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(54) Title: ANTIBODY COCKTAIL AGAINST SARS-COV-2 SPIKE PROTEIN

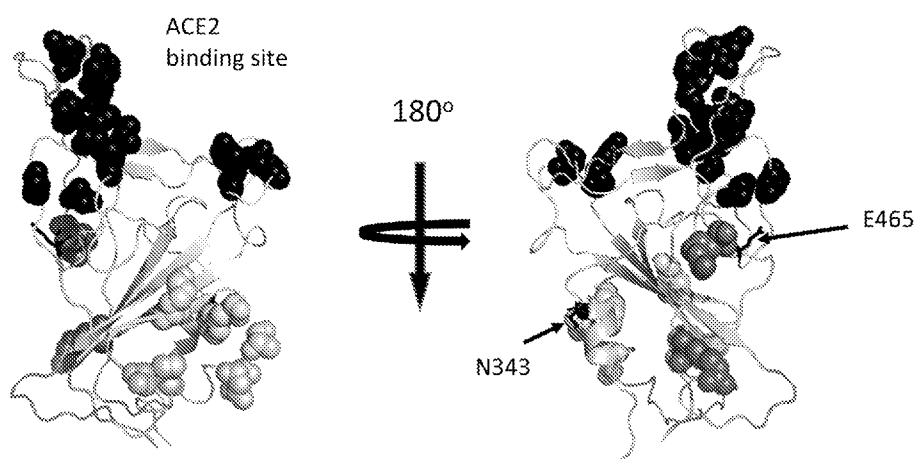


Fig 2.

(57) Abstract: Provided herein are antibodies that are useful for treating SARS-CoV-2 infections in a subject. Also provided herein are compositions comprising one or more antibodies, methods of treatment comprising administering one or more antibodies, and kits comprising one or more antibodies.



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Antibody Cocktail Against SARs-CoV-2 Spike Protein

Cross-reference to related applications

[0001] This application claims the priority benefit of U.S. Provisional Application No. 63/134,159 filed January 5, 2021, U.S. Provisional Application No. 63/150,070 filed February 16, 2021, U.S. Provisional Application No. 63/178,848 filed April 23, 2021, U.S. Provisional Application No. 63/220,881 filed July 12, 2021, U.S. Provisional Application No. 63/236,479 filed August 24, 2021, U.S. Provisional Application No. 63/270,665 filed October 22, 2021, and U.S. Provisional Application No. 63/284,963 filed December 1, 2021, the disclosure of each of which is incorporated herein by reference in its entirety.

Sequence listing

[0002] The content of the following submission on ASCII text file is incorporated herein by reference in its entirety: a computer readable form (CRF) of the Sequence Listing (file name: 224192000140SEQLIST.TXT, date recorded: December 30, 2021, size: 98,788 bytes).

Field of the Invention

[0003] The present invention relates to antibodies used for treatment of SARS-CoV-2 infections.

Background

[0004] Since its emergence in Wuhan, China in late 2019 [Zhou et al. 2020], the prolonged spread of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus has resulted in one of the most devastating global health challenges of the last century [Nature Editorial 2020, Morens & Fauci 2020, Chakraborty & Maity 2020]. With greater than 289 million confirmed cases and over 5.43 million deaths world-wide, the virus continues to pose an extraordinary challenge to the scientific community, consequently becoming an unprecedented socio-economic disaster and burdening healthcare systems around the world. Infection with SARS-CoV-2 results in a myriad of pathologies [Berlin et al. 2020] collectively referred to as COVID-19 [3]. While a majority of individuals who become infected with the virus are capable of generating a productive anti-viral response, for many their anti-viral humoral response will not be sufficient to shield them from a potentially deadly infection. Therefore, as the global community braces for the next Spike in infection and mortality rates, the urgency to develop effective therapeutics recapitulating the productive anti-viral response to combat the swelling health crisis has never been greater.

[0005] By the end of October 2020, a mere 11 months after the virus was first identified, the Clinicaltrials.gov database listed more than 3500 distinct clinical trial activities directed at patients infected with SARS-CoV-2. There is significant diversity among these efforts, from the assessment of existing drugs to the use of convalescent plasma from recovered patients, to the use of specific vaccines and antibodies directed at the viral S protein. It is not yet apparent that there will be a single approach that will prove to be uniformly effective at preventing viral infections or accelerating viral clearance in all groups of COVID-19 patients.

[0006] SARS-CoV-2 genomic RNA contains a large viral replicase gene, genes encoding non-structural proteins at its 5' end, and a region encoding four major structural and multiple accessory proteins at the 3' end. Structural proteins include Spike or Surface glycoprotein (S), Membrane protein (M), Envelope protein (E) and Nucleocapsid protein (N) [Fehr & Perlman 2015]. The membrane surface glycoprotein S consists of two subunits, S1 and S2, that mediate viral binding to the host receptor ACE2 and fusion with the host cell membrane, respectively. The S1 subunit contains the receptor binding domain (RBD) that directly interacts with ACE2 and is a target of multiple neutralizing antibodies currently in clinical trials [Lan et al. 2020, Robbiani et al. 2020]. The vast majority of the ongoing efforts are all targeting the S protein. Both passive (therapeutic antibodies) and active (vaccine) approaches directed at S protein are expected to promote virus neutralization, that is, inhibition of viral entry into healthy cells. Unfortunately, mutations in S protein have arisen, including ones the Center for Disease Control (CDC) has identified in a series of viral variants for which there is evidence of an increase in transmissibility, increased levels of hospitalization and/or deaths, significant reduction in neutralization by antibodies generated during previous infections or vaccinations, reduced effectiveness of treatments or vaccines, or diagnostic detection failures. These virus variants are considered Variants of Concern include Alpha (U.K./B.1.1.7) variant of SARS-CoV-2, the Beta (South African/B.1.351) variant of SARS-CoV-2, the Gamma (Brazilian/P.1) variant of SARS-CoV-2, the Delta (India/B.1.617.2), B.1.617 (L452R/E484Q)), the Epsilon (California/B.1.429/427, New York/B.1.526/526.1) variant of SARS-CoV-2, the UK/Nigeria (B.1.525) variant of SARS-CoV-2, the Brazilian (P.2) variant of SARS-CoV-2, the lambda (C.37) variant of SARS-CoV-2, or the Omicron (B.1.1.529) variant of SARS-CoV-2. Additionally, the CDC has identified Variants of Interests, which are defined as having specific genetic markers that are predicted to affect transmission, diagnostics, therapeutics, or immune escape. Data also demonstrates these variants of interest were the cause of an increased proportion of cases or outbreak, but they are of limited prevalence in

the US or other countries (<https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/variant-surveillance/variant-info.html#Concern>).

[0007] Studies are described herein that elucidate the memory B cell antibody response in convalescent patients, using an approach that enables the generation of large, stable hybridoma libraries from primary human B cells. This approach was previously used to identify a panel of monoclonal antibodies from convalescent patients infected with natural polio virus (PV), oral PV-vaccinated and inactivated PV-boosted healthy subjects [Puligedda et al. 2014, Puligedda et al. 2017, Puligedda et al. 2020], and, most recently, an anti-amyloid antibody with the anti-biofilm activity [Tursi et al. 2020] from a hybridoma library generated with memory B cells from an Alzheimer's Disease patient [Levites et al. 2015].

[0008] Hybridoma libraries were generated from the memory B cells of convalescent COVID-19 blood donors who were eligible to donate convalescent plasma based upon their high titer of IgG antibodies against the SARS-CoV-2 virus. Monoclonal antibodies derived from those libraries were selected on the basis of their selective binding to one of multiple SARS-CoV-2 proteins used as targets in both cell-based and soluble protein-based screens. Characterization of these antibodies revealed broad responses to diverse viral antigens. Fewer than half of the antibodies were directed at S protein, while the remainder were directed at other viral proteins including N and ORF-encoded proteins. Even though the antibodies were directed at highly diverse SARS-CoV-2 antigens, they were generally characterized as having variable levels of somatic hypermutation (SHM) and a diversity of VH and VL gene usage. Functional properties of anti-Spike antibodies were successfully confirmed against reference strains (e.g., USA/WA_CDC-WA1/2020), as well as multiple variants including the CDC variants of concern, in series of tests ranging from *in vitro* neutralization of both pseudovirus and live virus isolates to *in vivo* neutralization activity in a hamster model of COVID-19. Three anti-Spike antibodies were identified that when mixed together in a cocktail exhibited combinatorial effects against those variants. These studies indicate that an unbiased interrogation of COVID-19 patient B cell repertoires is an effective approach to identifying specific antiviral antibodies and antibody mixtures with the desired binding and functional properties. Antibodies identified and characterized in this manner could be recombinantly produced to yield therapeutic or prophylactic products to address the COVID-19 pandemic. The rapidity with which antibodies from convalescent patients can be identified and characterized suggests that this platform could be a useful component of a rapid response to future pandemics.

Summary of the Invention

[0009] Provided herein is composition comprising at least first and second recombinant antibodies that specifically bind to distinct epitopes of a Spike protein of SARS-CoV-2, wherein the first antibody binds to an epitope in an ACE2 receptor binding site of the Spike protein and the second antibody binds to an epitope outside of the ACE2 receptor binding site of the Spike protein.

[0010] Also provided herein composition comprising at least first and second antibodies that specifically bind to distinct epitopes of a Spike protein of SARS-CoV-2, wherein the first antibody neutralizes SARS-CoV-2 via an ACE2 independent mechanism and the second antibody neutralizes SARS-CoV-2 via an ACE2 dependent mechanism, wherein the first and second antibodies are recombinant antibodies.

[0011] In some embodiments, the composition further comprises a third antibody that specifically binds to the Spike protein of SARS-CoV-2 at an epitope distinct from the first and second antibodies. In some embodiment,s the third antibody binds to an epitope outside of the ACE2 receptor binding site of the Spike protein. In some embodiments, the third recombinant antibody neutralizes SARS-CoV-2 via an ACE2 dependent mechanism.

