	85	86	87	88	89	90	91	92	93	94	AAS	95	96
BA.4/5-12	97	98	99	100	101	102	103	104	105	106	DAS	107	108
BA.4/5-13	109	110	111	112	113	114	115	116	117	118	DVS	119	120
BA.4/5-15	121	122	123	124	125	126	127	128	129	130	TNN	131	132
BA.4/5-17	133	134	135	136	137	138	139	140	141	142	DNN	143	144
BA.4/5-18	145	146	147	148	149	150	151	152	153	154	DVS	155	156
BA.4/5-20	157	158	159	160	161	162	163	164	165	166	SNN	167	168
BA.4/5-21	169	170	171	172	173	174	175	176	177	178	AAS	179	180
BA.4/5-22	181	182	183	184	185	186	187	188	189	190	KVF	191	192

BA.4/5-23	193	194	195	196	197	198	199	200	201	202	DAS	203	204
BA.4/5-24	205	206	207	208	209	210	211	212	213	214	TAS	215	216
BA.4/5-25	217	218	219	220	221	222	223	224	225	226	DAS	227	228
BA.4/5-28	229	230	231	232	233	234	235	236	237	238	STR	239	240
BA.4/5-31	241	242	243	244	245	246	247	248	249	250	TAS	251	252
BA.4/5-32	253	254	255	256	257	258	259	260	261	262	ADS	263	264
BA.4/5-33	265	266	267	268	269	270	271	272	273	274	GAS	275	276
BA.4/5-34	277	278	279	280	281	282	283	284	285	286	KVS	287	288

Table 2 – Properties of antibodies

Ab id.	Protein-Specific	Heavy chain									
		V-GENE and allele	V-REGION identity %	V-REGION mutation %	V-REGION identity nt	V-REGION Nb of AA changes	V-REGION Nb of mutations	V-REGION Nb of silent mutations	V-REGION Nb of nonsilent mutations	J-GENE and allele	D-GENE and allele	CDR3-IMGT length
BA.4/5-1	RBD	4-39*01 F	97.25	2.75	283/291 nt	5	8	3	5	4*02 F	1-26*01 F	9
BA.4/5-2	RBD	3-30*03 F, or 3-30*18 F or 3-30-5*01 F	93.75	6.25	270/288 nt	14	19	3	16	6*02 F	2-15*01 F	16
BA.4/5-6	RBD	3-53*04 F	94.74	5.26	270/285 nt	10	16	3	13	4*02 F	4-17*01 F	11
BA.4/5-7	RBD	3-53*02 F	92.63	7.37	264/285 nt	14	22	5	17	4*02 F	4-17*01 F	11
BA.4/5-8	RBD	3-66*02 F	95.79	4.21	273/285 nt	6	12	6	6	6*02 F	1-26*01 F	13
BA.4/5-9	RBD	1-46*01 F, or 1-46*02 F or 1-46*03 F	93.75	6.25	270/288 nt	13	19	4	15	4*02 F	4-23*01 ORF	13
BA.4/5-10	RBD	3-66*02 F	98.60	1.40	281/285 nt	2	4	2	2	6*02 F	1-26*01 F	13
BA.4/5-11	RBD	3-33*01 F, or 3-33*03 F or 3-33*06 F	97.57	2.43	281/288 nt	6	7	1	6	3*02 F	3-22*01 F	18
BA.4/5-12	RBD	3-30*03 F, or, 3-30*18 F, or 3-30-5*01 F	95.14	4.86	274/288 nt	9	15	5	10	6*02 F	3-9*01 F	22

BA.4/5-13	RBD	1-69*01 F, or 1-69D*01 F	95.49	4.51	275/288 nt	9	13	3	10	6*02 F	5-18*01 F	21
BA.4/5-15	RBD	3-9*01 F	96.18	3.82	277/288 nt	6	11	4	7	6*02 F	3-9*01 F	17
BA.4/5-17	RBD	3-53*04 F	95.44	4.56	272/285 nt	8	13	5	8	6*02 F	6-19*01 F	16
BA.4/5-18	RBD	1-69*01 F, or 1-69D*01 F	94.10	5.90	271/288 nt	11	18	6	12	6*02 F	5-18*01 F	21
BA.4/5-20	RBD	3-9*01 F	94.44	5.56	272/288 nt	11	16	3	13	6*02 F	3-9*01 F	17
BA.4/5-21	RBD	3-9*01 F	94.44	5.56	272/288 nt	11	17	4	13	4*02 F	3-22*01 F	18
BA.4/5-22	RBD	1-69*01 F, or 1-69D*01 F	90.97	9.03	262/288 nt	13	26	11	15	4*02 F	5-12*01 F	14
BA.4/5-23	RBD	3-53*01 F	90.53	9.47	258/285 nt	15	27	9	18	4*02 F	4-17*01 F	11
BA.4/5-24	RBD	3-9*01 F	94.44	5.56	272/288 nt	9	16	7	9	5*02 F	3-22*01 F	18
BA.4/5-25	RBD	1-69*09 F	90.63	9.38	261/288 nt	16	27	7	20	4*02 F	5-18*01 F	9
BA.4/5-28	RBD	3-66*01 F, or 3-66*04 F	94.39	5.61	269/285 nt	10	16	3	13	6*02 F	1-1*01 F	12
BA.4/5-31	RBD	4-39*01 F	96.56	3.44	281/291 nt	6	10	4	6	4*02 F	1-26*01 F	9
BA.4/5-32	RBD	3-66*02 F	93.68	6.32	267/285 nt	12	18	3	15	3*01 F	3-10*02 F	10
BA.4/5-33	NTD	3-23*04 F	92.71	7.29	267/288 nt	13	21	5	16 (18)	4*02 F	5-18*01 F	8
BA.4/5-34	RBD	1-69*01 F, or1-69D*01 F	91.67	8.33	264/288 nt	12	24	8	16	4*02 F	5-12*01 F	14

Table 2 Cont.

Ab id.	Protein-Specific	Light chain									
		Light Chain	V-GENE and allele	V-REGION Nb of AA changes	V-REGION identity %	V-REGION mutation %	V-REGION identity nt	V-REGION Nb of mutations	V-REGION Nb of silent mutations	V-REGION Nb of nonsilent mutations	J-GENE and allele	CDR3-IMGT length
BA.4/5-1	RBD	K	1-NL1*01 F	7.00	96.77	3.23	270/279 nt	9	1	8	2*01 F	9
BA.4/5-2	RBD	K	3-11*01 F	5.00	98.21	1.79	274/279 nt	7	1	6	3*01 F	9
BA.4/5-6	RBD	K	3-20*01 F	9.00	93.62	6.38	264/282 nt	18	5	13	2*02	9
BA.4/5-7	RBD	K	3-15*01 F	5.00	97.85	2.15	273/279 nt	6	1	5	1*01 F	9
BA.4/5-8	RBD	K	1-33*01 F, or 1D-33*01 F	4.00	97.85	2.15	273/279 nt	6	2	4	2*01 F	9
BA.4/5-9	RBD	K	3-11*01 F	6.00	96.06	3.94	268/279 nt	11	4	7	2*03	10
BA.4/5-10	RBD	K	1-33*01 F, or 1D-33*01 F	5.00	97.85	2.15	273/279 nt	6	1	5	2*01 F	9
BA.4/5-11	RBD	K	1-39*01 F, or 1D-39*01 F	3.00	98.57	1.43	275/279 nt	4	1	3	2*01 F	10
BA.4/5-12	RBD	K	1-33*01 F,or 1D-33*01 F	5.00	97.13	2.87	271/279 nt	8	3	5	5*01 F	9
BA.4/5-13	RBD	K	1-33*01 F, or 1D-33*01 F	9.00	95.34	4.66	266/279 nt	14	3	11	3*01 F	8
BA.4/5-15	RBD	λ	1-44*01 F	6.00	96.84	3.16	276/285 nt	9	3	6	1*01 F	12
BA.4/5-17	RBD	λ	1-51*01 F	4.00	97.54	2.46	278/285 nt	7	2	5	1*01 F	11
BA.4/5-18	RBD	K	1-33*01 F, or 1D-33*01 F	12.00	93.91	6.09	262/279 nt	18	3	15	3*01 F	8

BA.4/5-20	RBD	λ	1-44*01 F	5.00	97.54	2.46	278/285 nt	8	3	5	1*01 F	12
BA.4/5-21	RBD	K	1-9*01 F	8.00	95.70	4.30	267/279 nt	12	2	10	4*01 F	9
BA.4/5-22	RBD	K	2-30*01 F	6.00	96.26	3.74	283/294 nt	11	5	6	1*01 F	9
BA.4/5-23	RBD	K	3-20*01 F	5.00	95.74	4.26	270/282 nt	12	6	6	1*01 F	9
BA.4/5-24	RBD	K	1-9*01 F	17.00	91.40	8.60	255/279 nt	24	4	20	3*01 F, or 4*01 F	9
BA.4/5-25	RBD	K	1-5*01 F	9.00	96.06	3.94	268/279 nt	12	2	10	2*02 (F)	9
BA.4/5-28	RBD	λ	3-21*04 F	16.00	91.40	8.60	255/279 nt	25	3	22	2*01 F, or 3*01 F or 3*02 F	11
BA.4/5-31	RBD	K	1-NL1*01 F	9.00	94.62	5.38	264/279 nt	15	3	12	2*01 F	9
BA.4/5-32	RBD	λ	3-21*02 F	10.00	95.34	4.66	266/279 nt	14	1	13	1*01 F	11
BA.4/5-33	NTD	K	3-15*01 F	5.00	97.49	2.51	272/279 nt	7	2	5	2*01 F	10
BA.4/5-34	RBD	K	2-30*01 F	8.00	94.56	5.44	278/294 nt	16	8	8	1*01 F	9

Table 3 – Examples of the mixed chain antibodies generated from antibodies derived from the same germline heavy chain v-gene 4-39

Heavy chain (H) / light chain (L) of antibody	**BA.4/5-1H**	**BA.4/5-31H**
BA.4/5-1L	-	BA.4/5-31H BA.4/5-1L
BA.4/5-31L	BA.4/5-1H BA.4/5-31L	-

Table 4 – Examples of the mixed chain antibodies generated from antibodies derived from the same germline heavy chain v-gene 3-30

Heavy chain (H) / light chain (L) of antibody	**BA.4/5-2H**	**BA.4/5-12H**
BA.4/5-2L	-	BA.4/5-12H BA.4/5-2L
BA.4/5-12L	BA.4/5-2H BA.4/5-12L	-

Table 5 – Examples of the mixed chain antibodies generated from antibodies derived from the same germline heavy chain v-gene 3-53

Heavy chain (H) / light chain (L) of antibody	**BA.4/5-6H**	**BA.4/5-7H**	**BA.4/5-17H**	**BA.4/5-23H**
BA.4/5-6L	-	BA.4/5-7H BA.4/5-6L	BA.4/5-17H BA.4/5-6L	BA.4/5-23H BA.4/5-6L
BA.4/5-7L	BA.4/5-6H BA.4/5-7L	-	BA.4/5-17H BA.4/5-7L	BA.4/5-23H BA.4/5-7L
BA.4/5-17L	BA.4/5-6H BA.4/5-17L	BA.4/5-7H BA.4/5-17L	-	BA.4/5-23H BA.4/5-17L
BA.4/5-23L	BA.4/5-6H BA.4/5-23L	BA.4/5-7H BA.4/5-23L	BA.4/5-17H BA.4/5-23L	-

Table 6 – Examples of the mixed chain antibodies generated from antibodies derived from the same germline heavy chain v-gene 3-66

Heavy chain (H) / light chain (L) of antibody	**BA.4/5-8H**	**BA.4/5-10H**	**BA.4/5-28H**	**BA.4/5-32H**
BA.4/5-8L	-	BA.4/5-10H BA.4/5-8L	BA.4/5-28H BA.4/5-8L	BA.4/5-32H BA.4/5-8L
BA.4/5-10L	BA.4/5-8H BA.4/5-10L	-	BA.4/5-28H BA.4/5-10L	BA.4/5-32H BA.4/5-10L
BA.4/5-28L	BA.4/5-8H BA.4/5-28L	BA.4/5-10H BA.4/5-28L	-	BA.4/5-32H BA.4/5-28L
BA.4/5-32L	BA.4/5-8H BA.4/5-32L	BA.4/5-10H BA.4/5-32L	BA.4/5-28H BA.4/5-32L	-

Table 7 – Examples of the mixed chain antibodies generated from antibodies derived from the same germline heavy chain v-genes 3-53 and 3-66

Heavy chain (H) / light chain (L) of antibody	**BA.4/5-6H**	**BA.4/5-7H**	**BA.4/5-17H**	**BA.4/5-23H**	**BA.4/5-8H**	**BA.4/5-10H**	**BA.4/5-28H**	**BA.4/5-32H**
BA.4/5-6L	-	BA.4/5-7H BA.4/5-6L	BA.4/5-17H BA.4/5-6L	BA.4/5-23H BA.4/5-6L	BA.4/5-8H BA.4/5-6L	BA.4/5-10H BA.4/5-6L	BA.4/5-28H BA.4/5-6L	BA.4/5-32H BA.4/5-6L
BA.4/5-7L	BA.4/5-6H BA.4/5-7L	-	BA.4/5-17H BA.4/5-7L	BA.4/5-23H BA.4/5-7L	BA.4/5-8H BA.4/5-7L	BA.4/5-10H BA.4/5-7L	BA.4/5-28H BA.4/5-7L	BA.4/5-32H BA.4/5-7L
BA.4/5-17L	BA.4/5-6H BA.4/5-17L	BA.4/5-7H BA.4/5-17L	-	BA.4/5-23H BA.4/5-17L	BA.4/5-8H BA.4/5-17L	BA.4/5-10H BA.4/5-17L	BA.4/5-28H BA.4/5-17L	BA.4/5-32H BA.4/5-17L
BA.4/5-23L	BA.4/5-6H BA.4/5-23L	BA.4/5-7H BA.4/5-23L	BA.4/5-17H BA.4/5-23L	-	BA.4/5-8H BA.4/5-23L	BA.4/5-10H BA.4/5-23L	BA.4/5-28H BA.4/5-23L	BA.4/5-32H BA.4/5-23L

BA.4/5-8L	BA.4/5-6H BA.4/5-8L	BA.4/5-7H BA.4/5-8L	BA.4/5-17H BA.4/5-8L	BA.4/5-23H BA.4/5-8L	-	BA.4/5-10H BA.4/5-8L	BA.4/5-28H BA.4/5-8L	BA.4/5-32H BA.4/5-8L
BA.4/5-10L	BA.4/5-6H BA.4/5-10L	BA.4/5-7H BA.4/5-10L	BA.4/5-17H BA.4/5-10L	BA.4/5-23H BA.4/5-10L	BA.4/5-8H BA.4/5-10L	-	BA.4/5-28H BA.4/5-10L	BA.4/5-32H BA.4/5-10L
BA.4/5-28L	BA.4/5-6H BA.4/5-28L	BA.4/5-7H BA.4/5-28L	BA.4/5-17H BA.4/5-28L	BA.4/5-23H BA.4/5-28L	BA.4/5-8H BA.4/5-28L	BA.4/5-10H BA.4/5-28L	-	BA.4/5-32H BA.4/5-28L
BA.4/5-32L	BA.4/5-6H BA.4/5-32L	BA.4/5-7H BA.4/5-32L	BA.4/5-17H BA.4/5-32L	BA.4/5-23H BA.4/5-32L	BA.4/5-8H BA.4/5-32L	BA.4/5-10H BA.4/5-32L	BA.4/5-28H BA.4/5-32L	-

Table 8 – Examples of the mixed chain antibodies generated from antibodies derived from the same germline heavy chain v-gene 1-69