[0012] Also provided herein is an antibody or antigen-binding fragment thereof that binds a SARS-CoV-2 Spike protein comprising

[0013] a HCDR1, HCDR2, and HCDR3 of a heavy chain variable region (HCVR) comprising the amino acid sequence set forth in SEQ ID NO: 1, and a LCDR1, LCDR2, and LCDR3 of a light chain variable region (LCVR) comprising the amino acid sequence is set forth in SEQ ID NO: 2;

[0014] a HCDR1, HCDR2, and HCDR3 of a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 3, and a LCDR1, LCDR2, and LCDR3 of a LCVR comprising the amino acid sequence is set forth in SEQ ID NO: 4;

[0015] a HCDR1, HCDR2, and HCDR3 of a HCVR comprising the amino acid sequence set forth in SEQ ID NO: 5, and a LCDR1, LCDR2, and LCDR3 of a LCVR comprising the amino acid sequence is set forth in SEQ ID NO: 6;

[0016] a HCDR1, HCDR2, and HCDR3 of a HCVR comprising the amino acid sequence set forth in SEQ ID NO: 7, and a LCDR1, LCDR2, and LCDR3 of a LCVR comprising the amino acid sequence is set forth in SEQ ID NO: 8;

[0017] a HCDR1, HCDR2, and HCDR3 of a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 9, and a LCDR1, LCDR2, and LCDR3 of a

light chain variable region (LCVR) comprising the amino acid sequence is set forth in SEQ ID NO: 10;

[0018] a HCDR1, HCDR2, and HCDR3 of a HCVR comprising the amino acid sequence set forth in SEQ ID NO: 11, and a LCDR1, LCDR2, and LCDR3 of a LCVR comprising the amino acid sequence is set forth in SEQ ID NO: 12;

[0019] a HCDR1, HCDR2, and HCDR3 of a HCVR comprising the amino acid sequence set forth in SEQ ID NO: 13, a LCDR1, LCDR2, and LCDR3 of a LCVR comprising the amino acid sequence is set forth in SEQ ID NO: 14;

[0020] a HCDR1, HCDR2, and HCDR3 of a HCVR comprising the amino acid sequence set forth in SEQ ID NO: 15, and a LCDR1, LCDR2, and LCDR3 of a LCVR comprising the amino acid sequence is set forth in SEQ ID NO: 16

[0021] a HCDR1, HCDR2, and HCDR3 of a HCVR comprising the amino acid sequence set forth in SEQ ID NO: 17, and a LCDR1, LCDR2, and LCDR3 of a LCVR comprising the amino acid sequence is set forth in SEQ ID NO: 18

[0022] a HCDR1, HCDR2, and HCDR3 of a HCVR comprising the amino acid sequence set forth in SEQ ID NO: 19, and a LCDR1, LCDR2, and LCDR3 of a LCVR comprising the amino acid sequence is set forth in SEQ ID NO: 20;

[0023] a HCDR1, HCDR2, and HCDR3 of a HCVR comprising the amino acid sequence set forth in SEQ ID NO: 21, and a LCDR1, LCDR2, and LCDR3 of a LCVR comprising the amino acid sequence is set forth in SEQ ID NO: 22;

[0024] a HCDR1, HCDR2, and HCDR3 of a HCVR comprising the amino acid sequence set forth in SEQ ID NO: 23, and a LCDR1, LCDR2, and LCDR3 of a LCVR comprising the amino acid sequence is set forth in SEQ ID NO: 24; or

[0025] a HCDR1, HCDR2, and HCDR3 of a HCVR comprising the amino acid sequence set forth in SEQ ID NO: 25 and a LCDR1, LCDR2, and LCDR3 of a LCVR comprising the amino acid sequence is set forth in SEQ ID NO: 26.

[0026] In some embodiments, the antibody comprises

[0027] a HCVR comprising the amino acid sequence set forth in SEQ ID NO: 1, and a LCVR comprising the amino acid sequence is set forth in SEQ ID NO: 2;

[0028] a HCVR comprising the amino acid sequence set forth in SEQ ID NO: 3, and a LCVR comprising the amino acid sequence is set forth in SEQ ID NO: 4;

[0029] a HCVR comprising the amino acid sequence set forth in SEQ ID NO: 5, and a LCVR comprising the amino acid sequence is set forth in SEQ ID NO: 6;

- [0030] a HCVR comprising the amino acid sequence set forth in SEQ ID NO: 7, and a LCVR comprising the amino acid sequence is set forth in SEQ ID NO: 8;
- [0031] a HCVR comprising the amino acid sequence set forth in SEQ ID NO: 9, and a LCVR comprising the amino acid sequence is set forth in SEQ ID NO: 10;
- [0032] a HCVR comprising the amino acid sequence set forth in SEQ ID NO: 11, and a LCVR comprising the amino acid sequence is set forth in SEQ ID NO: 12;
- [0033] a HCVR comprising the amino acid sequence set forth in SEQ ID NO: 13, a LCVR comprising the amino acid sequence is set forth in SEQ ID NO: 14;
- [0034] a HCVR comprising the amino acid sequence set forth in SEQ ID NO: 15, and a LCVR comprising the amino acid sequence is set forth in SEQ ID NO: 16;
- [0035] a HCVR comprising the amino acid sequence set forth in SEQ ID NO: SEQ ID NO: 17, and a LCVR comprising the amino acid sequence is set forth in SEQ ID NO: 18;
- [0036] a HCVR comprising the amino acid sequence set forth in SEQ ID NO: 19, and a LCVR comprising the amino acid sequence is set forth in SEQ ID NO: 20;
- [0037] a HCVR comprising the amino acid sequence set forth in SEQ ID NO: 21, and a LCVR comprising the amino acid sequence is set forth in SEQ ID NO: 22;
- [0038] a HCVR comprising the amino acid sequence set forth in SEQ ID NO: 23, and a LCVR comprising the amino acid sequence is set forth in SEQ ID NO: 24; or
- [0039] a HCVR comprising the amino acid sequence set forth in SEQ ID NO: 25 and a LCVR comprising the amino acid sequence is set forth in SEQ ID NO: 26.
- [0040] In some embodiments, provided herein is an antibody or antigen-binding fragment thereof that binds a SARS-CoV-2 Spike protein comprising
- [0041] a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:55, a HCDR2 comprising the amino acid sequence of SEQ ID NO:56, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:57; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:58, a LCDR2 comprising the amino acid sequence of SEQ ID NO:59, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:60;
- [0042] a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:61, a HCDR2 comprising the amino acid sequence of SEQ ID NO:62, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:63; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:64 a LCDR2 comprising the amino acid sequence of SEQ ID NO:65, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:66;
- [0043] a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:67, a HCDR2 comprising the amino acid sequence of SEQ ID NO:68, and a HCDR3 comprising

the amino acid sequence of SEQ ID NO:69; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:70, a LCDR2 comprising the amino acid sequence of SEQ ID NO:71, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:72; or [0044] a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:109, a HCDR2 comprising the amino acid sequence of SEQ ID NO:110, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:111; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:112, a LCDR2 comprising the amino acid sequence of SEQ ID NO:113, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:114.

[0045] In some embodiments, the antibody is an an Fc IgG1, IgG2, IgG3, IgG4, IgM, IgD, IgA1, IgA2 or IgE isotype. The antibody or antigen-binding fragment thereof of claim 9, wherein the antibody is an IgG1. In some embodiments, the IgG1 is a G1m1 or nG1m1 allotype. In some embodiments, The antibody comprises an immunoglobulin Fc region or fragment thereof of a human IgM. In some embodiments, the antibody is a fully human antibody. In some embodiments, the antibody is a full length antibody.

[0046] In some embodiments, the antibody or antigen-binding fragment thereof: inhibits binding of a SARS-CoV-2 virus to a host ACE2 receptor; fixes complement to a SARS-CoV-2 virus; induces phagocytosis of a SARS-CoV-2 virus; or any combination thereof.

[0047] In some embodiment,s the binding of the antibody or antigen-binding fragment thereof neutralizes a SARS-CoV-2 virus by blocking binding of the receptor binding domain (RBD) of the virus with an ACE2 receptor. In some embodiments, the antibody is isolated.

[0048] Also provided herein is a composition comprising an antibody provided here. In some embodiments, the composition comprises two, three, or four of the antibodies provided herein.

[0049] In some embodiments, the composition comprises

[0050] a) a first antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:55, a HCDR2 comprising the amino acid sequence of SEQ ID NO:56, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:57; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:58, a LCDR2 comprising the amino acid sequence of SEQ ID NO:59, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:60, and

[0051] a second antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:61, a HCDR2 comprising the amino acid sequence

of SEQ ID NO:62, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:63; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:64 a LCDR2 comprising the amino acid sequence of SEQ ID NO:65, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:66;

[0052]

[0053] b) a first antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:55, a HCDR2 comprising the amino acid sequence of SEQ ID NO:56, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:57; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:58, a LCDR2 comprising the amino acid sequence of SEQ ID NO:59, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:60, and

[0054] a second antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:67, a HCDR2 comprising the amino acid sequence of SEQ ID NO:68, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:69; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:70, a LCDR2 comprising the amino acid sequence of SEQ ID NO:71, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:72;

[0055] c) a first antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:55, a HCDR2 comprising the amino acid sequence of SEQ ID NO:56, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:57; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:58, a LCDR2 comprising the amino acid sequence of SEQ ID NO:59, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:60, and

[0056] a second antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:109, a HCDR2 comprising the amino acid sequence of SEQ ID NO:110, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:111; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:112, a LCDR2 comprising the amino acid sequence of SEQ ID NO:113, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:114;

[0057] d) a first antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:61, a HCDR2 comprising the amino acid sequence of SEQ ID NO:62, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:63; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:64 a LCDR2

comprising the amino acid sequence of SEQ ID NO:65, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:66, and

[0058] a second antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:67, a HCDR2 comprising the amino acid sequence of SEQ ID NO:68, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:69; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:70, a LCDR2 comprising the amino acid sequence of SEQ ID NO:71, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:72;

[0059]

[0060] e) a first antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:61, a HCDR2 comprising the amino acid sequence of SEQ ID NO:62, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:63; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:64 a LCDR2 comprising the amino acid sequence of SEQ ID NO:65, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:66, and

[0061] a second antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:109, a HCDR2 comprising the amino acid sequence of SEQ ID NO:110, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:111; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:112, a LCDR2 comprising the amino acid sequence of SEQ ID NO:113, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:114; or

[0062] f) a first antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:67, a HCDR2 comprising the amino acid sequence of SEQ ID NO:68, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:69; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:70, a LCDR2 comprising the amino acid sequence of SEQ ID NO:71, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:72, and

[0063] a second antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:109, a HCDR2 comprising the amino acid sequence of SEQ ID NO:110, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:111; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:112, a LCDR2 comprising the amino acid sequence of SEQ ID NO:113, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:114.