Heavy chain (H) / light chain (L) of antibody	**BA.4/5-13H**	**BA.4/5-18H**	**BA.4/5-22H**	**BA.4/5-25H**	**BA.4/5-34H**
BA.4/5-13L	-	BA.4/5-18H BA.4/5-13L	BA.4/5-22H BA.4/5-13L	BA.4/5-25H BA.4/5-13L	BA.4/5-34H BA.4/5-13L
BA.4/5-18L	BA.4/5-13H BA.4/5-18L	-	BA.4/5-22H BA.4/5-18L	BA.4/5-25H BA.4/5-18L	BA.4/5-34H BA.4/5-18L
BA.4/5-22L	BA.4/5-13H BA.4/5-22L	BA.4/5-18H BA.4/5-22L	-	BA.4/5-25H BA.4/5-22L	BA.4/5-34H BA.4/5-22L
BA.4/5-25L	BA.4/5-13H BA.4/5-25L	BA.4/5-18H BA.4/5-25L	BA.4/5-22H BA.4/5-25L	-	BA.4/5-34H BA.4/5-25L
BA.4/5-34L	BA.4/5-13H BA.4/5-34L	BA.4/5-18H BA.4/5-34L	BA.4/5-22H BA.4/5-34L	BA.4/5-25H BA.4/5-34L	-

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Table 9 – Examples of the mixed chain antibodies generated from antibodies derived from the same germline heavy chain v-gene 3-9

Heavy chain (H) / light chain (L) of antibody	**BA.4/5-15H**	**BA.4/5-20H**	**BA.4/5-21H**	**BA.4/5-24H**
BA.4/5-15L	-	BA.4/5-20H BA.4/5-15L	BA.4/5-21H BA.4/5-15L	BA.4/5-24H BA.4/5-15L
BA.4/5-20L	BA.4/5-15H BA.4/5-20L	-	BA.4/5-21H BA.4/5-20L	BA.4/5-24H BA.4/5-20L
BA.4/5-21L	BA.4/5-15H BA.4/5-21L	BA.4/5-20H BA.4/5-21L	-	BA.4/5-24H BA.4/5-21L
BA.4/5-24L	BA.4/5-15H BA.4/5-24L	BA.4/5-20H BA.4/5-24L	BA.4/5-21H BA.4/5-24L	-

Sequence Listing

Amino acid and nucleotide sequences of heavy chain and light chain variable regions of selected antibodies

Antibody	Heavy Chain			
	Nt Sequence	SEQ ID NO:	AA Sequence	SEQ ID NO:
BA.4/5-1	caggtgcagctgcaggagtcgggcccaggact ggtgaagccttcggagaccctgtccctcacctgc actgtctctggtggctccatcagcagtagtaatta ctactggggctggatccgccagcccccaggga aggggctggagtggattgggagtatctattatagt gggagctcctactatagcccgtccctcaagagtc gggtcaccatatccgtagacacgtccaagagcc agttctccctgaagctgagctctgtgaccgccgc agacacggctgtttattactgtgcgagcacactg ggagctacgttctactggggccagggaaccctg gtcaccgtctcctcag	1	QVQLQESGPGLVK PSETLSLTCTVSGG SISSSNYYWGWIRQ PPGKGLEWIGSIYY SGSSYYSPSLKSRV TISVDTSKSQFSLK LSSVTAADTAVYY CASTLGATFYWGQ GTLVTVSS	2
BA.4/5-2	gaagtgcagctggtggagtctgggggaggcgt ggtccagcctgggaggtccctgagactctcctgt gcagcctctggtttcaccctcagaagctttggcat acactgggtccgccaggctccaggcaaggggc tggagtgggtggcatttatttcatatgatggaagta atcaatactatgaagactccgtgaagggccgatt caccatctccagagacaattccaagaacacggtg gatctgcagatgaacagcctgagtactgaggac acggctgtgtattggtgtgcgaaagatcttttgcc gctactcgctctgtactacggtatggacgtctggg gccaagggaccacggtcaccgtctcttca	13	EVQLVESGGGVVQ PGRSLRLSCAASGF TLRSFGIHWVRQAP GKGLEWVAFISYD GSNQYYEDSVKGR FTISRDNSKNTVDL QMNSLSTEDTAVY WCAKDLLPLLALY YGMDVWGQGTTV TVSS	14
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Antibody	Light Chain			
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BA.4/5-9	gaaatagggatgacgcagtctccggccaccctg tctttgtctccaggggaaagaggcaccctctcct gcagagccagtcagagtgttagcagctacttag cctggtaccaacagaaacctggccaggctccca ggctcctcatctataatgcatccaacagggccac tggcatcccagccaggttcagtggcagtgggtct gggacagacttcactctcaccatcagcagccta gagcctgaagattttgcagtttattactgtcagca gcattacaactggcctcggtacagttttggccag gggaccaaagtggatatcaaac	67	EIGMTQSPATLSLS PGERGTLSCRASQS VSSYLAWYQQKPG QAPRLLIYNASNRA TGIPARFSGSGSGT DFTLTISSLEPEDFA VYYCQQHYNWPR YSFGQGTKVDIK	68
BA.4/5-10	gacatccagatgacccagtctccatcctccctgt ctgcatctgtaggagacagagtcaccatcacttg ccaggcgagtcaggacattaacaactatttaaatt ggtatcaacagaaaccagggaaagcccctaag ctcctgatctacgctgcatccaatttggaaacagg	79	DIQMTQSPSSLSAS VGDRVTITCQASQ DINNYLNWYQQKP GKAPKLLIYAASNL ETGVPSKFSGSGSG	80

	ggtcccatcaaagttcagtggaagtggatctggg acagattttactttcaccatcaacagcctgcagcc tgaagatattgcaacatattactgtcaccagtatg ataatctcccgtacacttttggccaggggaccaa ggtggaaatcaaac		TDFTFTINSLQPEDI ATYYCHQYDNLPY TFGQGTKVEIK	
BA.4/5-11	gccatccagttgacccagtctccatcctccctgtc tgcatctgtaggagacagagtcaccatcacttgc cgggcaagtcagagcattagcagctatttaaatt ggtatcagcagaaaccagggaaagcccctaag ctccttatctatgctgcatccactttgcaaagtggg gtcccatcaaggttcagtggcagtggatctggga cagatttcactctcaccatcagcagtctgcaacct gaagattttgcaacttactactgtcaacagagtta cagtaccctcatgtacacttttggccaggggacc aaggtggagatcaaac	91	AIQLTQSPSSLSASV GDRVTITCRASQSI SSYLNWYQQKPGK APKLLIYAASTLQS GVPSRFSGSGSGTD FTLTISSLQPEDFAT YYCQQSYSTLMYT FGQGTKVEIK	92
BA.4/5-12	gccatccagttgacccagtctccatcctccctgtc tgcatctgtaggagatagagtcaccatcacttgc caggcgagtcaggacattagcaactatttaaatt ggtatcagcagaaatcagggaaagcccctgag ctcctgatctacgatgcatccaatttggaaacagg ggtcccatcaaggttcagtggaagtggatctgg gacagattttactttcaccatcagcagcctgcagc ctgaagattttgcaacatattactgtcaacaatatg acaatctccccctcaccttcggccaagggacac gactggagattaaac	103	AIQLTQSPSSLSASV GDRVTITCQASQDI SNYLNWYQQKSG KAPELLIYDASNLE TGVPSRFSGSGSGT DFTFTISSLQPEDFA TYYCQQYDNLPLT FGQGTRLEIK	104
BA.4/5-13	gccatccggatgacccagtctccatcctccctgt ctgcatctataggagacagagtcaccatcacttg ccaggcgagtcaggacataagcaaccacttaaa ttggtatcagcagaaaccagggaaagcccctaa gctcctgatctacgatgtttccgatttggaaacag gggtcccctcaaggttcagtggaagtggatctg ggacagaatttactttcactatcagcagcctgcag cctgaagatattgcaacatattactgtcaacagtat gatgatttccctcttttcggccctgggaccaaagt ggatatcaaac	115	AIRMTQSPSSLSASI GDRVTITCQASQDI SNHLNWYQQKPG KAPKLLIYDVSDLE TGVPSRFSGSGSGT EFTFTISSLQPEDIA TYYCQQYDDFPLF GPGTKVDIK	116
BA.4/5-15	cagtctgtcgtgacgcagccaccctcagcgtctg agacccccgggcggagggtcaccatctcttgtt ctggaagcagctccaacatcggaattaatactgt aaactggtaccagcagctccccggaacggccc ccaaactcctcatctatactaataatcagcggccc tcaggggtccctgaccgattctctggctccaagt ctggcacctcagcctccctggccatcagtgggct ccagtctgaggatgaggctgattattactgtgcat catgggatgacagcctgaatggtttttatgtcttcg gaactgggaccaaggtcaccgtcctag	127	QSVVTQPPSASETP GRRVTISCSGSSSNI GINTVNWYQQLPG TAPKLLIYTNNQRP SGVPDRFSGSKSGT SASLAISGLQSEDE ADYYCASWDDSLN GFYVFGTGTKVTV L	128
BA.4/5-17	aattttatgctgactcagccgccctcagtgtctgc ggccccaggacagaaggtcaccatctcctgctc tggaagcatctccaacattgggaataattatgtat cctggtaccagcagctcccaggaacagccccc aaactcctcatttatgacaataataagcgaccctc	139	NFMLTQPPSVSAAP GQKVTISCSGSISNI GNNYVSWYQQLP GTAPKLLIYDNNK RPSGIPDRFSGSKS	140

	agggattcctgaccgattctctggctccaagtctg gcacgtcagccaccctgggcatcaccggactcc agactggggacgaggccgattattactgcggaa catgggatagcagcctgagtgctcttgtcttcgg aactgggaccgaggtcaccgtcctcg		GTSATLGITGLQTG DEADYYCGTWDSS LSALVFGTGTEVTV L	
BA.4/5-18	gtcatctggatgacccagtctccatcctccctgtc tgcatctataggagacagagtcaccatcacttgc caggcgagtcaggacataagcaatcacttaaatt ggtatcagcagaaaccagggaaagcccctaag ctcctgatctacgatgtgtccgatttggaaacagg ggtcccctcaaggttcagtggaggtggatctgg gacagaatttactttcaccatcagcagcctgcag cctgaagatgttgcaacatattactgtcaagagta tgatgatttccctcttttcggccctgggaccaagg tggaaatcaaac	151	VIWMTQSPSSLSAS IGDRVTITCQASQD ISNHLNWYQQKPG KAPKLLIYDVSDLE TGVPSRFSGGGSGT EFTFTISSLQPEDVA TYYCQEYDDFPLF GPGTKVEIK	152
BA.4/5-20	cagtctgtggtgactcagccaccctcagcgtctg ggacccccgggcagagggtcaccatctcttgtt ccggaagcagctccaacatcggaagcaatactg taaactggttccagcagttcccaggaacggccc ccaaactcctcatctatagtaataatcagcggccc tcaggggtccctgaccgattctctggctccaagt ctggcacctcagcctccctggccatcagtgggct ccggtctgaggatgaggctgattattactgtgca gcttgggatgacagcctgagtggtttttatgtcttc ggaactgggaccaaggtcagcgtcctag	163	QSVVTQPPSASGTP GQRVTISCSGSSSNI GSNTVNWFQQFPG TAPKLLIYSNNQRP SGVPDRFSGSKSGT SASLAISGLRSEDE ADYYCAAWDDSLS GFYVFGTGTKVSV L	164
BA.4/5-21	gacatccagttgacccagtctccatccttcctgtct gcgtctgtaggagacagagtcgttatcacttgcc gggccagtcaggacattagcacttatttagcctg gtatcagcaagaaccagggaaagcccctaagct cctgatctatgctgcatccactttgcaaagtgggg tcccatcaaggttcagcggcagtggatctgggc cagagttcactctcacaatcagcagcctgcagcc tgaagattttgcaacttattactgtcaacagcattat acttacccagtcactttcggcggagggaccaag gtggagatcaaac	175	DIQLTQSPSFLSASV GDRVVITCRASQDI STYLAWYQQEPGK APKLLIYAASTLQS GVPSRFSGSGSGPE FTLTISSLQPEDFAT YYCQQHYTYPVTF GGGTKVEIK	176
BA.4/5-22	gatattgtgatgactcagtctccactctccctgcc cgtcacccttggacagccggcctccatctcctgc aggtctaatctaagcctcgtatacagagatggag acacctacttgaattggtttcagcagaggccagg ccaatctccaaggcgcctcatttataaagtttttaa ccgggactctggggtcccagacagattcagcg gcagtgggtccggcactgatttcacactgaaaat cagcagagtggaggctgaggatgttggggtttat tactgcatgcaaggtacgcactggccggggac gttcggccaagggaccaaggtggagatcaaac	187	DIVMTQSPLSLPVT LGQPASISCRSNLS LVYRDGDTYLNWF QQRPGQSPRRLIYK VFNRDSGVPDRFS GSGSGTDFTLKISR VEAEDVGVYYCM QGTHWPGTFGQGT KVEIK	188
BA.4/5-23	gacatccagttgacgcagtctccaggcaccctgt ctttgtctccaggggaaagagccaccctctcctg cagggccagtcagagtctttctagcagttacttag cctggtaccagcagaaacctggccaggctccca ggctcctcatctatgatgcatccagcagggccac	199	DIQLTQSPGTLSLSP GERATLSCRASQSL SSSYLAWYQQKPG QAPRLLIYDASSRA TGIPDRFSGSGSGT	200

	tggcatcccagacaggttcagtggcagtgggtct gggacagacttcactctcaccatcagcagactg gaacctgaagattttgcagtgtattactgtcagca gtatggtaggtcacctcggacgttcggccaagg gaccaaagtggatatcaaac		DFTLTISRLEPEDFA VYYCQQYGRSPRT FGQGTKVDIK	
BA.4/5-24	gccatccggatgacccagtctccatcctttctgtc tgcatctgtaggagacagagtcaccgtcacttgc cgggccagtgaagacattagtacttatgtagcct ggtatcagcaaaaaccaggtaaagcccctaggc tcctgatctatactgcatccactttgcataatgatgt cccatcaaggttcagcggcagtggatctggggc agaattcactctcacaatcagcagcctgcagcct gacgattttgcaacttattactgtcaacaacttcat acctacccagtcactttcggcggagggaccaaa gtggatatcaaac	211	AIRMTQSPSFLSAS VGDRVTVTCRASE DISTYVAWYQQKP GKAPRLLIYTASTL HNDVPSRFSGSGSG AEFTLTISSLQPDDF ATYYCQQLHTYPV TFGGGTKVDIK	212
BA.4/5-25	gccatccagatgacccagtctccttccaccctgt ctgcatctgtaggaggcagagtcaccatcacttg ccgggccagtcagactattaattcctggttggcct ggtatcagcacaaaccagggaaagcccctcaa ctcctgatctatgatgcctccagtttgcaaagtgg ggtcccatcaaggttcagcggcagtggatctgg gacagaattcactctcaccatcagcagcctgcag cctgatgattttgcaacttattactgccaacagtat aaaagttatccttgcacttttggccaggggacca aagtggatatcaaac	223	AIQMTQSPSTLSAS VGGRVTITCRASQT INSWLAWYQHKPG KAPQLLIYDASSLQ SGVPSRFSGSGSGT EFTLTISSLQPDDFA TYYCQQYKSYPCT FGQGTKVDIK	224
BA.4/5-28	caggctgtgctgactcagccaccctcaatgtcgg tggccccaggaaagacggccaccattacctgtg gggggagacaactttggaggtcaaagtgtgcact ggtaccagcagaggccaggccaggccctgtc ttggtcatctattctactcgcgaccggccctcagg ggtccctgagcgattctctggctccgcctctggg aacacggccaccctgaccatcaccagggtcga agccggggatgaggccgactattactgtcaggt gtgggatagtagtaatgatcatcaggttttcggcg gagggaccaagctgaccgtcctag	235	QAVLTQPPSMSVA PGKTATITCGGDNF GGQSVHWYQQRP GQAPVLVIYSTRDR PSGVPERFSGSASG NTATLTITRVEAGD EADYYCQVWDSSN DHQVFGGGTKLTV L	236
BA.4/5-31	gatgttgtgatgactcagtctccatcctccctgtct gcatctgtaggagacaaaatcaccatcacttgcc gggcgagtcagggcattagcaattctttagcctg gtatcagcagaacccagggaaagcccctaaact cctgctctatactgcatccacattggaaagtggg gtcccatccaggttcagtggcagtggatctggga cggatttcactctcaccatcagcagcctgcagcc tgaagattttgcaacttattactgtcaacagtattat gatacctggtacacttttggccaggggaccaaa gtggatatcaaac	247	DVVMTQSPSSLSAS VGDKITITCRASQG ISNSLAWYQQNPG KAPKLLLYTASTLE SGVPSRFSGSGSGT DFTLTISSLQPEDFA TYYCQQYYDTWY TFGQGTKVDIK	248
BA.4/5-32	cagactgtggtgactcagccaccctcggtgtca gtggccccaggacagacggccaggattacctgt gggggaaacgacattggaagtaaaggtgtgca ctggtaccagcagaagccgggccaggcccctg tgctggtcgtctctgctgatagcgaccggccctc	259	QTVVTQPPSVSVAP GQTARITCGGNDIG SKGVHWYQQKPG QAPVLVVSADSDR PSGIPERFSGSNSGN	260