[0064] In some embodiments, provided herein is a composition comprising

[0065] a) a first antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:55, a HCDR2 comprising the amino acid sequence of SEQ ID NO:56, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:57; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:58, a LCDR2 comprising the amino acid sequence of SEQ ID NO:59, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:60,

[0066] a second antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:61, a HCDR2 comprising the amino acid sequence of SEQ ID NO:62, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:63; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:64 a LCDR2 comprising the amino acid sequence of SEQ ID NO:65, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:66, and

[0067] a third antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:67, a HCDR2 comprising the amino acid sequence of SEQ ID NO:68, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:69; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:70, a LCDR2 comprising the amino acid sequence of SEQ ID NO:71, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:72;

[0068] b) a first antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:55, a HCDR2 comprising the amino acid sequence of SEQ ID NO:56, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:57; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:58, a LCDR2 comprising the amino acid sequence of SEQ ID NO:59, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:60,

[0069] a second antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:61, a HCDR2 comprising the amino acid sequence of SEQ ID NO:62, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:63; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:64 a LCDR2 comprising the amino acid sequence of SEQ ID NO:65, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:66, and

[0070] a third antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:109, a HCDR2 comprising the amino acid sequence of SEQ ID NO:110, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:111; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:112, a

LCDR2 comprising the amino acid sequence of SEQ ID NO:113, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:114; or

[0071] c) a first antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:61, a HCDR2 comprising the amino acid sequence of SEQ ID NO:62, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:63; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:64 a LCDR2 comprising the amino acid sequence of SEQ ID NO:65, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:66, and

[0072] a second antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:67, a HCDR2 comprising the amino acid sequence of SEQ ID NO:68, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:69; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:70, a LCDR2 comprising the amino acid sequence of SEQ ID NO:71, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:72, and

[0073] a third antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:109, a HCDR2 comprising the amino acid sequence of SEQ ID NO:110, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:111; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:112, a LCDR2 comprising the amino acid sequence of SEQ ID NO:113, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:114.

[0074] In some embodiments, provided herein is a composition comprising

[0075] a first antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:55, a HCDR2 comprising the amino acid sequence of SEQ ID NO:56, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:57; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:58, a LCDR2 comprising the amino acid sequence of SEQ ID NO:59, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:60,

[0076] a second antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:61, a HCDR2 comprising the amino acid sequence of SEQ ID NO:62, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:63; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:64 a LCDR2 comprising the amino acid sequence of SEQ ID NO:65, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:66,

[0077] a third antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:67, a HCDR2 comprising the amino acid sequence of SEQ ID NO:68, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:69; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:70, a LCDR2 comprising the amino acid sequence of SEQ ID NO:71, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:72, and

[0078] a fourth antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:109, a HCDR2 comprising the amino acid sequence of SEQ ID NO:110, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:111; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:112, a LCDR2 comprising the amino acid sequence of SEQ ID NO:113, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:114.

[0079] In some embodiments, the ratio between the first and the second recombinant antibodies is about 1 : 1. In some embodiments, the ratios between the first, second, and third antibodies are about 1 : 1 : 1. In some embodiments, the ratio between the first, second, third, and fourth antibodies is about 1 : 1 : 1 : 1. In some embodiments, the composition neutralizes at least 50% of one or more of the following variants of SARS-CoV-2: U.K. B.1.1.7; South African B.1.351; Brazil P.1; Omicron B.1.1.529 variant; and California B.1.429/427 relative to the neutralization of the USA/WA_CDC-WA1/2020 SARS-CoV-2 by the composition. In some embodiments, the composition neutralizes about 100% of one or more of the following variants of SARS-CoV-2: U.K. B.1.1.7; South African B.1.351; Brazil P.1; Omicron B.1.1.529 variant; and California B.1.429/427 relative to the neutralization of the USA/WA_CDC-WA1/2020 SARS-CoV-2 by the composition.

[0080] In some embodiments, the composition further comprises a pharmaceutically acceptable carrier or diluent.

[0081] Also provided herein is method of treating or preventing a SARS-CoV-2 infection in a subject, comprising administering a first antibody that neutralizes SARS-CoV-2 via an ACE2 independent mechanism and a second antibody that neutralizes SARS-CoV-2 via an ACE2 dependent mechanism. In some embodiments, the method comprises administering a composition or antibody provided herein to the subject. In some embodiments, the method comprises administering two, three, or four of the antibodies.

[0082] In some embodiments, provided herein is a method of treating or preventing a SARS-CoV-2 infection in a subject, comprising administering

[0083] a) a first antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:55, a HCDR2 comprising the amino acid sequence of SEQ ID NO:56, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:57; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:58, a LCDR2 comprising the amino acid sequence of SEQ ID NO:59, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:60, and

[0084] a second antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:61, a HCDR2 comprising the amino acid sequence of SEQ ID NO:62, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:63; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:64 a LCDR2 comprising the amino acid sequence of SEQ ID NO:65, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:66;

[0085] b) a first antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:55, a HCDR2 comprising the amino acid sequence of SEQ ID NO:56, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:57; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:58, a LCDR2 comprising the amino acid sequence of SEQ ID NO:59, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:60, and

[0086] a second antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:67, a HCDR2 comprising the amino acid sequence of SEQ ID NO:68, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:69; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:70, a LCDR2 comprising the amino acid sequence of SEQ ID NO:71, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:72;

[0087] c) a first antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:55, a HCDR2 comprising the amino acid sequence of SEQ ID NO:56, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:57; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:58, a LCDR2 comprising the amino acid sequence of SEQ ID NO:59, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:60, and

[0088] a second antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:109, a HCDR2 comprising the amino acid sequence of SEQ ID NO:110, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:111; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:112, a

LCDR2 comprising the amino acid sequence of SEQ ID NO:113, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:114;

[0089] d) a first antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:61, a HCDR2 comprising the amino acid sequence of SEQ ID NO:62, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:63; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:64 a LCDR2 comprising the amino acid sequence of SEQ ID NO:65, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:66, and

[0090] a second antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:67, a HCDR2 comprising the amino acid sequence of SEQ ID NO:68, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:69; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:70, a LCDR2 comprising the amino acid sequence of SEQ ID NO:71, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:72;

[0091] e) a first antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:61, a HCDR2 comprising the amino acid sequence of SEQ ID NO:62, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:63; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:64 a LCDR2 comprising the amino acid sequence of SEQ ID NO:65, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:66, and

[0092] a second antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:109, a HCDR2 comprising the amino acid sequence of SEQ ID NO:110, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:111; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:112, a LCDR2 comprising the amino acid sequence of SEQ ID NO:113, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:114; or

[0093] f) a first antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:67, a HCDR2 comprising the amino acid sequence of SEQ ID NO:68, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:69; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:70, a LCDR2 comprising the amino acid sequence of SEQ ID NO:71, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:72, and

[0094] a second antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:109, a HCDR2 comprising the amino acid sequence

of SEQ ID NO:110, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:111; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:112, a LCDR2 comprising the amino acid sequence of SEQ ID NO:113, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:114.

[0095] Also provided herein is a method of treating or preventing a SARS-CoV-2 infection in a subject, comprising administering

[0096] a) a first antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:55, a HCDR2 comprising the amino acid sequence of SEQ ID NO:56, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:57; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:58, a LCDR2 comprising the amino acid sequence of SEQ ID NO:59, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:60,

[0097] a second antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:61, a HCDR2 comprising the amino acid sequence of SEQ ID NO:62, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:63; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:64 a LCDR2 comprising the amino acid sequence of SEQ ID NO:65, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:66, and

[0098] a third antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:67, a HCDR2 comprising the amino acid sequence of SEQ ID NO:68, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:69; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:70, a LCDR2 comprising the amino acid sequence of SEQ ID NO:71, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:72;

[0099] b) a first antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:55, a HCDR2 comprising the amino acid sequence of SEQ ID NO:56, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:57; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:58, a LCDR2 comprising the amino acid sequence of SEQ ID NO:59, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:60,

[0100] a second antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:61, a HCDR2 comprising the amino acid sequence of SEQ ID NO:62, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:63; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:64 a LCDR2

comprising the amino acid sequence of SEQ ID NO:65, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:66, and

[0101] a third antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:109, a HCDR2 comprising the amino acid sequence of SEQ ID NO:110, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:111; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:112, a LCDR2 comprising the amino acid sequence of SEQ ID NO:113, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:114; or

[0102] c) a first antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:61, a HCDR2 comprising the amino acid sequence of SEQ ID NO:62, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:63; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:64 a LCDR2 comprising the amino acid sequence of SEQ ID NO:65, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:66, and

[0103] a second antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:67, a HCDR2 comprising the amino acid sequence of SEQ ID NO:68, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:69; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:70, a LCDR2 comprising the amino acid sequence of SEQ ID NO:71, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:72, and

[0104] a third antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:109, a HCDR2 comprising the amino acid sequence of SEQ ID NO:110, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:111; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:112, a LCDR2 comprising the amino acid sequence of SEQ ID NO:113, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:114.

[0105] In some embodiments, provided herein is a method of treating or preventing a SARS-CoV-2 infection in a subject, comprising administering a first antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:55, a HCDR2 comprising the amino acid sequence of SEQ ID NO:56, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:57; and a VL comprising a LCDR1 comprising the amino acid

sequence of SEQ ID NO:58, a LCDR2 comprising the amino acid sequence of SEQ ID NO:59, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:60,

[0106] a second antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:61, a HCDR2 comprising the amino acid sequence of SEQ ID NO:62, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:63; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:64 a LCDR2 comprising the amino acid sequence of SEQ ID NO:65, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:66,

[0107] a third antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:67, a HCDR2 comprising the amino acid sequence of SEQ ID NO:68, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:69; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:70, a LCDR2 comprising the amino acid sequence of SEQ ID NO:71, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:72, and

[0108] a fourth antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:109, a HCDR2 comprising the amino acid sequence of SEQ ID NO:110, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:111; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:112, a LCDR2 comprising the amino acid sequence of SEQ ID NO:113, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:114.

[0109] In some embodiments, the administering of the antibody or composition to the subject in need thereof comprises administering the composition into the body of the subject subcutaneously, intravenously, intranasally or intramuscularly.

[0110] In some embodiments, the method is for treating a SARS-CoV-2 infection.

[0111] Also provided herein are kits for treating or preventing a SARS-CoV-2 infection in a subject comprising a first antibody that specifically binds to a Spike protein of SARS-CoV-2 and neutralizes SARS-CoV-2 via an ACE2 independent mechanism and a second antibody that specifically binds to a Spike protein of SARS-CoV-2 and neutralizes SARS-CoV-2 via an ACE2 dependent mechanism.

[0112] In some embodiments, the kit comprises two, three, or four of the antibodies provided herein.

[0113] In some embodiments provided herein is a kit for treating or preventing a SARS-CoV-2 infection in a subject comprising

[0114] a) a first antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:55, a HCDR2 comprising the amino acid sequence of SEQ ID NO:56, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:57; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:58, a LCDR2 comprising the amino acid sequence of SEQ ID NO:59, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:60, and

[0115] a second antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:61, a HCDR2 comprising the amino acid sequence of SEQ ID NO:62, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:63; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:64 a LCDR2 comprising the amino acid sequence of SEQ ID NO:65, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:66;

[0116] b) a first antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:55, a HCDR2 comprising the amino acid sequence of SEQ ID NO:56, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:57; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:58, a LCDR2 comprising the amino acid sequence of SEQ ID NO:59, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:60, and

[0117] a second antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:67, a HCDR2 comprising the amino acid sequence of SEQ ID NO:68, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:69; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:70, a LCDR2 comprising the amino acid sequence of SEQ ID NO:71, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:72;

[0118] c) a first antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:55, a HCDR2 comprising the amino acid sequence

of SEQ ID NO:56, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:57; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:58, a LCDR2 comprising the amino acid sequence of SEQ ID NO:59, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:60, and

[0119] a second antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:109, a HCDR2 comprising the amino acid sequence of SEQ ID NO:110, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:111; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:112, a LCDR2 comprising the amino acid sequence of SEQ ID NO:113, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:114;

[0120] d) a first antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:61, a HCDR2 comprising the amino acid sequence of SEQ ID NO:62, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:63; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:64 a LCDR2 comprising the amino acid sequence of SEQ ID NO:65, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:66, and

[0121] a second antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:67, a HCDR2 comprising the amino acid sequence of SEQ ID NO:68, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:69; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:70, a LCDR2 comprising the amino acid sequence of SEQ ID NO:71, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:72;

[0122] e) a first antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:61, a HCDR2 comprising the amino acid sequence of SEQ ID NO:62, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:63; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:64 a LCDR2 comprising the amino acid sequence of SEQ ID NO:65, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:66, and

[0123] a second antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:109, a HCDR2 comprising the amino acid sequence of SEQ ID NO:110, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:111; and

a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:112, a LCDR2 comprising the amino acid sequence of SEQ ID NO:113, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:114; or

[0124] f) a first antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:67, a HCDR2 comprising the amino acid sequence of SEQ ID NO:68, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:69; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:70, a LCDR2 comprising the amino acid sequence of SEQ ID NO:71, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:72, and

[0125] a second antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:109, a HCDR2 comprising the amino acid sequence of SEQ ID NO:110, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:111; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:112, a LCDR2 comprising the amino acid sequence of SEQ ID NO:113, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:114.

[0126] In some embodiments, provided herein is a kit treating or preventing a SARS-CoV-2 infection in a subject comprising

[0127] a) a first antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:55, a HCDR2 comprising the amino acid sequence of SEQ ID NO:56, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:57; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:58, a LCDR2 comprising the amino acid sequence of SEQ ID NO:59, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:60,

[0128] a second antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:61, a HCDR2 comprising the amino acid sequence of SEQ ID NO:62, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:63; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:64 a LCDR2 comprising the amino acid sequence of SEQ ID NO:65, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:66, and

[0129] a third antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:67, a HCDR2 comprising the amino acid sequence of SEQ ID NO:68, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:69; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:70, a LCDR2 comprising the amino acid sequence of SEQ ID NO:71, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:72;

[0130] b) a first antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:55, a HCDR2 comprising the amino acid sequence of SEQ ID NO:56, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:57; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:58, a LCDR2 comprising the amino acid sequence of SEQ ID NO:59, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:60,

[0131] a second antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:61, a HCDR2 comprising the amino acid sequence of SEQ ID NO:62, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:63; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:64 a LCDR2 comprising the amino acid sequence of SEQ ID NO:65, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:66, and

[0132] a third antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:109, a HCDR2 comprising the amino acid sequence of SEQ ID NO:110, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:111; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:112, a LCDR2 comprising the amino acid sequence of SEQ ID NO:113, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:114; or

[0133] c) a first antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:61, a HCDR2 comprising the amino acid sequence of SEQ ID NO:62, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:63; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:64 a LCDR2 comprising the amino acid sequence of SEQ ID NO:65, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:66, and

[0134] a second antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:67, a HCDR2 comprising the amino acid sequence of SEQ ID NO:68, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:69; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:70, a LCDR2 comprising the amino acid sequence of SEQ ID NO:71, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:72, and

[0135] a third antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:109, a HCDR2 comprising the amino acid sequence of SEQ ID NO:110, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:111; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:112, a LCDR2 comprising the amino acid sequence of SEQ ID NO:113, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:114.

[0136] Also provided herein is a kit for treating or preventing a SARS-CoV-2 infection in a subject comprising

[0137] a first antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:55, a HCDR2 comprising the amino acid sequence of SEQ ID NO:56, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:57; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:58, a LCDR2 comprising the amino acid sequence of SEQ ID NO:59, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:60,

[0138] a second antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:61, a HCDR2 comprising the amino acid sequence of SEQ ID NO:62, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:63; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:64 a LCDR2 comprising the amino acid sequence of SEQ ID NO:65, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:66,

[0139] a third antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:67, a HCDR2 comprising the amino acid sequence of SEQ ID NO:68, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:69; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:70, a LCDR2

comprising the amino acid sequence of SEQ ID NO:71, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:72, and

[0140] a fourth antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:109, a HCDR2 comprising the amino acid sequence of SEQ ID NO:110, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:111; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:112, a LCDR2 comprising the amino acid sequence of SEQ ID NO:113, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:114.

[0141] In some embodiments the kit comprises instructions for use according to the methods provided herein.

[0142] In some embodiments, the SARS-CoV-2 virus is a SARS-CoV-2 variant.

[0143] In some embodiments, the antibody or composition treats or prevents SARS-CoV-2 variant and nonvariant infections with about equivalent efficacies.

In some embodiments, the SARS-CoV-2 variant is the U.K. (B.1.1.7) variant of SARS-CoV-2, the South African (B.1.351) variant of SARS-CoV-2, the California (B.1.429) variant of SARS-CoV-2, the California (B.1.427) variant of SARS-CoV-2, the Brazilian (P.1) variant of SARS-CoV-2, the New York (B.1.526) variant of SARS-CoV-2, the New York (B.1.526.1) variant of SARS-CoV-2, the UK/Nigeria (B.1.525) variant of SARS-CoV-2, the Brazilian (P.2) variant of SARS-CoV-2 or the Omicron (B.1.1.529) variant.

[0144] In some embodiments, the inventions described here include antibody compositions with at least first and second recombinant anti-SARS-CoV-2 antibodies that bind distinct epitopes of SARS-CoV-2, wherein at least one of the antibodies is selected from the group consisting of:

- (a) an anti-Spike antibody comprising a heavy chain variable region (HCVR) as set forth in the amino acid sequence set forth in SEQ ID NO: 5 or fragment thereof, and a light chain variable region (LCVR) as set forth in the amino acid sequence set forth in SEQ ID NO: 6 or fragment thereof;
- (b) an anti-Spike antibody comprising a HCVR as set forth in the amino acid sequence set forth in SEQ ID NO: 3 or fragment thereof, and a LCVR as set forth in the amino acid sequence set forth in SEQ ID NO: 4 or fragment thereof;