	agggatccctgagcgattctctggctccaactct gggaacacggccaccctgaccatcagcagggt cgaagtcggggatgaggccgactattactgtca ggtgtgggatattagtattgatcattatgtcttcgg gactgggaccaaggtcaccgtcctag		TATLTISRVEVGDE ADYYCQVWDISID HYVFGTGTKVTVL	
BA.4/5-33	gaaatagtgatgacgcagtctccagccaccctgt ctgtgtctccaggggaaagagccaccctctcctg cagggccagtcagagtgttaacagcgacttagc ctggtaccagcagaaacctggccgggctccca ggctcctcatctatggtgcgtccaccagggccac tggtatcccagccaggttcagcggcagtgggtct gggacagagttcactctcaccatcagcagcctg cagtctgaagattttgcagtttattactgtcagcac tataatagctggcctccgtacacttttggccaggg gaccaaagtggatatcaaac	271	EIVMTQSPATLSVS PGERATLSCRASQS VNSDLAWYQQKP GRAPRLLIYGASTR ATGIPARFSGSGSG TEFTLTISSLQSEDF AVYYCQHYNSWPP YTFGQGTKVDIK	272
BA.4/5-34	gaaattgtgttgacgcagtctccgctctccctgcc cgtcacccttggacagccggcctccatctcctgc aggtctagtcaaagcctcgtatacagtgatggag acacctacttgaattggtttcagcagaggccgggg ccaatctccaaggcgcctaatttataaggtttctaa tcgagagtctggggtcccagacagattcagcgg cagtggttcaggcactgaattcacactgaaaatc agcagggtggaggccgaggatattgggatttatt actgcatgcaaggaacacactggccggggacg ttcggccaagggaccaaggtggagatcaaac	283	EIVLTQSPLSLPVTL GQPASISCRSSQSL VYSDGDTYLNWFQ QRPGQSPRRLIYKV SNRESGVPDRFSGS GSGTEFTLKISRVE AEDIGIYYCMQGT HWPGTFGQGTKVE IK	284

CDR sequences of selected antibodies

Antibody	Heavy Chain							
	CDR1-IMGT	SEQ ID NO:	CDR2-IMGT	SEQ ID NO:	CDR3-IMGT	SEQ ID NO:	CDR3 AA Junction	SEQ ID NO:
BA.4/5-1	GGSISS SNYY	3	IYYSG SS	4	ASTLGA TFY	5	CASTLG ATFYW	6
BA.4/5-2	GFTLRS FG	15	ISYDG SNQ	16	AKDLLP LLALYY GMDV	17	CAKDLL PLLALY YGMDV W	18
BA.4/5-6	ETIVSR NY	27	IYPGG ST	28	VRDFGD FYFDY	29	CVRDFG DFYFDY W	30
BA.4/5-7	EIIVSR NY	39	LYSG GST	40	ARSYGD FYIDI	41	CARSYG DFYIDIW	42
BA.4/5-8	GITVSS NY	51	IYSGG TT	52	ARPIMG AISGMD V	53	CARPIM GAISGM DVW	54

BA.4/5-9	GDTFINSF	63	INPSGVST	64	ARENGGNSGDFDY	65	CARENGGNSGDFDYW	66
BA.4/5-10	GFTVSRNY	75	IYSGGST	76	ARPIVGVISGMDV	77	CARPIVGVISGMDVW	78
BA.4/5-11	GFTFSNYG	87	IWSDGNSK	88	ARDHYYDSSGYTLDAFDI	89	CARDHYYDSSGYTLDAFDIW	90
BA.4/5-12	GFTFSIYG	99	ISYDGSNK	100	AKDSKGYVDWSLGTYYYYAMDV	101	CAKDSKGYVDWSLGTYYYYAMDVW	102
BA.4/5-13	GGSFSRYA	111	IIPMYGTP	112	ARESNKYTYGFPSYYYYGMDV	113	CARESNKYTYGFPSYYYYGMDVW	114
BA.4/5-15	GFTFDDSA	123	ISWNSASI	124	AKDITSILTDKDYGMDV	125	CAKDITSILTDKDYGMDVW	126
BA.4/5-17	GLIVSSNY	135	IYSGGST	136	ARSIAVAAHGAYGVDV	137	CARSIAVAAHGAYGVDVW	138
BA.4/5-18	GDNFSRYA	147	IIPMYGTP	148	ARESNKYTYGFPSYYYYGMNI	149	CARESNKYTYGFPSYYYYGMNIW	150
BA.4/5-20	RFTFADYA	159	IAWNSANI	160	AKDITPILTDQEYGMDV	161	CAKDITPILTDQEYGMDVW	162
BA.4/5-21	GFIFDHHA	171	ISWNSGTI	172	VKDLNYDFSGYFKNGFED	173	CVKDLNYDFSGYFKNGFEDW	174
BA.4/5-22	GGSIRNYA	183	IIPIFGPA	184	APLGYSGYNFGFQH	185	CAPLGYSGYNFGFQHW	186
BA.4/5-23	EFIVSRNY	195	IYPGGST	196	ARDYGDFFFDY	197	CARDYGDFFFDYW	198
BA.4/5-24	GFTFDDFA	207	ISWNSGNI	208	AKDLNYDSSGYLYNGFAL	209	CAKDLNYDSSGYLYNGFALW	210
BA.4/5-25	GDTFSLSA	219	IVPIPNIA	220	ARGDEAMAF	221	CARGDEAMAFW	222

BA.4/5-28	GVTVSHNY	231	IYAGGTT	232	ARDLLERGGMDV	233	CARDLLERGGMDVW	234
BA.4/5-31	GGSISSSNYY	243	IYYSGRS	244	ASTLGATFY	245	CASTLGATFYW	246
BA.4/5-32	EIIVSRNY	255	LYPGGTT	256	ARDVRDAFDV	257	CARDVRDAFDVW	258
BA.4/5-33	GFTFSSSA	267	ISDAGLNT	268	AIGYSPDY	269	CAIGYSPDYW	270
BA.4/5-34	GGSFRNYA	279	IIPIFGPA	280	APLGYSGYNFGFEY	281	CAPLGYSGYNFGFEYW	282

Antibody	Light Chain							
	CDR1-IMGT	SEQ ID NO:	CDR2-IMGT	SEQ ID NO:	CDR3-IMGT	SEQ ID NO:	CDR3 AA Junction	SEQ ID NO:
BA.4/5-1	QGISNS	9	TAS	10	QQYYDTWYT	11	CQQYYDTWYTF	12
BA.4/5-2	QSVSSY	21	EAS	22	QQRSNFPFI	23	CQQRSNFPFIF	24
BA.4/5-6	QSVDSGS	33	DAS	34	QQYSSSPRT	35	CQQYSSSPRTF	36
BA.4/5-7	QSVSSN	45	GAS	46	QQYNDWPGT	47	CQQYNDWPGTF	48
BA.4/5-8	QDLNKY	57	DAS	58	QQYDNLPYT	59	CQQYDNLPYTF	60
BA.4/5-9	QSVSSY	69	NAS	70	QQHYNWPRYS	71	CQQHYNWPRYSF	72
BA.4/5-10	QDINNY	81	AAS	82	HQYDNLPYT	83	CHQYDNLPYTF	84
BA.4/5-11	QSISSY	93	AAS	94	QQSYSTLMYT	95	CQQSYSTLMYTF	96
BA.4/5-12	QDISNY	105	DAS	106	QQYDNLPLT	107	CQQYDNLPLTF	108
BA.4/5-13	QDISNH	117	DVS	118	QQYDDFPL	119	CQQYDDFPLF	120
BA.4/5-15	SSNIGINT	129	TNN	130	ASWDDSLNGFYV	131	CASWDDSLNGFYVF	132
BA.4/5-17	ISNIGNNY	141	DNN	142	GTWDSSLSALV	143	CGTWDSSLSALVF	144
BA.4/5-18	QDISNH	153	DVS	154	QEYDDFPL	155	CQEYDDFPLF	156
BA.4/5-20	SSNIGSNT	165	SNN	166	AAWDDSLSGFYV	167	CAAWDDSLSGFYVF	168

BA.4/5-21	QDISTY	177	AAS	178	QQHYTY PVT	179	CQQHYT YPVTF	180
BA.4/5-22	LSLVYR DGDTY	189	KVF	190	MQGTH WPGT	191	CMQGTH WPGTF	192
BA.4/5-23	QSLSSSY	201	DAS	202	QQYGRS PRT	203	CQQYGR SPRTF	204
BA.4/5-24	EDISTY	213	TAS	214	QQLHTY PVT	215	CQQLHT YPVTF	216
BA.4/5-25	QTINSW	225	DAS	226	QQYKSY PCT	227	CQQYKS YPCTF	228
BA.4/5-28	NFGGQS	237	STR	238	QVWDSS NDHQV	239	CQVWDS SNDHQV F	240
BA.4/5-31	QGISNS	249	TAS	250	QQYYDT WYT	251	CQQYYD TWYTF	252
BA.4/5-32	DIGSKG	261	ADS	262	QVWDISI DHYV	263	CQVWDI SIDHYVF	264
BA.4/5-33	QSVNSD	273	GAS	274	QHYNSW PPYT	275	CQHYNS WPPYTF	276
BA.4/5-34	QSLVYS DGDTY	285	KVS	286	MQGTH WPGT	287	CMQGTH WPGTF	288

Claims

1. An antibody capable of binding to the spike protein of coronavirus SARS-CoV-2, wherein the antibody comprises the six CDRs of antibody BA.4/5-2, or of any one of the antibodies in Tables 1 and 3 to 9.

2. The antibody according to claim 1, comprising a heavy chain variable domain and a light chain variable domain comprising or consisting of an amino acid sequence having at least 80% identity to the heavy chain variable domain and light chain variable domain, respectively, of an antibody in any one of Tables 1 and 3 to 9.

3. The antibody of claim 1 or claim 2, wherein the antibody is selected from the group consisting of BA.4/5-2, BA.4/5-1, BA.4/5-8, BA.4/5-9, BA.4/5-22, BA.4/5-28, BA.4/5-31 and BA.4/5-34, optionally wherein:

(i) the antibody comprises a CDRH1, CDRH2, CDRH3, CDRL1, CDRL2 and CDRL3 having the amino acid sequences specified in SEQ ID NOs: 15, 16, 17, 21, 22 and 23, respectively, optionally wherein the antibody comprises a heavy chain variable domain and a light chain variable domain having at least 80% identity to the amino acid sequences specified in SEQ ID NOs: 14 and 20, respectively;

(ii) the antibody comprises a CDRH1, CDRH2, CDRH3, CDRL1, CDRL2 and CDRL3 having the amino acid sequences specified in SEQ ID NOs: 3, 4, 5, 9, 10 and 11, respectively, optionally wherein the antibody comprises a heavy chain variable domain and a light chain variable domain having at least 80% identity to the amino acid sequences specified in SEQ ID NOs: 2 and 8, respectively;

(iii) the antibody comprises a CDRH1, CDRH2, CDRH3, CDRL1, CDRL2 and CDRL3 having the amino acid sequences specified in SEQ ID NOs: 51, 52, 53, 57, 58 and 59, respectively, optionally wherein the antibody comprises a heavy chain variable domain and a light chain variable domain having at least 80% identity to the amino acid sequences specified in SEQ ID NOs: 50 and 56, respectively;

(iv) the antibody comprises a CDRH1, CDRH2, CDRH3, CDRL1, CDRL2 and CDRL3 having the amino acid sequences specified in SEQ ID NOs: 63, 64, 65, 69, 70 and 71, respectively, optionally wherein the antibody comprises a heavy chain variable domain

and a light chain variable domain having at least 80% identity to the amino acid sequences specified in SEQ ID NOs: 62 and 68, respectively;

(v) the antibody comprises a CDRH1, CDRH2, CDRH3, CDRL1, CDRL2 and CDRL3 having the amino acid sequences specified in SEQ ID NOs: 183, 184, 185, 189, 190 and 191, respectively, optionally wherein the antibody comprises a heavy chain variable domain and a light chain variable domain having at least 80% identity to the amino acid sequences specified in SEQ ID NOs: 182 and 188, respectively;

(vi) the antibody comprises a CDRH1, CDRH2, CDRH3, CDRL1, CDRL2 and CDRL3 having the amino acid sequences specified in SEQ ID NOs: 231, 232, 233, 237, 238 and 239, respectively, optionally wherein the antibody comprises a heavy chain variable domain and a light chain variable domain having at least 80% identity to the amino acid sequences specified in SEQ ID NOs: 230 and 236, respectively;

(vii) the antibody comprises a CDRH1, CDRH2, CDRH3, CDRL1, CDRL2 and CDRL3 having the amino acid sequences specified in SEQ ID NOs: 243, 244, 245, 249, 250 and 251, respectively, optionally wherein the antibody comprises a heavy chain variable domain and a light chain variable domain having at least 80% identity to the amino acid sequences specified in SEQ ID NOs: 242 and 248, respectively; or

(viii) the antibody comprises a CDRH1, CDRH2, CDRH3, CDRL1, CDRL2 and CDRL3 having the amino acid sequences specified in SEQ ID NOs: 279, 280, 281, 285, 286 and 287, respectively, optionally wherein the antibody comprises a heavy chain variable domain and a light chain variable domain having at least 80% identity to the amino acid sequences specified in SEQ ID NOs: 278 and 284, respectively.

4. An antibody capable of binding to the spike protein of coronavirus SARS-CoV-2, wherein the antibody comprises CDRH1, CDRH2 and CDRH3, from a first antibody in Table 1 and CDRL1, CDRL2 and CDRL3 from a second antibody in Table 1, with the proviso that the first antibody and the second antibody are different.

5. The antibody according to claim 4, comprising a heavy chain variable domain amino acid sequence having at least 80% sequence identity to the heavy chain variable domain from a first antibody in Table 1, and a light chain variable domain amino acid sequence having at least 80% sequence identity to the light chain variable domain from a second antibody in Table 1.

6. The antibody according to claim 4 or claim 5, wherein the first and second antibodies derive from the same germline heavy chain v-region, optionally wherein the heavy chain v-region is IGHV4-39, IGHV3-30, IGHV3-53/3-66, IGHV1-69, or IGHV3-9.