- (c) an anti-Spike antibody comprising a HCVR as set forth in the amino acid sequence set forth in SEQ ID NO: 1 or fragment thereof, and a LCVR as set forth in the amino acid sequence set forth in SEQ ID NO: 2 or fragment thereof;
- (d) an anti-Spike antibody comprising a HCVR as set forth in the amino acid sequence set forth in SEQ ID NO: 7 or fragment thereof, and a LCVR as set forth in the amino acid sequence set forth in SEQ ID NO: 8 or fragment thereof;
- (e) an anti-Spike antibody comprising a HCVR as set forth in the amino acid sequence set forth in SEQ ID NO: 9 or fragment thereof, and a LCVR as set forth in the amino acid sequence set forth in SEQ ID NO: 10 or fragment thereof;
- (f) an anti-Spike antibody comprising a HCVR as set forth in the amino acid sequence set forth in SEQ ID NO: 11 or fragment thereof, and a LCVR as set forth in the amino acid sequence set forth in SEQ ID NO: 12 or fragment thereof;
- (g) an anti-Spike antibody comprising a HCVR as set forth in the amino acid sequence set forth in SEQ ID NO: 13 or fragment thereof, and a LCVR as set forth in the amino acid sequence set forth in SEQ ID NO: 14 or fragment thereof;
- (h) an anti-Spike antibody comprising a HCVR as set forth in the amino acid sequence set forth in SEQ ID NO: 15 or fragment thereof, and a LCVR as set forth in the amino acid sequence set forth in SEQ ID NO: 16 or fragment thereof;
- (i) an anti-Spike antibody comprising a HCVR as set forth in the amino acid sequence set forth in SEQ ID NO: 17 or fragment thereof, and a LCVR as set forth in the amino acid sequence set forth in SEQ ID NO: 18 or fragment thereof;
- (j) an anti-Spike antibody comprising a HCVR as set forth in the amino acid sequence set forth in SEQ ID NO: 19 or fragment thereof, and a LCVR as set forth in the amino acid sequence set forth in SEQ ID NO: 20 or fragment thereof;
- (k) an anti-Spike antibody comprising a HCVR as set forth in the amino acid sequence set forth in SEQ ID NO: 21 or fragment thereof, and a LCVR as set forth in the amino acid sequence set forth in SEQ ID NO: 22 or fragment thereof;
- (l) an anti-Spike antibody comprising a HCVR as set forth in the amino acid sequence set forth in SEQ ID NO: 23 or fragment thereof, and a LCVR as set forth in the amino acid sequence set forth in SEQ ID NO: 24 or fragment thereof;
- (m) an anti-Spike antibody comprising a HCVR as set forth in the amino acid sequence set forth in SEQ ID NO: 25 or fragment thereof, and a LCVR as set forth in the amino acid sequence set forth in SEQ ID NO: 26 or fragment thereof;

- (n) an anti-ORF3a antibody comprising a HCVR as set forth in the amino acid sequence set forth in SEQ ID NO: 27 or fragment thereof, and a LCVR as set forth in the amino acid sequence set forth in SEQ ID NO: 28 or fragment thereof;
- (o) an anti-Membrane antibody comprising a HCVR as set forth in the amino acid sequence set forth in SEQ ID NO: 29 or fragment thereof, and a LCVR as set forth in the amino acid sequence set forth in SEQ ID NO: 30 or fragment thereof;
- (p) an anti-Nucleocapsid antibody comprising a HCVR as set forth in the amino acid sequence set forth in SEQ ID NO: 31 or fragment thereof, and a LCVR as set forth in the amino acid sequence set forth in SEQ ID NO: 32 or fragment thereof;
- (q) an anti-Nucleocapsid antibody comprising a HCVR as set forth in the amino acid sequence set forth in SEQ ID NO: 33 or fragment thereof, and a LCVR as set forth in the amino acid sequence set forth in SEQ ID NO: 34 or fragment thereof;
- (r) an anti-Nucleocapsid antibody comprising a HCVR as set forth in the amino acid sequence set forth in SEQ ID NO: 35 or fragment thereof, and a LCVR as set forth in the amino acid sequence set forth in SEQ ID NO: 36 or fragment thereof;
- (s) an anti-ORF8 antibody comprising a HCVR as set forth in the amino acid sequence set forth in SEQ ID NO: 37 or fragment thereof, and a LCVR as set forth in the amino acid sequence set forth in SEQ ID NO: 38 or fragment thereof; and
- (t) an anti-ORF8 antibody comprising a HCVR as set forth in the amino acid sequence set forth in SEQ ID NO: 39 or fragment thereof, and a LCVR as set forth in the amino acid sequence set forth in SEQ ID NO: 40 or fragment thereof.

[0145] The molar or weight ratios between antibodies or antigen-binding fragments thereof in a composition of the invention that are specific for different epitopes, (i.e., a first, second, third, fourth, fifth, sixth, and so on), generally ranges from about (1 : 10) to (10 : 1), but is not limited by this disclosure. Accordingly, for example, the molar or weight ratio between first and second antibodies may be 1 : 1, or 1 : 1 : 1 between first, second, and third antibodies, or 1 : 1 : 1 : 1 between first, second, third, and fourth antibodies.

[0146] Antibody compositions of the invention may effectively neutralize non-variant and variant SARS-CoV-2. For example, a composition may neutralize at least 50%, 60%, 70%, 80%, 90%, or 100% of the viral load of one or more of the following variants of SARS-CoV-2: U.K. (alpha, B.1.1.7); South African (beta, B.1.351); Brazil (gamma, P.1); India (delta, B.1.617.2); and California (epsilon, B.1.429/427) relative to the neutralization of the USA/WA_CDC-WA1/2020 SARS-CoV-2 by the composition.

Brief Description of the Drawings

[0147] Fig. 1 depicts the breadth of antibodies isolated against a range of SARS-CoV-2 viral proteins.

[0148] Fig. 2 depicts the epitopes for IMM20190 (black sphere, left panel), IMM20184 (light gray, left panel), and IMM20253 (dark gray, right panel), as determined by alanine scanning. ACE2 binding site and two other residues [N343 represents a site of potential glycosylation and E465 (Greaney et al 2021)]

[0149] Fig. 3 depicts in vitro pseudovirus neutralization activity of PR193_0018 (IMM20184), PR194_0023 (IMM20190), PR200_00253 (IMM20253), and PR190_00255 (IMM20279) against pseudoviruses expressing four different variations of Spike.

[0150] Fig. 4 depicts in vitro neutralizing activity of the identified anti-Spike antibody PR194_00232 against (A) the live virus isolate SAR-CoV-2/human/USA/WA_CDC-WA1/2020, which contains a reference Spike protein. (B) depicts in vitro neutralizing activity of the identified anti-Spike antibody PR194_00232 against the live virus isolate SAR-CoV-2/human/Germany/BavPA1/2020, which contains a mutated Spike protein (D614G).

[0151] Fig. 5. depicts in vitro neutralization activity of identified anti-Spike antibodies, as noted, against pseudovirus expressing the Spike protein from either the U.K. (B.1.1.7) or South African (B.1.351) variant of SARS-CoV-2

[0152] Fig. 6 depicts the concentration-dependent ability of the triple antibody cocktail (IMM20184/IMM20190/IMM20253) and the two antibody cocktail (IMM20184/IMM20253) to neutralize pseudoviruses expressing the reference (WA1/2020), alpha/UK, beta/S. African, gamma/Brazilian, or Epsilon/Californian Spike proteins.

[0153] Fig. 7 depicts the combinatorial activity of the IMM20184 / IMM20190 / IMM20253 triple combination against A) pseudoviruses expressing the Spike protein from the reference strain (WA_CDC-WA1/2020), U.K. (B.1.1.7/alpha), South African (B.1.351/beta), Californian (B.1.429/epsilon), or Brazilian (P.1/P.2/gamma) variants of SARS-CoV-2 and B) the live virus BavPat1/2020 that contains the D614G mutation. Dark gray area represent regions of synergy. Bottom portion of the figure lists the overall and peak HSA scores against each strain.

[0154] Fig. 8 depicts the crystal structure of the SARS-CoV-2 RBD (RCSB PDB: 7A97) represented in cartoon with the epitopes of IMM20184, IMM20190, and IMM20253 depicted in black spheres. The locations of residues L452, T478, and E484, which are mutated in B.1.617.1/kappa (L452R E484Q) and B.1.617.2/delta (L452R T478K), are depicted in gray spheres. The residues mutated in the delta and kappa SARS-CoV-2 variants lie outside of the IMM-20184, IMM20190, and IMM20253 epitopes.

[0155] Fig. 9 depicts the in vitro neutralization activity of triple antibody cocktail (IMM20184 / IMM20190 / IMM20253) against pseudovirus expressing either the WA1/2020 (REF), B.1.617(L452R, E484Q), B.1.617.2 (delta), or lambda (C.37) Spike proteins.

[0156] Fig. 10 depicts in vitro neutralization activity triple antibody cocktail (IMM20184 / IMM20190 / IMM20253) against pseudovirus expressing the Spike protein from the reference strain (WA_CDC-WA1/2020), D614G, B.1.1.7 (alpha/U.K.), B.1.351 (beta/S. African), P.1/P.2 (gamma/Brazilian), B.1.429 (Epsilon/Californian), B.1.617.1 (L452/E484Q), B.1.617.2 (delta/India), B.1.617.2 Ay.2 (Delta Plus), or C.37 (lambda) variants of SARS-CoV-2.

[0157] Fig. 11 depicts in vitro neutralization activity of the triple (IMM20184 / IMM20190 / IMM20253) and double (IMM20184 / IMM20253) combinations of antibodies against three live virus strains as measured by plaque forming assays; the reference strain (WA_CDC-WA1/2020), U.K. (B.1.1.7/alpha), South African (B.1.351/beta).

[0158] Fig. 12 depicts lung titer per gram tissue, as measured by plaque forming units, as an assessment of in vivo activity of the identified anti-Spike antibody PR194_00232, alone and in combination with either PR193_00018 or PR200_00622, against the live virus isolate SAR-CoV-2/human/USA/WA_CDC-WA1/2020, when dosed in the prophylactic setting.

[0159] Fig. 13 depicts lung titer per gram tissue, as measured by plaque forming units, as an assessment of in vivo activity of various combinations of anti-Spike antibodies, dosed in a therapeutic setting, in the hamster model of COVID-19. Error bars represent the median +/- 95% CI.

[0160] Fig. 14 depicts lung titer per gram tissue, measured by TCID50 assays, as an assessment of in vivo activity of the triple combination of

IMM20184/IMM20190/IMM20253, at two different ratios, dosed in a therapeutic setting, in hamster model of COVID-19. Error bars represent the median +/- interquartile range.

[0161] Fig. 15 depicts correlation of viral lung titer per gram tissue, as measured by TCID₅₀ assays, plotted against serum concentration of triple antibody cocktail (IMM20184/190/253, 1:1:1 ratio) at day 4 post administration of antibodies in a therapeutic setting. Antibody cocktail was administered at three dose levels, 0.1 mg each, 0.2 mg each, 0.3 mg each.