7. The antibody according to any one of claims 4 to 6, wherein the first antibody and the second antibody are both selected from one of the following groups:

(a) BA.4/5-1 and BA.4/5-31; optionally wherein the antibody comprises the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2 and CDRL3 of one of the antibodies as set out in Table 3, optionally wherein the antibody comprises a heavy chain variable domain and a light chain variable domain having at least 80% identity to the heavy chain variable domain and a light chain variable domain, respectively, to one of the antibodies as set out in Table 3;

(b) BA.4/5-2 and BA.4/5-12; optionally wherein the antibody comprises the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2 and CDRL3 of one of the antibodies as set out in Table 4, optionally wherein the antibody comprises a heavy chain variable domain and a light chain variable domain having at least 80% identity to the heavy chain variable domain and a light chain variable domain, respectively, to one of the antibodies as set out in Table 4;

(c) BA.4/5-6, BA.4/5-7, BA.4/5-17 and BA.4/5-23; optionally wherein the antibody comprises the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2 and CDRL3 of one of the antibodies as set out in Table 5, optionally wherein the antibody comprises a heavy chain variable domain and a light chain variable domain having at least 80% identity to the heavy chain variable domain and a light chain variable domain, respectively, to one of the antibodies as set out in Table 5;

(d) BA.4/5-8, BA.4/5-10, BA.4/5-28 and BA.4/5-32; optionally wherein the antibody comprises the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2 and CDRL3 of one of the antibodies as set out in Table 6, optionally wherein the antibody comprises a heavy chain variable domain and a light chain variable domain having at least 80% identity to the heavy chain variable domain and a light chain variable domain, respectively, to one of the antibodies as set out in Table 6;

(e) BA.4/5-6, BA.4/5-7, BA.4/5-17, BA.4/5-23, BA.4/5-8, BA.4/5-10, BA.4/5-28 and BA.4/5-32; optionally wherein the antibody comprises the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2 and CDRL3 of one of the antibodies as set out in Table 7, optionally wherein the antibody comprises a heavy chain variable domain and a light chain variable

domain having at least 80% identity to the heavy chain variable domain and a light chain variable domain, respectively, to one of the antibodies as set out in Table 7;

(f) BA.4/5-13, BA.4/5-18, BA.4/5-22, BA.4/5-25 and BA.4/5-34; optionally wherein the antibody comprises the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2 and CDRL3 of one of the antibodies as set out in Table 8, optionally wherein the antibody comprises a heavy chain variable domain and a light chain variable domain having at least 80% identity to the heavy chain variable domain and a light chain variable domain, respectively, to one of the antibodies as set out in Table 8; or

(g) BA.4/5-15, BA.4/5-20, BA.4/5-21 and BA.4/5-24; optionally wherein the antibody comprises the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2 and CDRL3 of one of the antibodies as set out in Table 9, optionally wherein the antibody comprises a heavy chain variable domain and a light chain variable domain having at least 80% identity to the heavy chain variable domain and a light chain variable domain, respectively, to one of the antibodies as set out in Table 9.

8. The antibody according to any one of the preceding claims, which is a full-length antibody, optionally (i) comprising an IgG1 constant region, and/or (ii) comprising an Fc region comprising at least one modification such that serum half-life is extended.

9. One or more polynucleotides encoding the antibody according to any one of the preceding claims, such as a first polynucleotide encoding the heavy chain variable domain of the antibody and a second polynucleotide encoding the light chain variable domain of the antibody, one or more vectors comprising said polynucleotides, or a host cell comprising said vectors.

10. A method for producing an antibody that is capable of binding to the spike protein of coronavirus SARS-CoV-2, the method comprising culturing the host cell of claim 9 and isolating the antibody from said culture.

11. A pharmaceutical composition comprising: (a) one or more antibody according to any one of claims 1 to 8, and (b) at least one pharmaceutically acceptable diluent or carrier.

12. The antibody according to any one of claims 1 to 8, or the pharmaceutical composition according to claim 11, for use in a method for treatment of a human or animal by therapy.

13. The antibody according to any one of claims 1 to 8, or the pharmaceutical composition according to claim 11, for use in a method of treating or preventing coronavirus infection, or a disease or complication associated with coronavirus infection.

14. A method of treating or preventing coronavirus infection, or a disease or complication associated with coronavirus infection in a subject, comprising administering a therapeutically effective amount of the antibody according to any one of claims 1 to 8, or the pharmaceutical composition according to claim 11, to said subject.

15. The method according to claim 14, wherein the method is for treating SARS-CoV-2 infection, or a disease or complication associated therewith, such as COVID-19.

16. A method of identifying the presence of coronavirus, or a protein fragment thereof, in a sample, comprising:

(i) contacting the sample with the antibody according to any one of claims 1 to 8, and

(ii) detecting the presence or absence of an antibody-antigen complex,

wherein the presence of the antibody-antigen complex indicates the presence of coronavirus, or a fragment thereof, in the sample.

17. A method of treating or preventing coronavirus infection, or a disease or complication associated therewith, in a subject, the method comprising identifying the presence of coronavirus according to the method of claim 16 in a sample, and treating the subject with the antibody according to any one of claims 1 to 8, an anti-viral drug or an anti-inflammatory agent.

18. Use of the antibody according to any one of claims 1 to 8, or the pharmaceutical composition according to claim 11, for preventing, treating and/or diagnosing coronavirus infection, or a disease or complication associated therewith.

19. Use of the antibody according to any one of claims 1 to 8, or the pharmaceutical composition according to claim 11, for the manufacture of a medicament for treating or preventing coronavirus infection, or a disease or complication associated therewith.

20. The antibody for use according to claim 12 or 13, the method according to any one of claims 14 to 17, or the use according to claim 18 or 19, wherein the coronavirus infection is caused by a SARS-CoV-2 strain of the lineage Victoria, alpha, beta, gamma, delta, omicron, BA.1, BA.1.1, BA.2, BA.2.10.4, BA.2.12.1, BA.2.30.2, BA.2.75, BA.2.75.2, BA.4/5, BA.4/6, BQ.1, BQ.1.1, BJ.1, BS.1, BF.7, BN.1, XBB, XBB.1 and/or XBB.1.5.

Fig. 1A

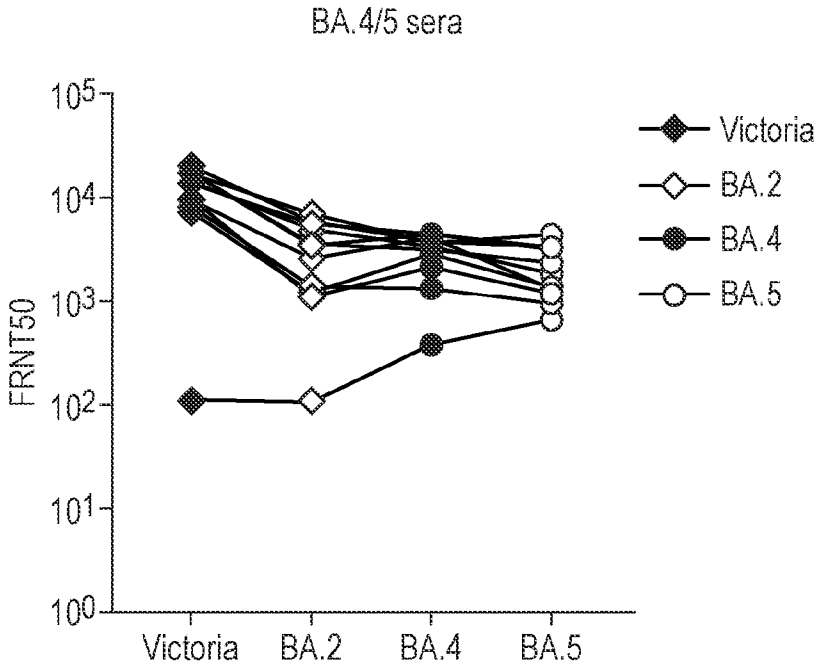

BA.4/5 sera
FRNT50
10^5
10^4
10^3
10^2
10^1
10^0
Victoria
BA.2
BA.4
BA.5
Victoria
BA.2
BA.4
BA.5

Fig. 1B

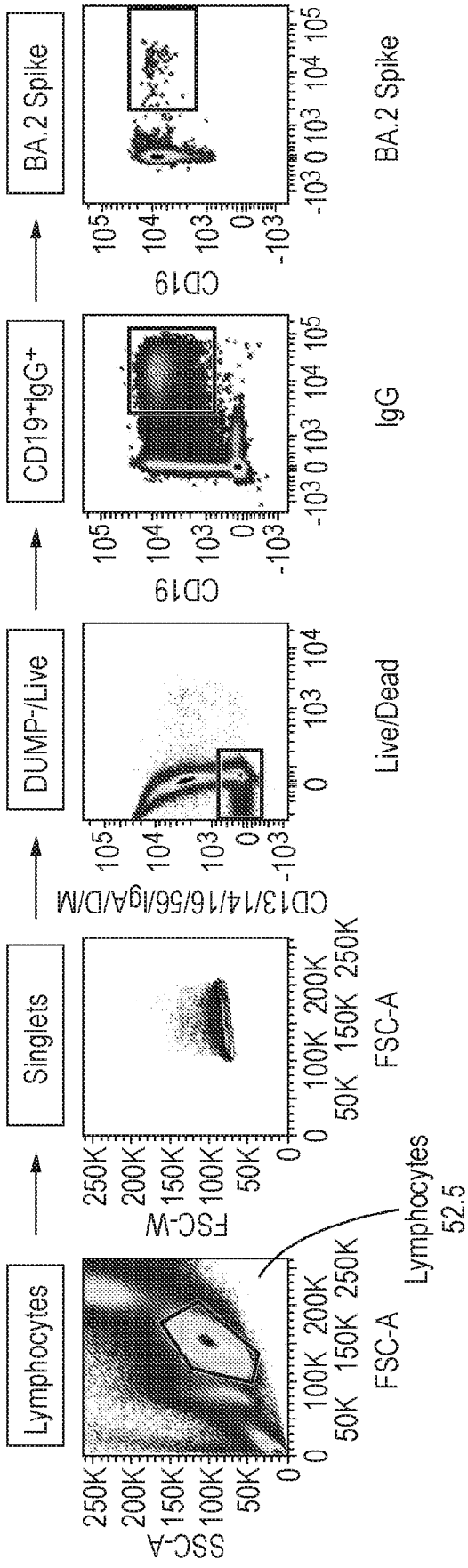

Lymphocytes
Singlets
DUMP-/Live
CD19+IgG+
BA.2 Spike
SSC-A
FSC-A
FSC-W
CD13/14/16/56/IgA/D/M
CD19
Lymphocytes
52.5
Live/Dead
IgG
BA.2 Spike

Fig. 1C

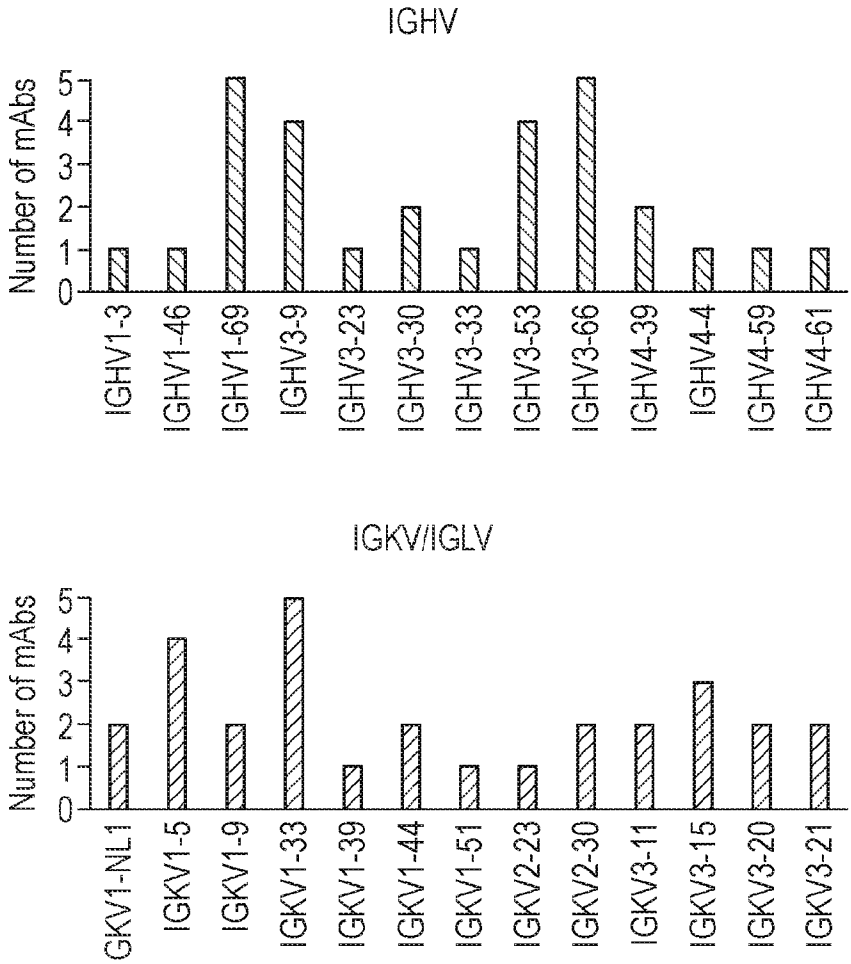

IGHV
Number of mAbs
0
1
2
3
4
5
IGHV1-3
IGHV1-46
IGHV1-69
IGHV3-9
IGHV3-23
IGHV3-30
IGHV3-33
IGHV3-53
IGHV3-66
IGHV4-39
IGHV4-4
IGHV4-59
IGHV4-61
IGKV/IGLV
Number of mAbs
0
1
2
3
4
5
IGKV1-NL1
IGKV1-5
IGKV1-9
IGKV1-33
IGKV1-39
IGKV1-44
IGKV1-51
IGKV2-23
IGKV2-30
IGKV3-11
IGKV3-15
IGKV3-20
IGKV3-21

Fig. 1D

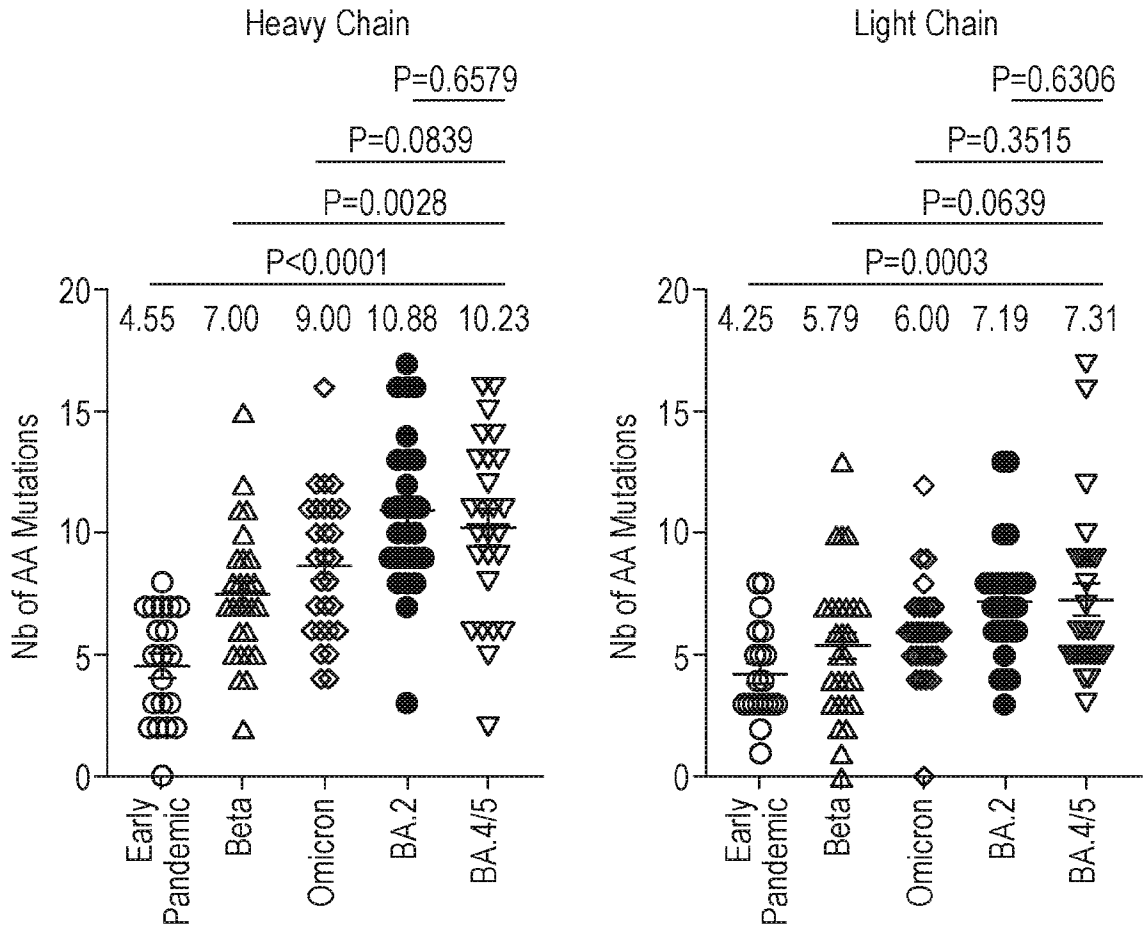

Heavy Chain
P=0.6579
P=0.0839
P=0.0028
P<0.0001
4.55
7.00
9.00
10.88
10.23
Nb of AA Mutations
0
5
10
15
20
Early Pandemic
Beta
Omicron
BA.2
BA.4/5
Light Chain
P=0.6306
P=0.3515
P=0.0639
P=0.0003
4.25
5.79
6.00
7.19
7.31
Nb of AA Mutations
0
5
10
15
20
Early Pandemic
Beta
Omicron
BA.2
BA.4/5

Fig. 1E

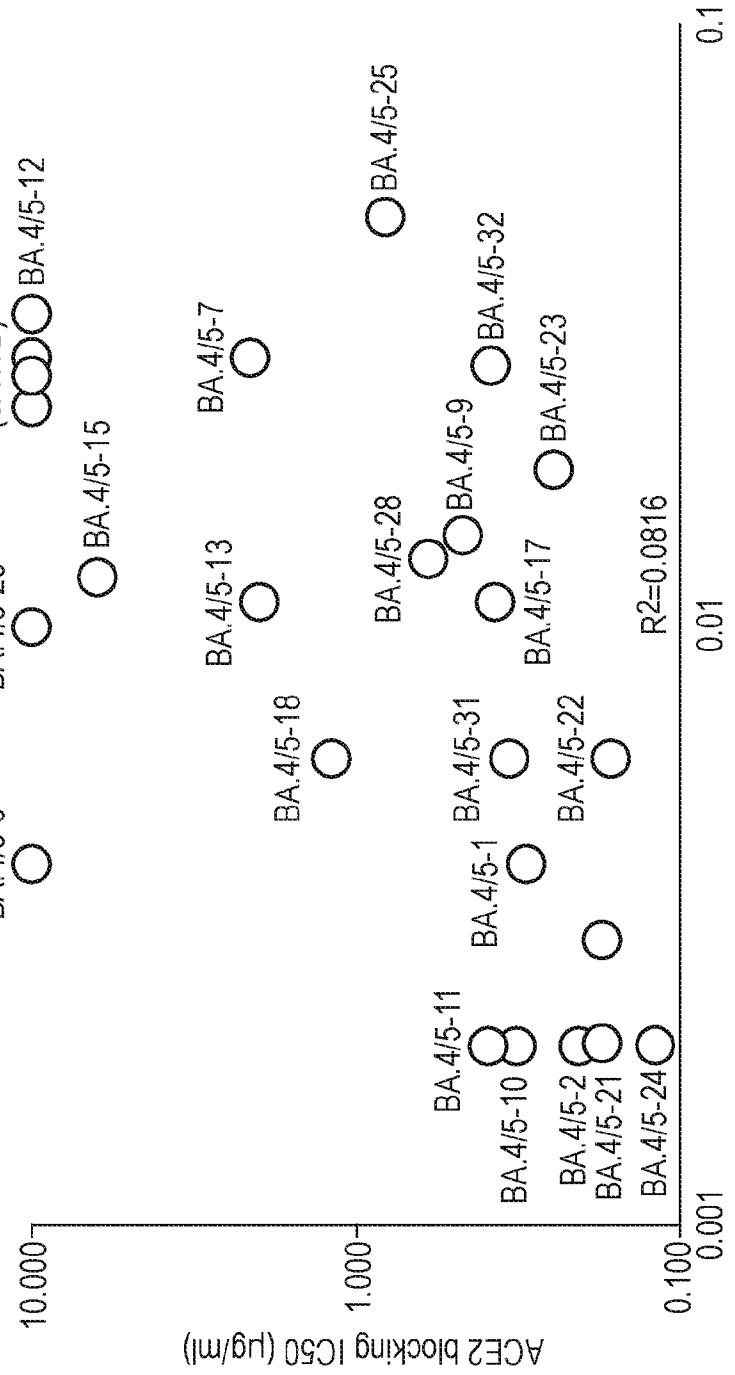

BA.4/5 mAbs ACE2 blocking
ACE2 blocking IC50 (µg/ml)
Neutralisation IC50 (µg/ml)
10.000
1.000
0.100
0.001
0.01
0.1
R2=0.0816
BA.4/5-6
BA.4/5-20
BA.4/5-33
(α-NTD)
BA.4/5-12
BA.4/5-15
BA.4/5-7
BA.4/5-13
BA.4/5-18
BA.4/5-25
BA.4/5-28
BA.4/5-9
BA.4/5-32
BA.4/5-17
BA.4/5-23
BA.4/5-31
BA.4/5-1
BA.4/5-22
BA.4/5-11
BA.4/5-10
BA.4/5-2
BA.4/5-21
BA.4/5-24

Fig. 2A

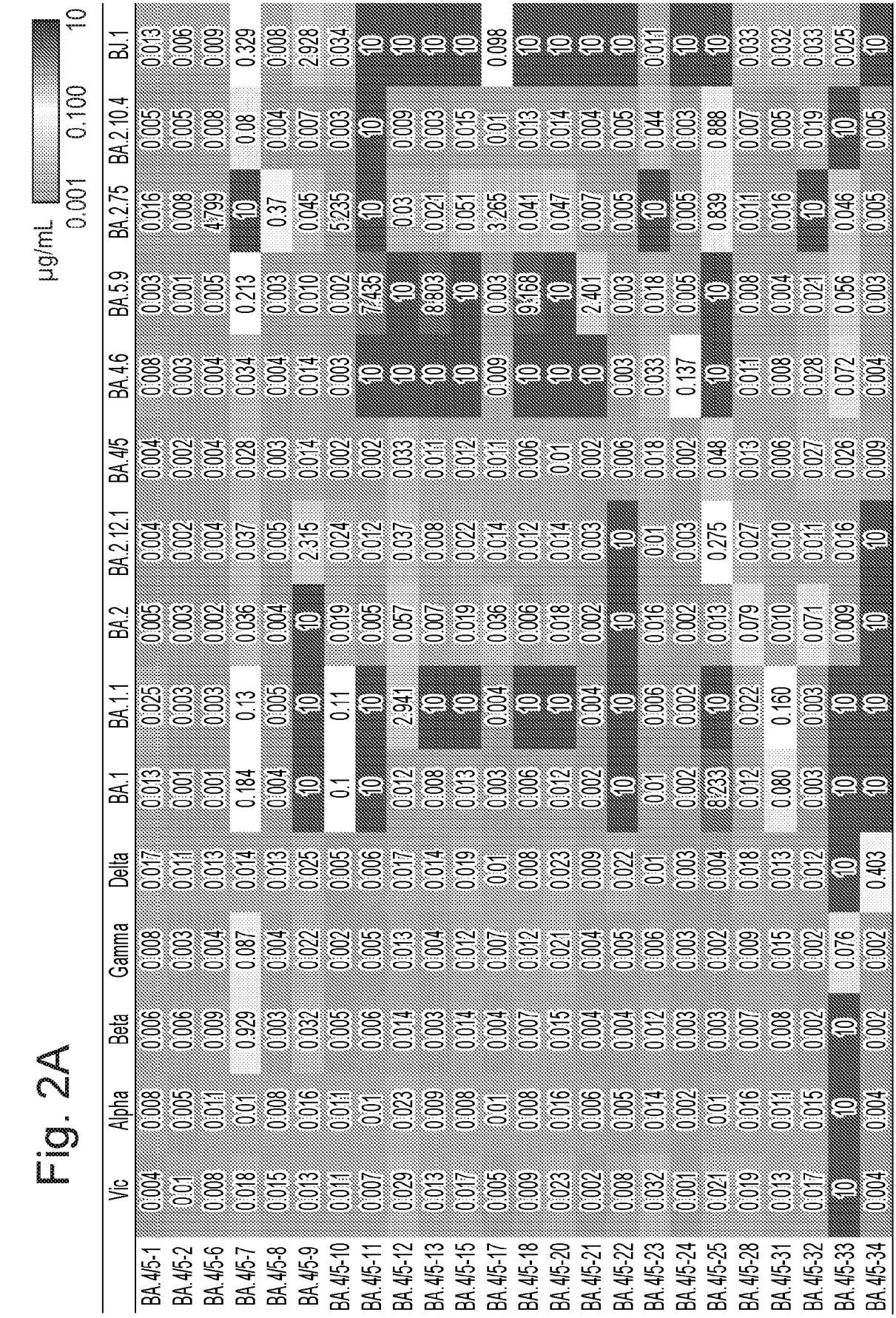
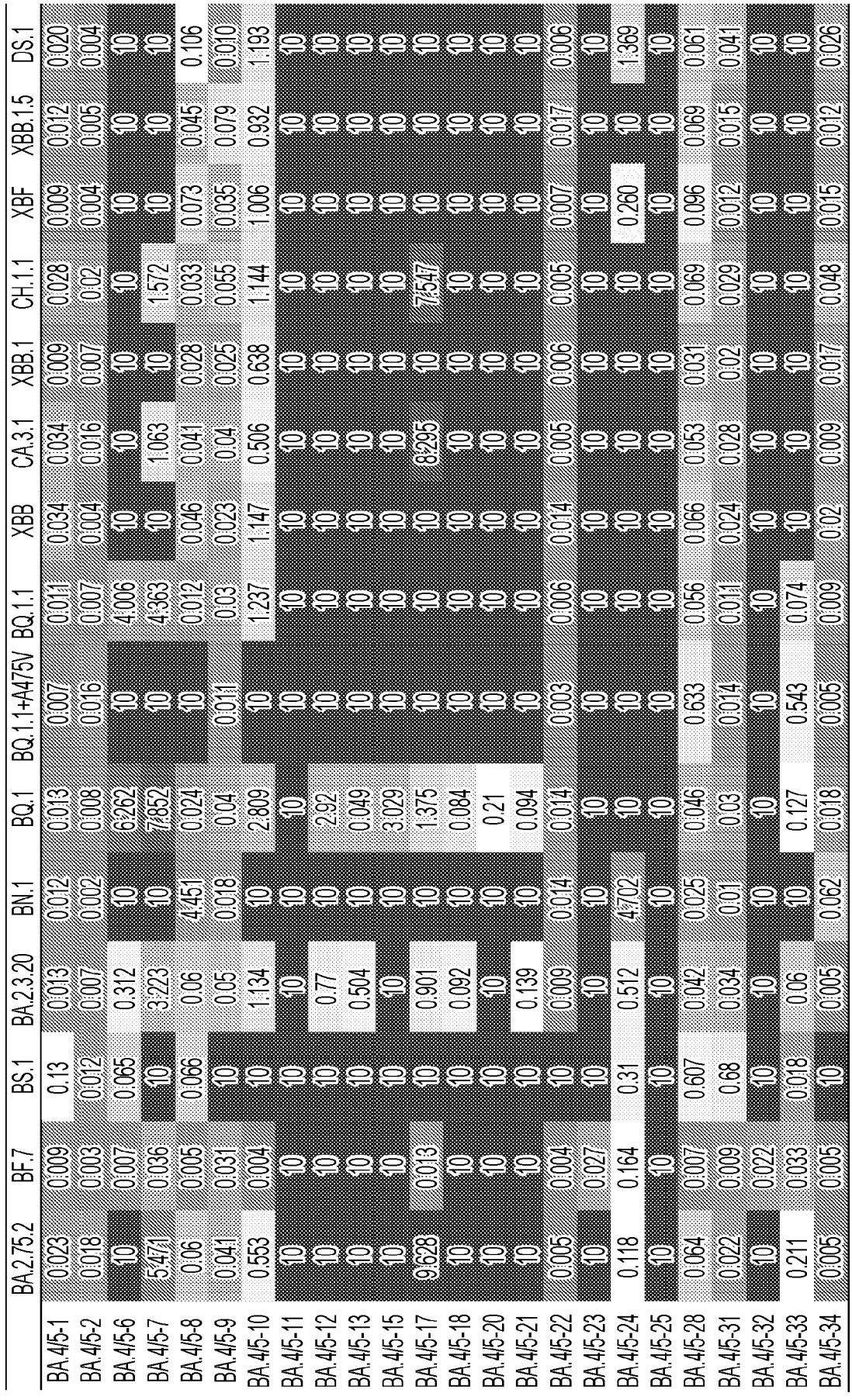
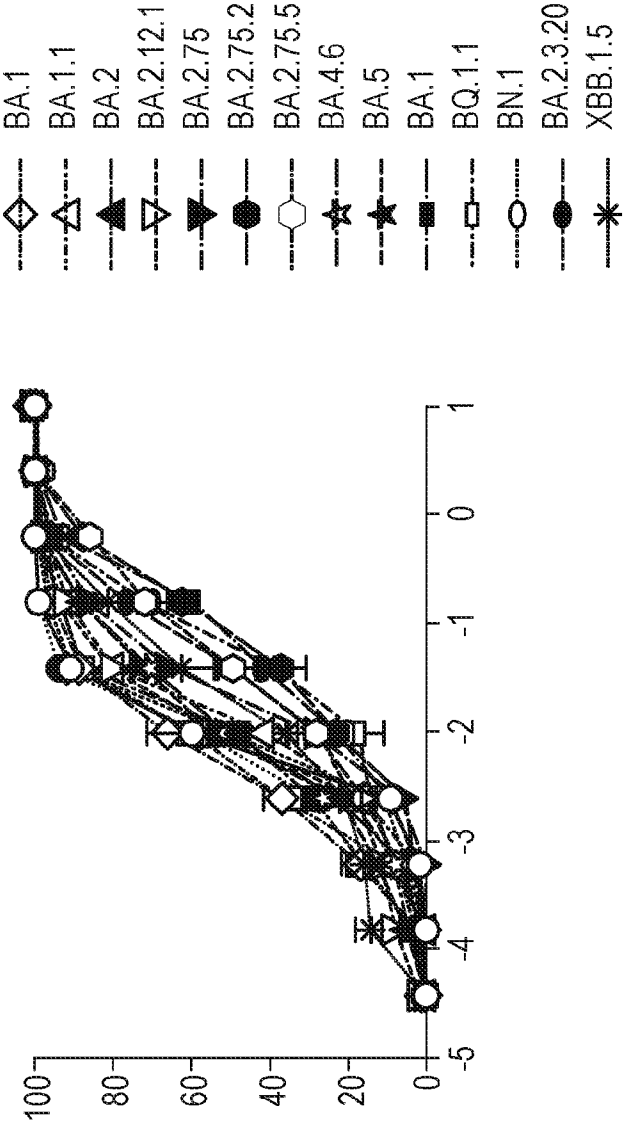

µg/mL
0.001
0.100
10
Vic
Alpha
Beta
Gamma
Delta
BA.1
BA.1.1
BA.2
BA.2.12.1
BA.4/5
BA.4.6
BA.5.9
BA.2.75
BA.2.10.4
BJ.1
BA.4/5-1
BA.4/5-2
BA.4/5-6
BA.4/5-7
BA.4/5-8
BA.4/5-9
BA.4/5-10
BA.4/5-11
BA.4/5-12
BA.4/5-13
BA.4/5-15
BA.4/5-17
BA.4/5-18
BA.4/5-20
BA.4/5-21
BA.4/5-22
BA.4/5-23
BA.4/5-24
BA.4/5-25
BA.4/5-28
BA.4/5-31
BA.4/5-32
BA.4/5-33
BA.4/5-34

Fig. 2A (Cont.)