[0162] Fig. 16 depicts lung titer per gram of tissue, as measured by plaque forming units. Hamsters infected with either the (A) WA1/2020 or (B) Beta isolate were treated in prophylactic setting with a dose response of triple antibody cocktail (IMM20184/IMM20190/IMM20253, 1:1:1)

[0163] Fig. 17 depicts anti-viral activity of a triple antibody cocktail (IMM20184/190/253, 1:1:1 ratio), dosed at 0.1mg each, into Syrian hamsters that were inoculated with either 3.3x10⁴ or 3.3x10⁵ virus. Viral titers in lungs were assessed four days post-inoculation via TCID₅₀ assays. Antibody was administered in a therapeutic setting.

[0164] Fig. 18 depicts the ability of IMM20184, IMM20190, and IMM20253 to bind to the isolated RBD and intact trimer of SARS-CoV-2 reference strain (WA1/2020) as measured by surface plasmon resonance.

[0165] Fig. 19 depicts the ability of IMM20184, IMM20190, and IMM20253 to block binding of ACE2 to isolated RBD corresponding to (A) WA1/2020, (B) Alpha, (C) Beta viral isolate

[0166] Fig. 20 depicts in vitro complement fixation activity of PR193_0018 (IMM20184), PR194_00190 (IMM20190), PR200_00253 (IMM20253), the two antibody cocktail of IMM20184/IMM20253, and the triple antibody cocktail (IMM20184/IMM20190/IMM20253) relative to control antibodies when assessed at defined (A & B) concentrations and in a concentration-dependent (C) manners.

[0167] Fig. 21 depicts in vitro phagocytosis activity of IMM20184, IMM20190, IMM20253, the IMM20184/IMM20253 two -antibody cocktail, and IMM-BCP-01 (three

antibody cocktail) relative to isotype control antibodies when assessed across a range of concentrations.

[0168] Fig. 22 depicts antibody-dependent cellular cytotoxicity activity of IMM20184, IMM20190, IMM20253, the two antibody cocktail of IMM20184/IMM20253, and the triple antibody cocktail (IMM20184/IMM20190/IMM20253; IMM-BCP-01) relative to isotype control antibodies when assessed in a concentration-dependent manner.

[0169] Fig. 23 depicts time-dependent conformational change in Spike protein, as measured by dynamic light scattering, upon binding of IMM20253 or IMM20190.

[0170] Fig. 24 depicts time-dependent protease digestion of Spike and Spike in complex with ACE2, IMM20253, or IMM20190.

[0171] Fig. 25 depicts the combinatorial neutralization activity of IMM20253 in combination with IMM20184, REGN987, or REGN933 against pseudoviruses expressing the Spike protein from the Delta Plus (B.1.617.2 ay1/2) variant. Dark grey area represent regions of synergy. Bottom portion of the figure lists the overall HSA scores for each combination.

[0172] Fig. 26 depicts the combinatorial neutralization activity of IMM20253 in combination with S309 against pseudoviruses expressing the Spike protein from the Delta Plus (B.1.617.2 ay1/2) variant. Grey areas represent areas of antagonism between the two antibodies. Bottom portion of the figure lists the overall HSA score for the combination.

[0173] Fig. 27A-D depicts the *in vitro* binding activity of individual antibodies (A) IMM20184, (B) IMM20190, (C) IMM20253, and (D) IMM20279 to the SARS-CoV-2 Spike-RBD Omicron variant relative to the reference strain.

[0174] Fig. 28 depicts the *in vitro* neutralization activity of the IMM20253 antibody against pseudovirus expressing the Spike protein from the reference strain (SARS-CoV-2/human/USA/WA CDC-WA1/2020), DG14G (SARS-CoV-2/human/Germany/BavPat 1/2020), B.1.351 (beta/S. African), B.1.617.2 Ay.2 (Delta Plus) and B.1.1.529 (Omicron) variants of SARS-CoV-2.

Detailed Description

[0175] Antibodies specific for the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus are described herein. These antibodies may be used to neutralize

SARS-CoV-2 by preventing the virus from infecting new host cells. Therefore, the inventions disclosed here also relate to pharmaceutical compositions that contain one or more antibodies of the invention, as well as relate to methods of preventing or treating a SARS-CoV-2 infection in a subject in need thereof. Accordingly, the inventions disclosed herein also relate to methods of administering antibody compositions of the invention to a subject in need thereof.

[0176] In some embodiments, the antibodies, compositions, and kits provided herein are especially effective for treating and/or preventing SARS-CoV-2 due to particular novel properties. In some embodiments, provided herein are antibodies that bind to the Spike protein at multiple different locations, for example at multiple non-overlapping epitopes. This is beneficial because SARS-CoV-2 variants may have one or more mutations in the Spike protein to evade the immune system. Thus providing multiple antibodies that bind to multiple different locations in the Spike protein allows binding and neutralization of such variants.

[0177] Moreover, some of the antibodies provided herein bind to an ACE2 binding site in the Spike protein, while others bind outside the ACE2 binding site. Without being bound by theory, providing multiple antibodies, some of which target the ACE2 binding site and some of which target regions outside of the ACE2 binding site may combine to provide more effective treatment for SARS-CoV-2.

[0178] Accordingly, in some embodiments, provided herein is a method of treating or preventing SARS-CoV-2 comprising administering multiple antibodies that bind to non-overlapping epitopes on the Spike protein. In some embodiments, the method comprises administering an antibody that binds to an ACE2 binding site of the Spike protein and an antibody that binds to an epitope outside of the ACE2 binding site of the Spike protein. In some embodiments, the method comprises administering an antibody that neutralizes SARS-CoV-2 through an ACE2-dependent mechanism and an antibody that neutralizes SARS-CoV-2 through an ACE2-independent mechanism.

[0179] In some embodiments, provided herein is a composition comprising administering antibodies that bind to non-overlapping epitopes on the Spike protein. In some embodiments, the composition comprises an antibody that binds to an ACE2 binding site of the Spike protein and an antibody that binds to an epitope outside of the ACE2 binding site of the Spike

protein. In some embodiments, the composition comprises an antibody that neutralizes SARS-CoV-2 through an ACE2-dependent mechanism and an antibody that neutralizes SARS-CoV-2 through an ACE2-independent mechanism.

[0180] In some embodiments, provided herein is a kit comprising administering antibodies that bind to non-overlapping epitopes on the Spike protein. In some embodiments, the kit comprises an antibody that binds to an ACE2 binding site of the Spike protein and an antibody that binds to an epitope outside of the ACE2 binding site of the Spike protein. In some embodiments, the kit comprises an antibody that neutralizes SARS-CoV-2 through an ACE2-dependent mechanism and an antibody that neutralizes SARS-CoV-2 through an ACE2-independent mechanism.

[0181] In some aspects, provided herein is an antibody that binds with high affinity to SARS-CoV-2 variants comprising mutated Spike protein. In some embodiment, the mutated Spike protein causes the Spike protein to be pre-cleaved (i.e. cleaved prior to binding the surface of the host cell) or more susceptible to cleavage when binding to the host cell. In some embodiments, such variants correlate with faster viral spread, thus underscoring the utility of the antibodies provided herein for treating and preventing SARS-CoV-2 infections.

[0182] Antibodies of the invention are typically monoclonal antibodies, meaning an antibody is produced by a single clonal B-lymphocyte population, a clonal hybridoma cell population, or a clonal population of cells into which the genes of a single antibody, or portions thereof, have been transfected. Monoclonal antibodies are produced by methods known to those of skill in the art, for instance by making hybrid antibody-forming cells from a fusion of myeloma cells with immune lymphocyte cells.

[0183] An antibody of the invention may also be an "antigen-binding fragment". An antigen-binding fragment refers to a polypeptide fragment of an immunoglobulin or antibody that binds antigen or competes with intact antibody (i.e., with the intact antibody from which they were derived) for antigen binding (i.e., specific binding to an epitope of SARS-CoV-2). As used herein, the term "fragment" of an antibody molecule includes antigen-binding fragments of antibodies, for example, an antibody light chain variable domain (VL), an antibody heavy chain variable domain (VH), a single chain antibody (scFv), a F(ab')₂ fragment, a Fab fragment, an Fd fragment, an Fv fragment, and a single domain antibody fragment (DAb). Fragments can be obtained, e.g., via chemical or enzymatic treatment of an

intact or complete antibody or antibody chain or by recombinant means. Examples of immunoglobulin variants that are considered antibodies according to the invention include single-domain antibodies (such as VH domain antibodies), Fab fragments, Fab' fragments, F(ab')₂ fragments, single chain Fv proteins ("scFv"), and disulfide stabilized Fv proteins ("dsFv"). A VH single-domain antibody is an immunoglobulin fragment consisting of a heavy chain variable domain. An Fab fragment contains a monovalent antigen-binding immunoglobulin fragment, which can be produced by digestion of whole antibody with the enzyme papain to yield an intact light chain and a portion of one heavy chain. Similarly, an Fab' fragment also contains a monovalent antigen-binding immunoglobulin fragment, which can be produced by digestion of whole antibody with the enzyme pepsin, followed by reduction, to yield an intact light chain and a portion of the heavy chain. Two Fab' fragments are obtained per immunoglobulin molecule. A (Fab')₂ fragment is a dimer of two Fab' fragments, that can be obtained by treating whole antibody with the enzyme pepsin without subsequent reduction, so Fab' monomers remain held together by two disulfide bonds. An Fv fragment is a genetically engineered fragment containing the variable region of the light chain and the variable region of the heavy chain expressed as two chains. A single chain ("sc") antibody, such as scFv fragment, is a genetically engineered molecule containing the VL region of a light chain, the VH region of a heavy chain, linked by a suitable polypeptide linker as a genetically fused single chain molecule. A dimer of a single chain antibody, such as a scFV₂ antibody, is a dimer of a scFV, and may also be known as a "miniantibody". A dsFvs variant also contains a VL region of an immunoglobulin and a VH region, but the chains have been mutated to introduce a disulfide bond to stabilize the association of the chains.

[0184] One of skill in the art will realize that conservative variants of the antibodies can be produced. Such conservative variants employed in antibody fragments, such as dsFv fragments or in scFv fragments, will retain critical amino acid residues necessary for correct folding and stabilizing between the VH and the VL regions, and will retain the charge characteristics of the residues in order to preserve the low pI and low toxicity of the molecules.