	BA.2.75.2	BF.7	BS.1	BA.2.3.20	BN.1	BQ.1	BQ.1.1+A475V	BQ.1.1	XBB	CA.3.1	XBB.1	CH.1.1	XBF	XBB.1.5	DS.1
BA.4/5-1	0.023	0.009	0.13	0.013	0.012	0.013	0.007	0.011	0.034	0.034	0.009	0.028	0.009	0.012	0.020
BA.4/5-2	0.018	0.003	0.012	0.007	0.002	0.008	0.016	0.007	0.004	0.016	0.007	0.02	0.004	0.005	0.004
BA.4/5-6	10	0.007	0.065	0.312	10	6.262	10	4.006	10	10	10	10	10	10	10
BA.4/5-7	5.471	0.036	10	3.223	10	7.852	10	4.363	10	1.063	10	1.572	10	10	10
BA.4/5-8	0.06	0.005	0.066	0.06	4.451	0.024	10	0.012	0.046	0.041	0.028	0.033	0.073	0.045	0.106
BA.4/5-9	0.041	0.031	10	0.05	0.018	0.04	0.011	0.03	0.023	0.04	0.025	0.055	0.035	0.079	0.010
BA.4/5-10	0.553	0.004	10	1.134	10	2.809	10	1.237	1.147	0.506	0.638	1.144	1.006	0.932	1.193
BA.4/5-11	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
BA.4/5-12	10	10	10	0.77	10	2.92	10	10	10	10	10	10	10	10	10
BA.4/5-13	10	10	10	0.504	10	0.049	10	10	10	10	10	10	10	10	10
BA.4/5-15	10	10	10	10	10	3.029	10	10	10	10	10	10	10	10	10
BA.4/5-17	9.628	0.013	10	0.901	10	1.375	10	10	10	8.295	10	7.547	10	10	10
BA.4/5-18	10	10	10	0.092	10	0.084	10	10	10	10	10	10	10	10	10
BA.4/5-20	10	10	10	10	10	0.21	10	10	10	10	10	10	10	10	10
BA.4/5-21	10	10	10	0.139	10	0.094	10	10	10	10	10	10	10	10	10
BA.4/5-22	0.005	0.004	10	0.009	0.014	0.014	0.003	0.006	0.014	0.005	0.006	0.005	0.007	0.017	0.006
BA.4/5-23	10	0.027	10	10	10	10	10	10	10	10	10	10	10	10	10
BA.4/5-24	0.118	0.164	0.31	0.512	4.702	10	10	10	10	10	10	10	0.260	10	1.369
BA.4/5-25	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
BA.4/5-28	0.064	0.007	0.607	0.042	0.025	0.046	0.633	0.056	0.066	0.053	0.031	0.069	0.096	0.069	0.061
BA.4/5-31	0.022	0.009	0.68	0.034	0.01	0.03	0.014	0.011	0.024	0.028	0.02	0.029	0.012	0.015	0.041
BA.4/5-32	10	0.022	10	10	10	10	10	10	10	10	10	10	10	10	10
BA.4/5-33	0.211	0.033	0.018	0.06	10	0.127	0.543	0.074	10	10	10	10	10	10	10
BA.4/5-34	0.005	0.005	10	0.005	0.062	0.018	0.005	0.009	0.02	0.009	0.017	0.048	0.015	0.012	0.026

Fig. 2B



	Vic	Alpha	Beta	Gamma	Delta	BA.1	BA.1.1	BA.2	BA.2.12.1
BA.4/5-2	0.009 ± 0.002	0.005 ± 0.000	0.006 ± 0.001	0.006 ± 0.000	0.009 ± 0.000	0.005 ± 0.001	0.013 ± 0.001	0.010 ± 0.002	0.008 ± 0.000

	BA.2.3.20	BA.2.75	BA.2.75.2	BA.2.75.5	BA.4.6	BA.5	BQ.1	BQ.1.1	BN.1	XBB.1.5
BA.4/5-2	0.029 ± 0.010	0.025 ± 0.002	0.058 ± 0.00	0.032 ± 0.00	0.012 ± 0.00	0.009 ± 0.00	0.049 ± 0.001	0.036 ± 0.001	0.017 ± 0.002	0.015 ± 0.008

Fig. 2C

	AZD1061	AZD8895	AZD7742	REGN10987	REGN10933	ADG20	Ly-CoV1404	S309
Victoria	0.002	0.001	0.001	0.002	0.001	0.003	0.001	0.079
BA.2	0.008	1.333	0.008	0.616	10	10	0.001	0.638
BA.4/5	0.015	10	0.065	10	10	10	0.002	0.689
BA.4.6	10	10	10	10	10	10	0.001	1.029
BA.5.9	10	10	10	1.85	10	10	0.002	2.802
BA.2.75	0.021	0.008	0.017	10	10	10	0.002	0.202
BA.2.10.4	0.072	10	0.098	10	10	10	0.003	0.41
BJ.1	10	0.085	0.228	10	10	10	10	0.839
BA.2.75.2	10	10	10	10	10	10	10	0.465
BF.7	10	10	10	3.925	10	10	0.002	0.801
BS.1	10	10	10	10	10	10	0.004	2.696
BA.2.3.20	10	0.007	0.026	10	8.624	10	0.018	0.977
BN.1	10	0.024	0.068	10	1.954	10	0.004	10
BQ.1	10	10	10	10	10	10	10	0.662
BQ.1.1+A475V	10	10	10	10	10	10	10	1.766
BQ.1.1	10	10	10	10	10	10	10	0.751
XBB	10	10	10	10	10	10	10	0.455
CA.3.1	10	10	10	10	10	10	10	2.254
XBB.1	10	10	10	10	10	10	10	0.142
CH.1.1	10	10	10	10	10	10	10	1.219
XBF	10	10	10	10	10	10	0.007	0.923
XBB.1.5	10	10	10	10	10	10	10	0.447
DS.1	10	10	10	10	10	10	0.006	10

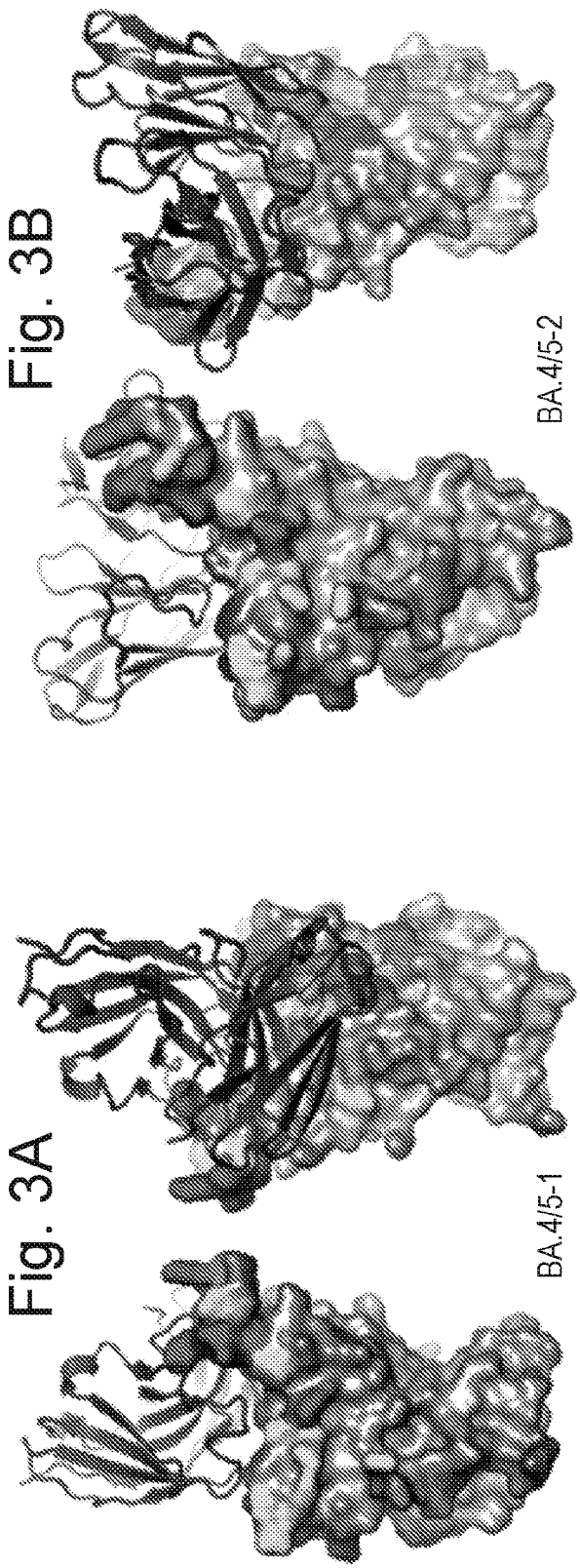


Fig. 3A
BA.4/5-1

Fig. 3B
BA.4/5-2

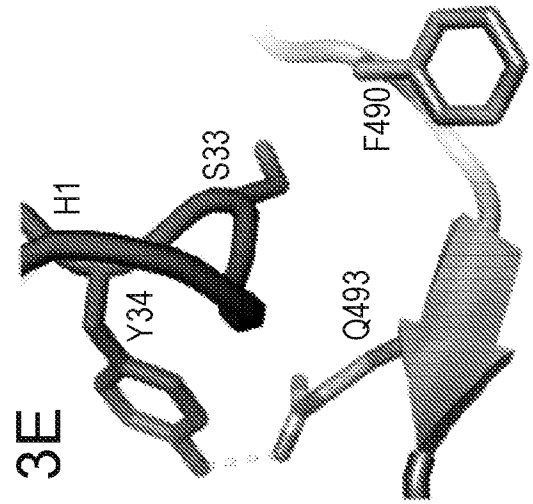


Fig. 3E
H1
S33
Y34
Q493
F490

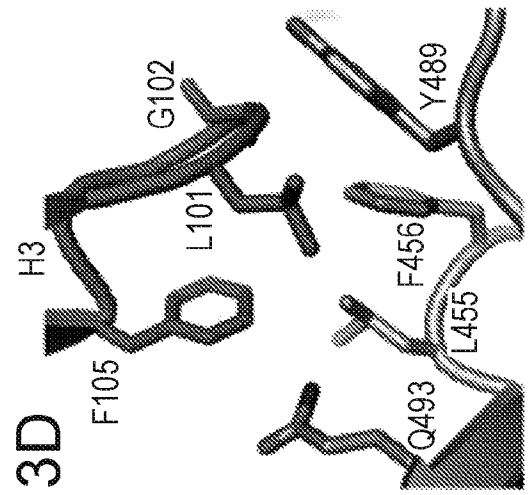


Fig. 3D
H3
G102
L101
F105
F456
Y489
L455
Q493

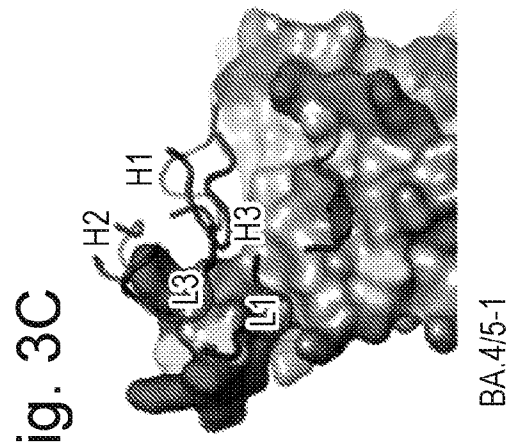


Fig. 3C
H2
H1
L3
H3
L1
BA.4/5-1

Fig. 3F

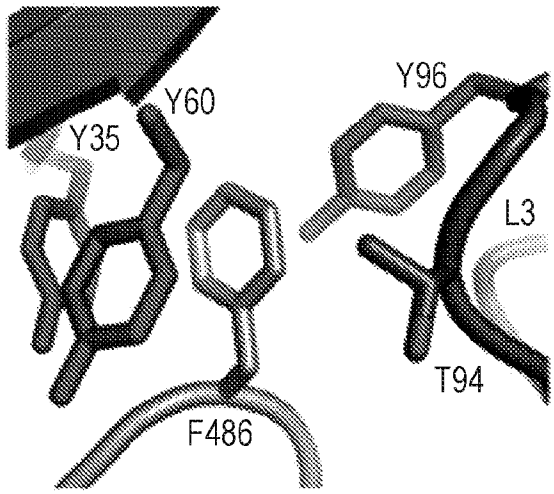
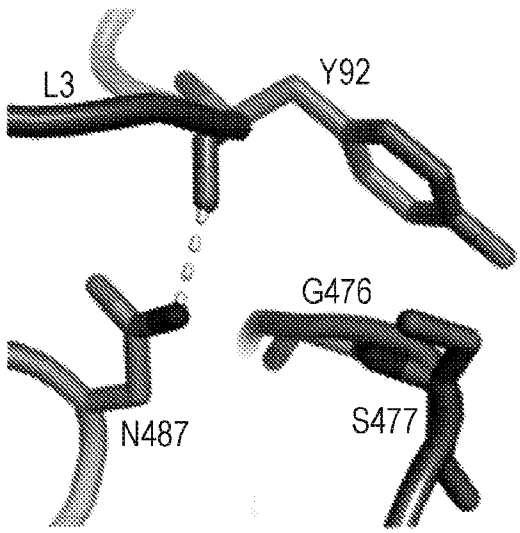


Fig. 3G



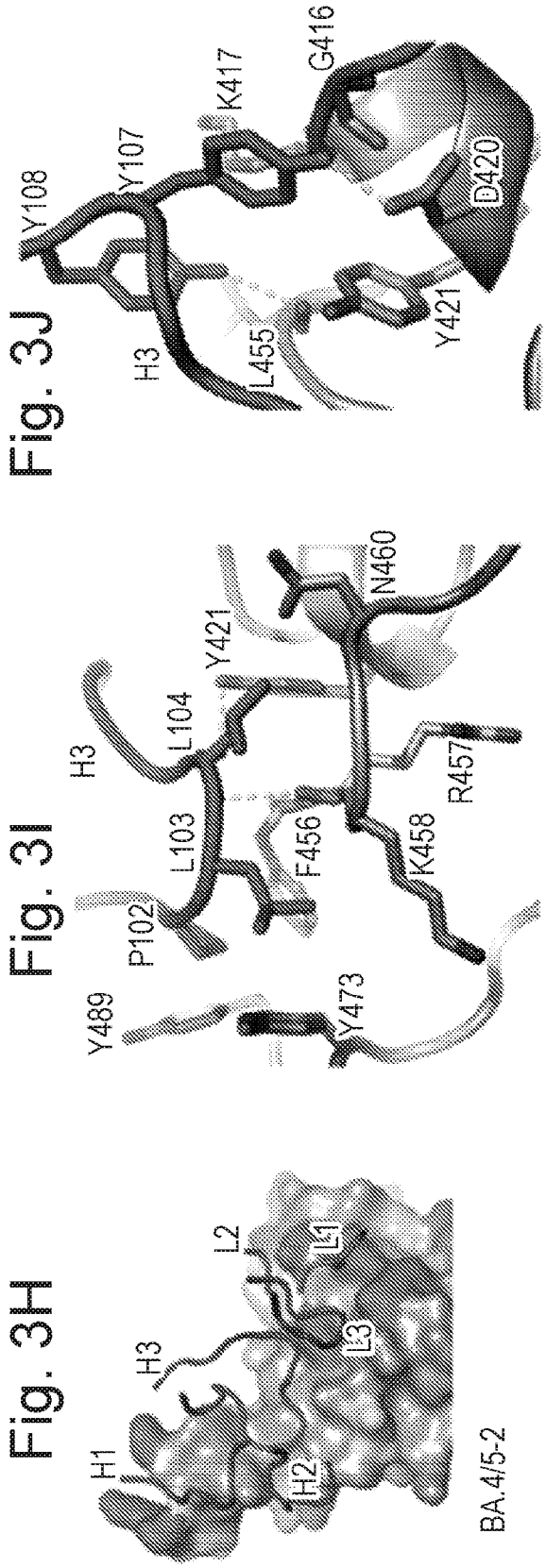


Fig. 3H
H1
H3
L2
L1
L3
H2
BA.4/5-2
Fig. 3I
H3
L104
Y421
L103
P102
F456
N460
K458
R457
Y489
Y473
Fig. 3J
Y108
Y107
K417
G416
H3
D420
L455
Y421
Fig. 3K
H1
F32
S31
Y489
T28
F27
G26
N487
A475
Y473
G476
F486
Fig. 3L
L2
D50
S52
Y505
L1
Y32
S31
R403
D405
S28
Q409
R408

Fig. 4A

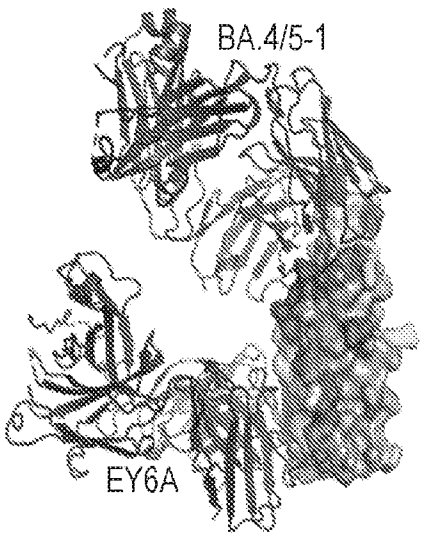


Fig. 4B

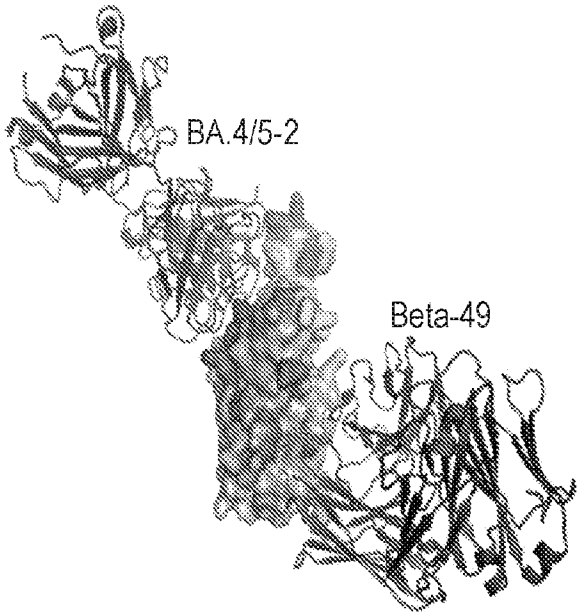


Fig. 4C

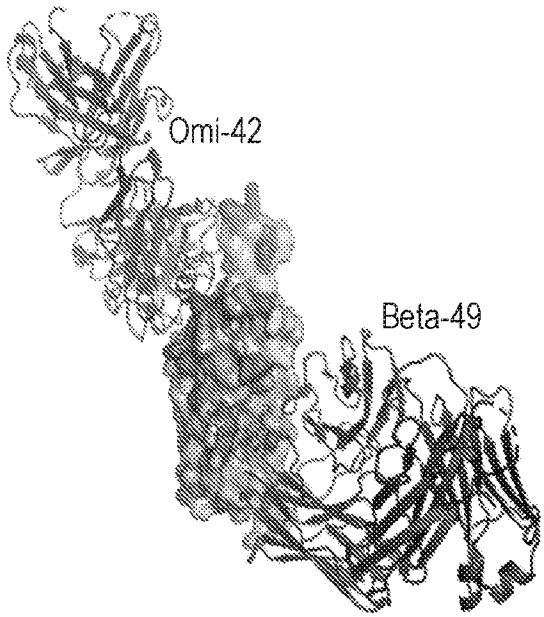


Fig. 4D

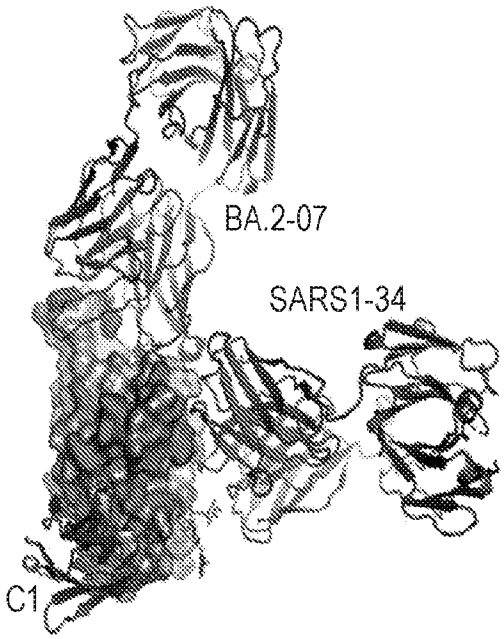


Fig. 4E

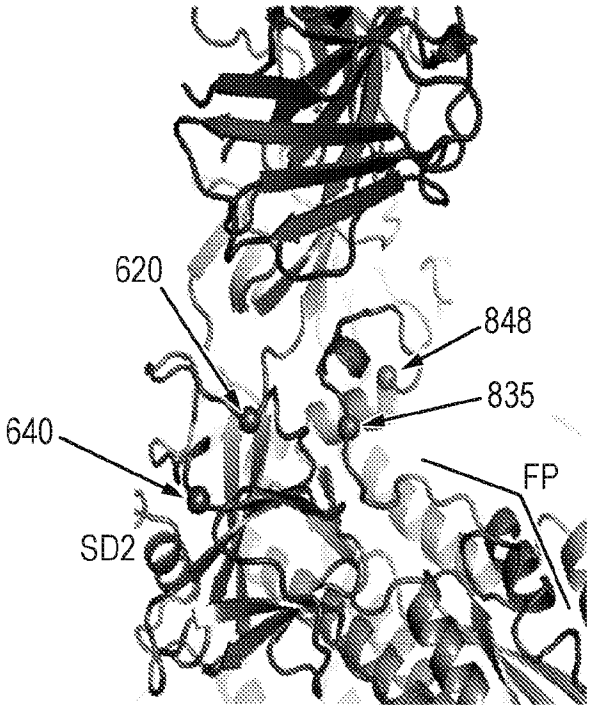


Fig. 4F

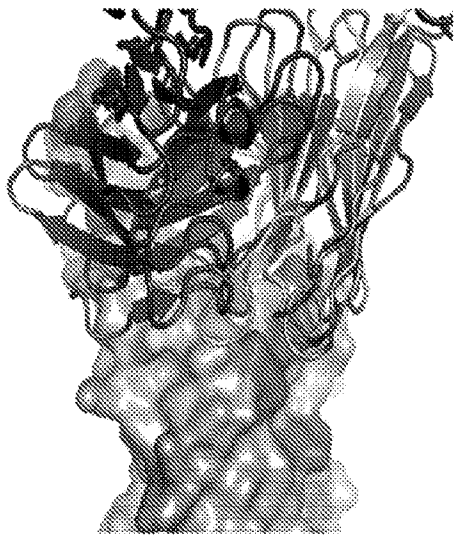


Fig. 4G

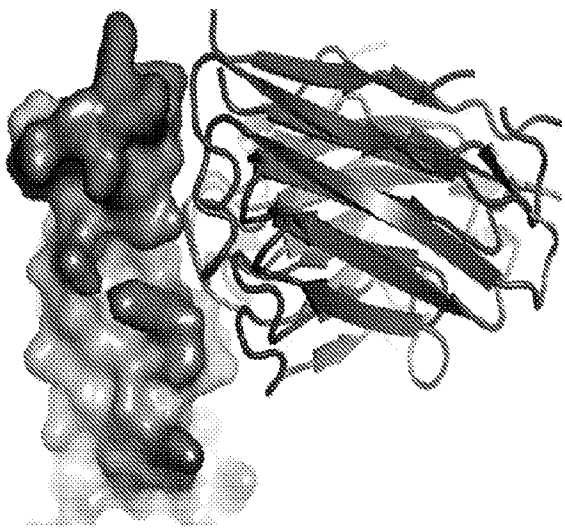


Fig. 4H

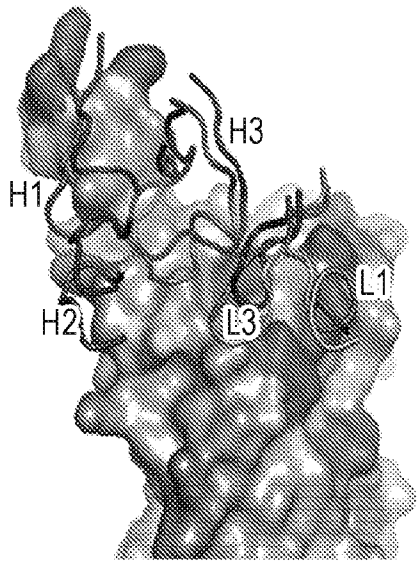


Fig. 5A

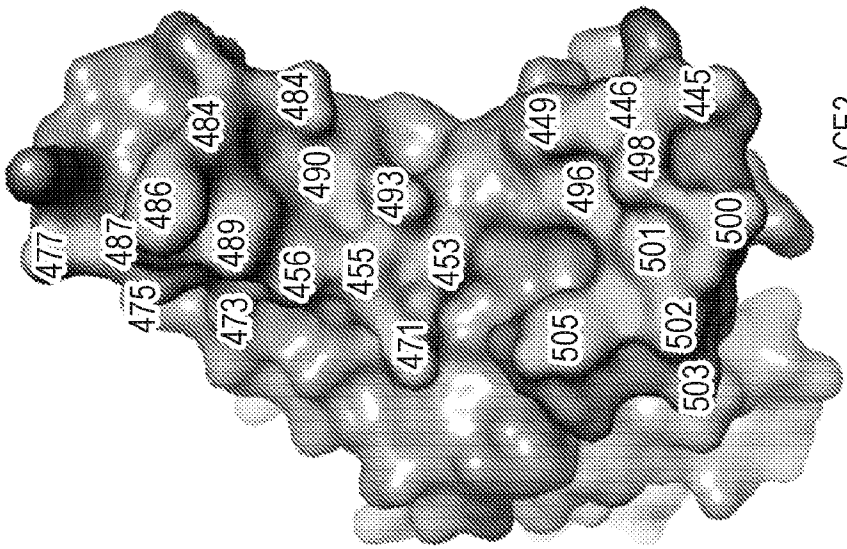


Fig. 5B

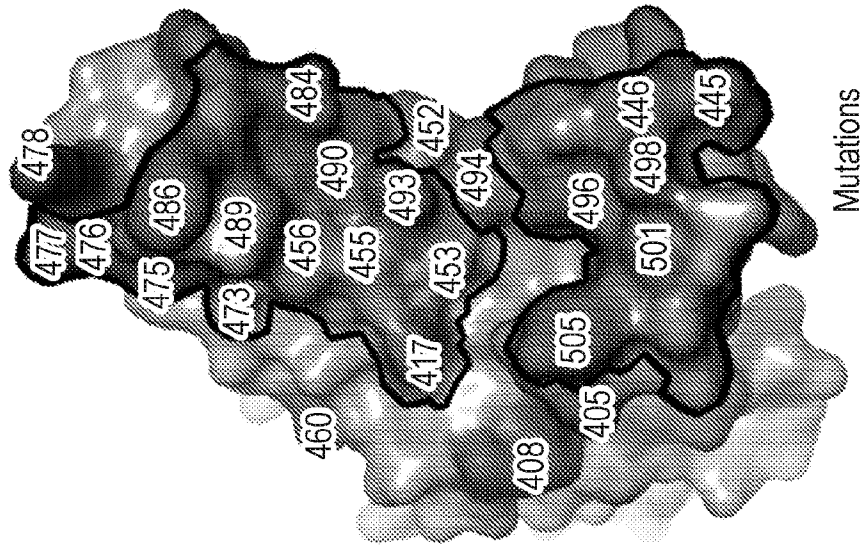


Fig. 5C

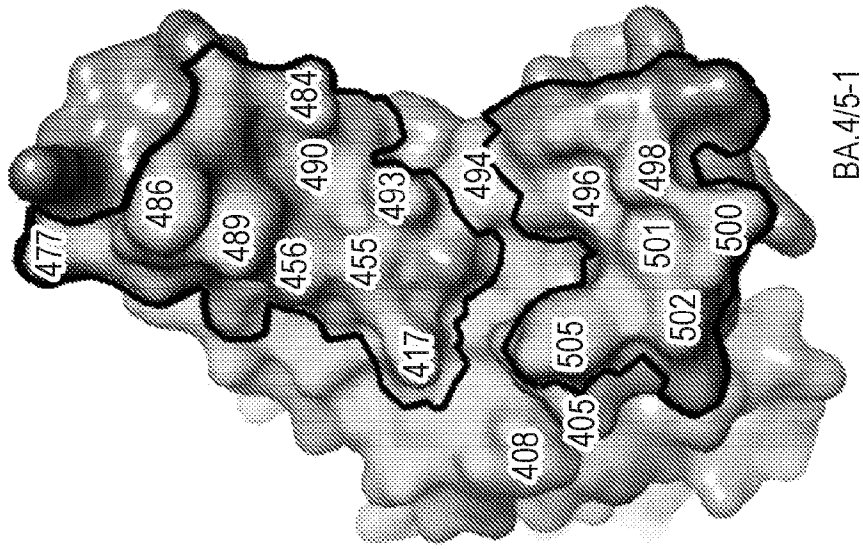
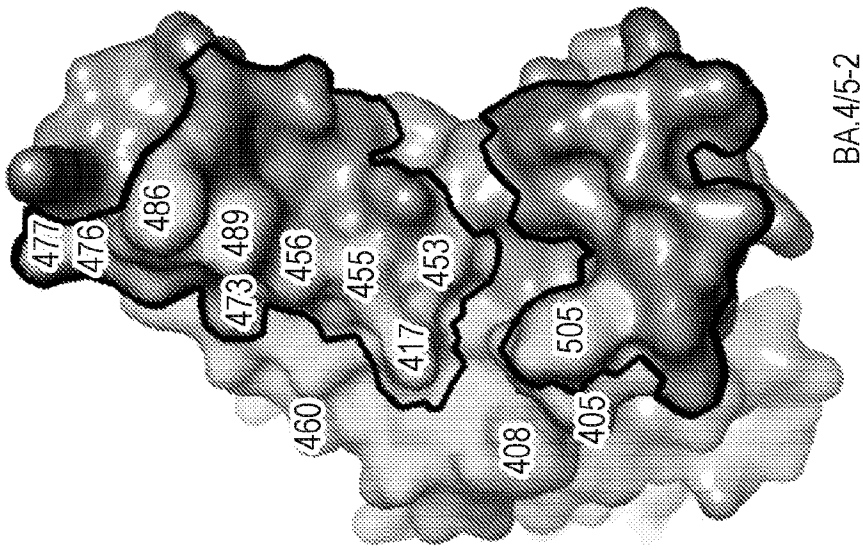
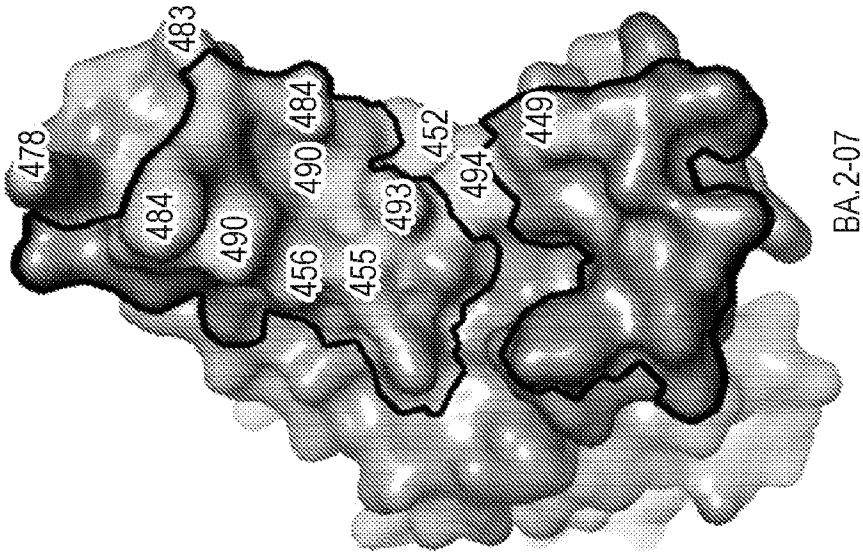