[0185] An antibody of the invention is typically a "human" antibody, which may also be referred to as a "fully human" antibody. An antibody which possess a human framework regions and CDRs from a human immunoglobulin is generally be considered to be a human

or humanized antibody. For example, a human or humanized antibody may contain the framework and the CDRs of an antibody from the same originating human heavy chain, or human light chain amino acid sequence, or both. Alternatively, the framework regions may originate from one human antibody, and be engineered to include CDRs from a different human antibody.

[0186] An antibody according to the invention may also comprise a "tagged" immunoglobulin CH3 domain to facilitate detection of the biologic against a background of endogenous antibodies. More particularly, a tagged CH3 domain is a heterogeneous antibody epitope that has been incorporated into one or more of the AB, EF, or CD structural loops of a human IgG-derived CH3 domain. For example a CH3 tag may be incorporated into the structural context of an IgG1 subclass antibody, other human IgG subclasses, including IgG2, IgG3, and IgG4. Epitope-tagged CH3 domains, also referred to as "CH3 scaffolds" can be incorporated into any antibody of the invention having a heavy chain constant region, generally in the form of an immunoglobulin Fc portion. Examples of CH3 scaffold tags, and methods for incorporating them into antibodies are disclosed in International Patent Application No. PCT/US2019/032780. Antibodies used to detect epitope tagged CH3 scaffolds, and antibodies of the invention, that comprise epitope tagged CH3 scaffolds, are generally referred to herein as "detector antibodies".

[0187] Some antibodies of the invention may be described as an "isolated" antibody or "isolated" antigen-binding fragment thereof. An isolated antibody or antigen-binding fragment thereof has been substantially separated or purified away from other biological components environment, such as a cell, proteins and organelles. Ordinarily, an isolated antibody or antigen-binding fragment thereof is prepared by a process involving at least one purification step, although the term "isolated" is not intended to refer to a complete absence of such biological molecules or to an absence of water, buffers, or salts or to components of a pharmaceutical formulation that includes an antibody or antigen-binding fragment of the invention.

[0188] In some embodiments of the invention, antibody or antigen-binding fragment thereof is specific for the Spike protein (S) of SARS-CoV-2. Thus, an antibody or antigen-binding fragment thereof may, in one embodiment, bind the S1 subunit of the Spike protein, while in another embodiment, an antibody or antigen-binding fragment thereof binds the S2 subunit. Moreover, some antibodies or antigen-binding fragments thereof bind to the

receptor-binding domain (RBD) of the S protein, while other antibodies of the invention bind to non-RBD epitopes of the S protein. RBD-binding antibodies or antigen-binding fragments thereof of the invention may, in certain embodiments, bind a soluble form of the RBD of the S protein. Some antibodies or antigen-binding fragments of the invention bind to sites on the RBD that are resistant to mutational drift. For example, in some embodiments, an antibody or antigen-binding fragment thereof binds the RBD at, or in close proximity of such a site described by Greaney et al. (2021) as the “the E465 patch”.

[0189] Indeed, among the antibodies of the invention that bind the Spike protein, there are some that bind to highly-conserved epitopes. Accordingly, binding of an antibody or antigen-binding fragment of the invention to a highly-conserved site of the SARS-CoV-2 Spike protein is not affected by point mutations in the Spike protein associated with variants of SARS-CoV-2, Alpha (U.K./B.1.1.7) variant of SARS-CoV-2, the Beta (South African/B.1.351) variant of SARS-CoV-2, the Gamma (Brazilian/P.1) variant of SARS-CoV-2, the Delta (India/B.1.617.2), B.1.617 (L452R/E484Q)), the Epsilon (California/B.1.429/427, New York/B.1.526/526.1) variant of SARS-CoV-2, the UK/Nigeria (B.1.525) variant of SARS-CoV-2, the Brazilian (P.2) variant of SARS-CoV-2, the lambda (C.37) variant of SARS-CoV-2, or the Omicron (B.1.1.529) variant of SARS-CoV-2.

[0190] In certain embodiments of the invention, an isolated antibody or antigen-binding fragment thereof contains a heavy chain variable region (HCVR) and a light chain variable region (LCVR) that is described in Table 1. In some embodiments, provided herein is an antibody comprising a HCDR1, a HCDR2, a HCDR3, a LCDR1, a LCDR2, and a LCDR3 of a heavy chain variable region (HCVR) and a light chain variable region (LCVR) that is described in Table 1. In some embodiments, provided herein is an antibody comprising a HCDR1, a HCDR2, a HCDR3, a LCDR1, a LCDR2, and a LCDR3 set forth in Table 1. In some embodiments, the CDRs are determined using Kabat, Chothia, or contact systems. In some embodiments, the CDRs are determined using the system described in North et al. J.M.B 406(8):228-56 (2011) as set forth in Table 1.

Table 1

Sequence Name	Binds	Description	Amino acid sequence	SEQ ID No.
PR193_00018_HC (derived from IMM200184)	S RBD	VH of IMM200184 antibody	EVQLVESGGGLVQPGGSLRLSCSASGF TFSSFWMSWVRQAPGKGLEWVATIRE DGSEKYYYVDSVKGRFSISRDNANKNSLY	1

Sequence Name	Binds	Description	Amino acid sequence	SEQ ID No.
			LQMNSLRAEDTAVYYCARSKWLRGSF DYWGQGTLLTVSS	
PR193_00018_ LC (derived from IMM200184)	S RBD	VL of IMM200184 antibody	NFMLTQPHSVSESPGKTVTISCTRRSGS IASNYVQWYQQRPGSAPTTVIYEDNQR PSGVPDRFSGSIDSSSNASLTISGLQTE DEADYYCQSYDSSNPPGASWVFGGGT KLTVL	2
PR194_00232_ HC (derived from IMM20190)	S RBD	VH of IMM20190 antibody	EVQLVESGGGLVQPGGSLRLSCSASGF TVSSNYMSWVRQAPRKGLEWVSVIYA GGSTFYADSVKGRFTISRDN SKNTLL QMNSLRAEDTAVYYCARDGGYLDY WGQGTLLTVSS	3
PR194_00232_ LC (derived from IMM20190)	S RBD	VL of IMM20190 antibody	DIQMTQSPSSLSASVGDRVTITCRASQG ISNYLAWYQQKPGKVPKLLIYAASLTQ SGVPSRFSGSGSGTDFTLTISSLQPEDV ATYYCQKYNAPGLTFGGGTKEIK	4
PR200_00622_ HC (derived from IMM20253)	S RBD	VH of IMM20253 antibody	QVQLVESGGGVVQPGRLRLSCTASGF TFSTYGMHWVRQAPGKGLEWVAVISY DGSSKHYAESVKGRFTISRDN SNNTLY LQMNRLRAEDTAVYYCARDGQPPGW GNYFDYWGQGTLLTVAS	5
PR200_00622_ LC (derived from IMM20253)	S RBD	VL of IMM20253 antibody	SYVLTQPPSVSVAPGKTARITCGGNGI GSKSVYWYQQKPGQAPEV VVYDDSD RPSGIPERFSGSNSGNTATLTISRVEAG DEADYYCQVWDSSSDPWVFGGGTKL TVL	6
PR194_00453_ HC	S RBD		QLQLQESGPGLVKPSETLSLTCTVSGG SISSSSSYWGWFRQPPGKGLGWIRSIYY SGSTYYNPSLKSRTMSVDTSKNQFSL KLSSVTAADTAVYYCARAKFSVWDN YRYPFDYWGQGILTVSS	7
PR194_00453_ LC	S RBD		QSVLTQPPSASGTPGQRTISCSGSSSNI GSNTVNWYQQLPGTAPKLLIYSNNQR PSGVPDRFSGSKSGTSASLAISGLQSED EADYYCAAWDDSLNGWVFGGGTKLT VL	8
PR196_00109_ b_HC	S Non- RBD		QVQLVESGGGVVQPGRLRLSCAASG FTFSNYGMHWVRQAPGKGLEWVAVI WYDGSNKYYADSVKGRFTISRDN SKN TLVYQMNSLRAEDTAVYYCARERLED TAMVNFLDYWGQGTLLTVSS	9
PR196_00109_ b_LC	S Non- RBD		SYELTQPPSVSVSPGQTASITCSGDKLG HKYASWFQQRPQGSPVLVIYQDAKRP SGIPERFSGSNSGNTATLTISGTQAMDE ADYYCQAWDSSTVVFGGGTKLTVL	10
PR196_00413_ a_HC	S Non- RBD		QVQLVQSGAEVKKPGSSVKVSCKASG GTFSSYAITWVRQAPGGGLEWMGGIIP IFGTANYAQKFQGRVTITADESTSTAY MELSSLRSED TAVYYCASDYGDSPLG YWGQGTLLTVSS	11
PR196_00413_ a_LC	S		DIVMTQSPDSLAVSLGEPASINCTSSQS VLYSSNNKNFLAWYQQKPGQP KLLI	12