Fig. 5D



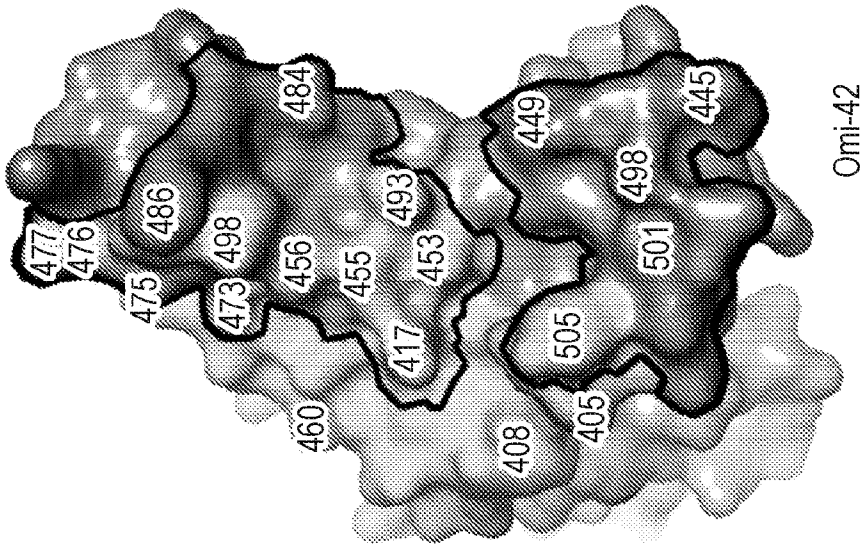
BA.4/5-2

Fig. 5E



BA.2-07

Fig. 5F



Omi-42

Fig. 6

Variant	Mutations in RBD area
BA.2 Victoria	G339D T376A D405N R408S E484A Q493R
BA.1	G339D G446S E484A Q493R G496S
BA.1.1	G339D R346K G446S E484A Q493R G496S
BA.2.12.1	G339D T376A D405N R408S L452Q E484A Q493R
BA.4/5	G339D T376A D405N R408S L452R E484A F486V R493Q
BA.4.6	G339D R346T T376A D405N R408S L452R E484A F486V R493Q
BA.5.9	G339D R346I T376A D405N R408S L452R E484A F486V R493Q
BA.2.75	G339H T376A D405N R408S G446S N460K E484A R493Q
BA.2.10.4	G339D T376A D405N R408S G446S E484A F486P R493Q S494P
BJ.1	G339H R346T L368I T376A D405N R408S V445P G446S V483A E484A F490V R493Q
BA.2.75.2	G339H R346T T376A D405N R408S G446S N460K E484A F486S R493Q
BF.7	G339D R346T T376A D405N R408S L452R E484A F486V R493Q
BS.1	G339D R346T T376A D405N R408S L452R N460K G476S E484A Q493R
BA.2.3.20	G339D T376A D405N R408S K444R N450D L452M N460K E484R R493Q
BN.1	G339H R346T K356T T376A D405N R408S G446S N460K E484A F490S R493Q
BQ.1	G339D T376A D405N R408S K444T L452R N460K E484A F486V R493Q
BQ.1.1 +A475V	G339D R346T T376A D405N R408S K444T L452R N460K A475V E484A F486V R493Q
BQ.1.1	G339D R346T T376A D405N R408S K444T L452R N460K E484A F486V R493Q
XBB	G339H R346T L368I T376A D405N R408S V445P G446S N460K E484A F486S F490S R493Q
CA.3.1	G339H R346T T376A D405N R408S K444M G446S L452R N460K E484A F486S R493Q
XBB.1	G339H R346T L368I T376A D405N R408S V445P G446S N460K E484A F486S F490S R493Q
CH.1.1	G339H R346T T376A D405N R408S K444T G446S L452R N460K E484A F486S R493Q
XBF	G339H R346T T376A D405N R408S G446S N460K E484A F486P F490S R493Q
XBB.1.5	G339H R346T L368I T376A D405N R408S V445P G446S N460K E484A F486P F490S R493Q
DS.1	G339H R346T K356T R403K T376A D405N R408S G446S N460K E484A F486S F490S R493Q

Fig. 7

Method	X-ray Crystallography					Cryo-EM		
Structure	Delta-RBD/BA.4/5-1/EY6A	Delta-RBD/BA.4/5-2/Beta-49	Delta-RBD/BA.4/5-35	Delta-RBD/Omi-42/Beta-49		BA.4-spike/BA.4/5-5	BA.2.12.1-Spike/BA.2-07	Delta-RBD/BA.2-07/SARS1-34/C1
PDB/EMBD ID	8CBD	8CBE	8CMA	8CBF		8CIN	8CIM	8CII
Data collection								
Space group	C2	$P2_12_12$	C2	$P2_12_12$	Voltage (kV)	300	300	300
Cell dimensions					Frames (EER fractions)	50	50	50
a, b, c (Å)	242.0, 139.4, 168.5	179.9, 147.0, 52.2	195.8, 85.1, 57.0	177.0, 144.3, 49.7	Dose rate (e^-/Å^2/s)	11.7	9.1	9.3
a, b, g (°)	90, 115.6, 90	90, 90, 90	90, 102.0, 90	90, 90, 90	Total dose (e^-/Å^2)	50	50	50
Resolution (Å)	75–3.52 (3.58–3.52)[a]	60–3.16 (3.21–3.16)	48–3.29 (3.35–3.29)	75–2.33 (2.37–2.33)	Calibrated pixel size (Å^2)	0.7303	0.7303	0.7303
R_{merge}	0.325 (---)	0.345 (---)	0.298 (---)	0.300 (---)	Defocus (μm)	0. 8-2.6	0.8-2.6	0.8-2.6
R_{pim}	0.133 (1.192)	0.098 (0.994)	0.121 (1.270)	0.086 (1.760)	Movies	10,383	10,619	13,121
I/s(I)	4.9 (0.4)	6.1 (0.5)	5.6 (0.5)	7.1 (0.4)	Particles (final)	108,365	61,491	1,207,910
$CC_{1/2}$	0.984 (0.351)	0.991 (0.322)	0.982 (0.340)	0.998 (0.332)	Symmetry	C3	C3	C1
Completeness (%)	99.7 (98.4)	100 (99.2)	98.9 (94.6)	99.8 (93.3)	Map resolution (Å)	2.7	3.0	2.7
Redundancy	7.1 (6.7)	13.3 (13.2)	7.0 (6.8)	13.0 (8.7)	Sharpening B-factor (Å^2)	70.2	65.6	129.8

Fig. 7 (Cont.)

Refinement								
Resolution (Å)	75–3.52	57–3.16	48–3.29	72–2.33	Resolution (Å)	2.7	2.9	2.7
No. reflections	59185/3023	23351/1206	13161/681	51927/2733	No. protein atoms	35187	29925	9023
R_{work}/R_{free}	0.219/0.267	0.227/0.268	0.231/0.268	0.215/0.255	B factors (Å^2)	132	72	149
No. atoms					r.m.s. deviations			
Protein	24090	8087	4718	8033	Bond lengths (Å)	0.006	0.004	0.004
Ligand/ion/water	14	49	14	342	Bond angles (°)	0.6	0.5	0.5
B factors (Å^2)					Clash score	5.2	4.5	4.3
Protein	169	108	125	62	Ramachandran outlier (%)	0	0	0
Ligand/ion/water	207	123	192	64	Rotamer outlier (%)	1.45	0.8	0.4
r.m.s. deviations					d FSC model (0.5)	3.0	3.2	2.9
Bond lengths (Å)	0.003	0.002	0.002	0.004	CC (mask)	0.87	0.81	0.87
Bond angles (°)	0.5	0.5	0.4	0.6				

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2024/050859

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

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

B. FIELDS SEARCHED

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

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2022/167816 A2 (UNIV OXFORD INNOVATION LTD [GB]) 11 August 2022 (2022-08-11) the whole document see in particular: Abstract; Examples 1-5, 11-16; Tables 1, 2, 13, 15; Figures 1-3, 5, 7, 12, 22 ----- -/--	3,8-20

[x] Further documents are listed in the continuation of Box C.

[x] See patent family annex.

* Special categories of cited documents :

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

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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

"Y" document of particular relevance;; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 June 2024	20/08/2024

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

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2024/050859

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	TUEKPRAKHON AEKKACHAI ET AL: "Antibody escape of SARS-CoV-2 Omicron BA.4 and BA.5 from vaccine and BA.1 serum", CELL, ELSEVIER, AMSTERDAM NL, vol. 185, no. 14, 9 June 2022 (2022-06-09) , page 2422, XP087112659, ISSN: 0092-8674, DOI: 10.1016/J.CELL.2022.06.005 [retrieved on 2022-06-09] cited in the application the whole document includes suppl. data; see in particular: summary; discussion; par. bridg. pages 2424/25; p. 2425- fig. 2-6, S2-S5 -----	3,8-20
X	CHANGROB SIRIRUK ET AL: "Site of vulnerability on SARS-CoV-2 spike induces broadly protective antibody against antigenically distinct Omicron subvariants", THE JOURNAL OF CLINICAL INVESTIGATION, vol. 133, no. 8, 2 March 2023 (2023-03-02) , XP093173807, US ISSN: 1558-8238, DOI: 10.1172/JCI166844 *Version history regarding publication date from the publisher's site: Version 1 (March 2, 2023): In-Press Preview Version 2 (April 17, 2023): Electronic publication see in particular abstract; introduction; discussion; fig. 1-5 -& CHANGROB SIRIRUK ET AL: "Suppl. Material: Site of vulnerability on SARS-CoV-2 spike induces broadly protective antibody to antigenically distinct omicron SARS-CoV-2 subvariants: Site of vulnerability on SARS-CoV-2 spike induces broadly protective antibody to antigenically distinct omicron SARS-CoV-2 subvariants", BIORXIV, 1 November 2022 (2022-11-01), XP093173816, DOI: 10.1101/2022.10.31.514592 the whole document see in particular: Fig. S1-S5; Table S3 ----- -/--	3,8-20

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2024/050859

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	LUO MENGXIAO ET AL: "EPUB VERSION: Structural insights into broadly neutralizing antibodies elicited by hybrid immunity against SARS-CoV-2", EMERGING MICROBES & INFECTIONS, vol. 12, no. 1, 3 January 2023 (2023-01-03), XP093174409, ISSN: 2222-1751, DOI: 10.1080/22221751.2022.2146538 the whole document see in particular: abstract; page 2, right-hand col. par. 1; page 4, right-hand col. 1st full par.; discussion; fig. 1-5; Fig. S1, S3, S5-S8, S11, tables S1-S2, S6 -& Mengxiao Luo ET AL: "Suppl. Data: Structural insights into broadly neutralizing antibodies elicited by hybrid immunity against SARS-CoV-2", , 3 January 2023 (2023-01-03), XP093173367, Retrieved from the Internet: URL:https://www.tandfonline.com/action/downloadSupplement?doi=10.1080%2F22221751.2022.2146538&file=temi_a_2146538_sm6437.pdf -----	3,8-20
X,P	WO 2023/156636 A1 (RQ BIOTECHNOLOGY LTD [GB]) 24 August 2023 (2023-08-24) the whole document see in particular: par. [0031], [0032]; [0048]; table 3; Examples 1-6, Fig. 1-8, 10-15, 19, 22, 23, 27, 28 -----	3,8-20
T	CUI LINGYAN ET AL: "Comprehensive Overview of Broadly Neutralizing Antibodies against SARS-CoV-2 Variants", VIRUSES, vol. 16, no. 6, 1 June 2024 (2024-06-01), page 900, XP093173370, CH ISSN: 1999-4915, DOI: 10.3390/v16060900 the whole document -----	

INTERNATIONAL SEARCH REPORT

International application No.

PCT/GB2024/050859

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

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

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

   b. [X] furnished subsequent to the international filing date for the purposes of international search (Rule 13*ter*.1(a)).

      [X] accompanied by a statement to the effect that the sequence listing does not go beyond the disclosure in the international application as filed.

2. [ ] With regard to any nucleotide and/or amino acid sequence disclosed in the international application, this report has been established to the extent that a meaningful search could be carried out without a WIPO Standard ST.26 compliant sequence listing.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB2024/050859

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1, 2, 4-7(completely); 8-20(partially)
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims;; it is covered by claims Nos.:
3, 8-20(all partially)

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 3, 8-20(all partially)

An antibody capable of binding to the spike protein of coronavirus SARS-CoV-2, wherein (i) the antibody comprises a CDRH1, CDRH2, CDRH3, CDRL1, CDRL2 and CDRL3 having the amino acid sequences specified in SEQ ID NOs: 15, 16, 17, 21, 22 and 23, respectively, optionally wherein the antibody comprises a heavy chain variable domain and a light chain variable domain having at least 80% identity to the amino acid sequences specified in SEQ ID NOs: 14 and 20, respectively.

2-8. claims: 3, 8-20(all partially)

An antibody capable of binding to the spike protein of coronavirus SARS-CoV-2, wherein the antibody is selected from one of the antibodies specified in claim 3 under items (ii) to (viii)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.2

Claims Nos.: 1, 2, 4-7(completely); 8-20(partially)

The subject matter of present claims 1, 2, 4 to 7 (completely) and 8 to 20 (partially) is unclear, not supported by the description and insufficiently disclosed according to Art. 6 and 5 PCT, respectively, to such an extend, that it is impossible to carry out a meaningful search regarding the state of the art on the basis of all or some of the subject-matter claimed and to form a meaningful opinion on the novelty, inventive step (non-obviousness), or industrial applicability, of said subject-matter claimed (Art. 17(2) and 34(4) PCT).

Foremost, "except where absolutely necessary, claims shall not rely on references to the description or drawings in specifying the technical features of the invention" (Rule 6.2(a) PCT). Hence, references to tables, such as any of tables 1 and 3 to 9, in the claims, e.g. claims 1, 4 and 7, introduce unclarity in the sense of Article 6 PCT. Similarly the reference to the claimed antibodies by internal arbitrary designations introduces further lack of clarity.

Moreover, by virtue of extension of the claimed subject-matter to any set of light chain CDRs 1-3 and set of heavy chain CDRs 1-3 combinations derived from two different antibodies of table 1, independent claim 4 relates to to extremely large number of possible antibodies.

It should be noted that support and disclosure within the meaning of Articles 6 and 5 PCT would only be found in the case of specific antibodies comprising the sets of 6 CDRs as listed in table 1 and specific "mixed-chain antibodies" of tables 3 to 9 which are further claimed in claim 7, provided that they were properly claimed by true structural features (e.g. sequences). Furthermore, it is noted that the references to CDRs of table 7 to 9 are only optional (see wording used "optionally").

The remaining "mixed-chain antibodies" covered by claims 1, 2, 4 to 6 are based on a plethora of light chain and heavy chain CDR combinations which cannot be searched without undue burden. Furthermore it is apparent that such a search would not be useful, since only an antibody defined by its exact 6 CDR sequences has any defined technical properties.

Moreover, this excessive number of light chain and heavy chain CDR combinations covered by claims 1, 2, 4 to 6 (completely) and 7 to 20 (partially), amounts to an equally unquantifiable and thus unreasonable amount of experimentation, imposing a severe and undue burden on all those wishing to ascertain the scope of the claim, which is not in compliance with the clarity requirement of Article 6 PCT.

The claims 1, 2 and 4-7 thus lack clarity and support

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

to this extent that a full meaningful search does not appear possible.

Consequently, the extent of the search and of the corresponding opinion has been limited to the subject-matter of claim 3 and the one of claims 8-20 as far as dependent on claim 3.

It should also be borne in mind that in the event of the finding as to lack of unity of invention, only the first invention mentioned in the claims will be searched and an invitation to pay additional fees will be issued.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guidelines C-IV, 7.3), should the problems which led to the Article 17(2) PCT declaration be overcome.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/GB2024/050859

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2022167816 A2	11-08-2022	EP 4288152 A2	13-12-2023
		EP 4288153 A1	13-12-2023
		JP 2024509054 A	29-02-2024
		JP 2024509055 A	29-02-2024
		US 2024036054 A1	01-02-2024
		US 2024043507 A1	08-02-2024
		WO 2022167815 A1	11-08-2022
		WO 2022167816 A2	11-08-2022
WO 2023156636 A1	24-08-2023	AR 128564 A1	22-05-2024
		EP 4230650 A1	23-08-2023
		TW 202342510 A	01-11-2023
		US 2023265170 A1	24-08-2023
		WO 2023156636 A1	24-08-2023