Sequence Name	Binds	Description	Amino acid sequence	SEQ ID No.
	Non-RBD		YWASTRESGVPDRFSGSGSGTDFTLTIS SLQAEDVAVYYCQQYYSAPLTFGGGT KVEIK	
PR194_00292_ HC	S Non- RBD		QVQLQQWGAGLLKPSETLSLTCVYVY GSLSGYYWSWIRQPPGKGLEWIGEINH SGSTNHNPSLKSRSVSVSDTSKNQFSLK LSSVTAADTAVYYCARAWKYSSSWYS GGIYYGMDVWGQGTITVTVSS	13
PR194_00292_ LC	S Non- RBD		QSALTQPASVSGSPGQSITISCSGTSSDV GSYNLVSWYQQHPGKAPKLMIEYETK RPSGVSNRFSSSKSGNTASLTISGLQAE DEADYYCCSYAGFSTWVFGGGTKLTV L	14
PR194_00364_ b_HC	S Non- RBD		EVQLVESGGGLVKPGGSLRLSCASGF TFTTYTMNWVRQAPGKGLEWVSSISS TGLSIYYADSVKGRFTISRDNANKSLY LQMNSLRAEDTAVYYCARDPSPTTIYY YYMDVWGKGTITVTVSS	15
PR194_00364_ b_LC	S Non- RBD		QSALTQPASVSGSPGQSITISCTGTSSD VGTYNLVSWYQHYPGKAPKLIIEVSK RPSGVSDRFSGSKSGNTASLTISGLQAE DEADYYCCSYAGSTTGYVVFGGGKTL TVL	16
PR197_00647_ HC	S Non- RBD		QVQLVESGGGVVQPGRSLRLSCAASG FTFSSYAMHWVRQAPGKGLQWVTLIS YDGGDKYYADSVRGRFTISRDNANKNT LYLQMNSLRTEDTAVYYCARDRPQTG DWFPPIPTGVLDVWGQGTITVTVSS	17
PR197_00647_ LC	S Non- RBD		DIQMTQSPSSLSASVGDRVTITCRASQG ISNYLAWFQQKPGKAPKSLIYAASSLQ SGVPSRFSGSGSGTDFTLTISLQPEDFA TYYCQQYHSYPITFGQGTTRLEIK	18
PR199_00255_ HC (derived from IMM20279)	S RBD	VH of IMM20279 antibody	QVQLVESGGGVVQPGRSLRLSCAASG FTFSTYGMHWVRQAPGKGLEWVAVI WYNGINKHYADSVKGRFTISRDNANKNT LYLQMNSLRVEDTAVYYCARDWGTL TTLFDVWGQGTITVTVSS	19
PR199_00255_ LC (derived from IMM20279)	S RBD	VL of IMM20279 antibody	DIQMTQSPSSLSASVGERATITCRASQS ISSHLNWFQQKPGKAPKFLIYGASSLQ SGVPSRFSGSGSGTDFTLTISLQPEDFA TYYCQQSYSTPPWTFGQGTTRLEIK	20
PR199_00255_ opt_HC	S RBD optimi zed		QVQLVESGGGVVQPGRSLRLSCAASG FTFSTYGMHWVRQAPGKGLEWVAVI WYNGINKYYADSVKGRFTISRDNANKNT LYLQMNSLRAEDTAVYYCARDWGTL LTLFDVWGQGTITVTVSS	21
PR199_00255_ opt_LC	S RBD optimi zed		DIQMTQSPSSLSASVGERATITCRASQS ISSHLNWFQQKPGKAPKFLIYGASSLQ SGVPSRFSGSGSGTDFTLTISLQPEDFA TYYCQQSYSTPPWTFGQGTTRLEIK	22
PR201_00151_ HC	S RBD		RVTLRSGPALVKPTQTLTLTCTFSGFS LNTSGMCSVSWIRQPPGKALEWLARID	23

Sequence Name	Binds	Description	Amino acid sequence	SEQ ID No.
			WDDDKYYSTSLETRLTISKDTSKNQVV LTMTNLDPVDTGTYYCARISIQSRGGG ADYWGQGTTLTVSS	
PR201_00151_ LC	S RBD		DIQMTQSPSSLSASVGDRVTITCRASQS ISSYLHWYQQKSGKAPKLLIFVASTLQ SGVPSRFSGSGSGTDFTLTISLQPEDSA AAYCQQSYSPPWTFGQGTKVEIK	24
PR194_00068_ HC	S Non- RBD		EVQLLESGGGLVQPGGSLRLSCSASGF TFTNYAMSWVRQAPGKGLEWVSTISG SGGSTYYADSVKGRFTISRDNSTLFL QMNSLRAEDTAIYYCANSIPTGDLTY WGQGTTLTVSS	25
PR194_00068_ LC	S Non- RBD		SYELTQPPSVSVSPGQTTLSTCSGDKL GNKYVCWYQQKPGQSPVLVIYQDTR PSGIPERVSGSNSGDTATLTISGTQAMD EADYYCQAWDSSTAVFGGGTKLTVL	26
PR198_00478_ HC	ORF3a		EVQLVESGGGLVKPGGSLRLSCTASGF TFNKAWMSWVRQPPGKGLEWVGRIQ SKTDDETTDYAAPVKGRFIVSRDDSKN TLYLQMNSLKIEDTAIYYCTSRHYGS GTSYTPFDYWGQGTTLTVSS	27
PR198_00478 LC	ORF3a		DIVMTQSPLSLPVTPGEQASISCRSSQS LLYSNGYNYLDWYLQKPGQSPRLIY MGSNRASGVDPDRFSGSGSGTDFTLKIS RVEAEDVGVYYCMQTLQTLFTFGPGT KVDIK	28
PR210_01029_ λ _v1_HC	M		QVQLQESGPGLVKPSETLSLTCAVYGG SFGSYYSWIRQPPGKGLEWIAEIDHS GSTNYPNPSLKSRTISVDTSKNQFSLKL RSVTAADTAVYYCARTTSITIFGILVAG GHNCFDSWGQGTTLTVSS	29
PR210_01029_ λ _v1_LC	M		QSALTQPASVSGSPGQSITISCSGTSSDV GNYDLVSWYQQHPGKAPKVMIEYEV KRPSGVSNRFSGSKSGNTASLTISGLQA EDEADYYCCSYTSSGTFWVFGGGTKL TVL	30
PR197_00350_ HC	NC		QVQLVQSGAEVKKPGSSVKVSCKASG GTFSNYAINWVRQAPGQGLEWMGGII PIFGTTNYAQSFQGRVTITADESTSTAY MELSSLRSEDTAVYYCARAGYSSSWY RSTILSYNNYYGLDVWGQGTTLTVSS	31
PR197_00350_ LC	NC		DIVMTQSPLSLPVTPGEPASISCRSSQSL LHSNGYNYLDWYLQKPGQSPQLLIYL GSNRASGVDPDRFSGSGSGTDFTLKISRV EAEDVGVYYCMQAQQTSGGQGTKLEI K	32
PR210_01524_ HC	NC		QVQLVESGGGVVQPGSLRLSCAASG FTFSDYGMHWVRQAPGKGLEWVAVI WYDGSYKYYADSVKGRFTISRDNSTN TVYLMHSLRAEDTAVYYCARDGQW LRILDYWGQGTTLTVSS	33

Sequence Name	Binds	Description	Amino acid sequence	SEQ ID No.
PR210_01524_LC	NC		EIVLTQSPGTLSPGERVTLSRASQS VRSSSLGWYQQKPGQAPRRILFGASNR ATGIPDRFSGSGSGTDFTLTISRLEPEDF AVYYCQQSGSSLFTFGQGTKLEIK	34
PR210_00852_HC	NC		QLQLQESGPGLVKPSETLSLTCTVSGA SISSTTYWGWIRQPPGKGLEWIGSIHY VGSTYYNSSLKSRVTISVDTSKNQFSL KLGSVTAADTAVYYCTLSVAGTFYGL DVWGQGTTVTVSS	35
PR210_00852_LC	NC		DIQMTQSPSSVSASVGDRVTITCRASQ GISSWLAWYQQKPGKAPNLLIYAASSL QSGVPSRFSGSGSGTDFTLTISLQPEDF ATYYCQQANSFPLTFGGGKVEIK	36
PR199_00106_b_λ_HC	ORF8		EVQLVESGGALVKPGGSLRLSCAASGF TFRNVWMNWVRQAPGKGLEWVGRIK SKTDGGTIDYAAPMKGRLLSRDDSKN MLYLQMSLKTDDTAVYYCTTHSIRG FEIWGQGTMTVTSS	37
PR199_00106_b_λ_LC	ORF8		SYELTQPPSVSVSPGQTARITCSGDALP KQYAYWYQQKAGQAPVLVIYKDSERP SGIPGRFSGSTSGTTVTLTISGVQAEDE ADYYCQSADSSGAPLVFGGGKLTVL	38
PR199_00179_κ_HC	ORF8		EVQLVESGGGLVKPGGSLRLSCAASGF TFSSYSMNWVRQAPGKGLEWVSSISS SSYIYYADSVKGRFTISRDNALNSLYL QMNSLRADTAVYYCARDRASGRVGS RFDYWGQGTLVTVSS	39
PR199_00179_κ_LC	ORF8		DIQMTQSPSSLSASVGERATLTCSRASQS ISSYLNWYQQKPGKAPKLLIYAASSLQ SGVPSRFSGSGSGTDFTLTISLQPEDFA TYYCQQSYSTPRVTFGQGTKVEIK	40
PR197_00705_HC	S RBD		QVQLQESGPGLVKPSQTLSTCTVSGD SVSSGDYYWGWIRQHPGKGLEWIGYI YYTGRTFDNPSLKSRLTMSVDTSKNQF SVRLYSVTAADTAVYYCARARDSEGF SQYYFDYWGQGTLVTVSS	41
PR197_00705_LC	S RBD		DIQMTQSPSSLSASVGDKNITCQASE DIDVYLSWYQQKPGKAPKLLIYDASNL ETGVPSRFSGSGSGTDFAFTISLQPED VATYYCQQYDNLPTFGGGKVEIK	42
PR194_00547_r_HC	S Non-S1		QVQLVQSGAEVKKPGASVKISKASG YTFTSYGISWVRQAPGQGLEWMGWIS AYNGNTNYAQKLQGRVTMTDISTST AYMELRSLKSDDTAVYYCAREVWGA GYYFDYWGQGTLVTVSS	43
PR194_00547_r_LC	S Non-S1		SYELTQPPSVSVSPGQTARITCSGDALP KQYAYWYQQKPGQAPVLVIYKDSERP SGIPERFSGSSSGTTVTLTISGVQAEDE ADYYCQSADSSGTYYVFGGGKLTVL	44
PR194_00195_HC	S Non-S1		QVQLVQSGAEVKKPGSSVKVSCKASG GTFSTNYAINWVRQAPGQGLEWMGGII PIFRTANYAQKFQGRVTITADESTTAC	45

Sequence Name	Binds	Description	Amino acid sequence	SEQ ID No.
			MELSSLRFEDTAVYYCAREYSSSSGFYFDYWGQGTTLVTVSS	
PR194_00195_LC	S Non-S1		QSALTQPASVSGSPGQSITISCSGTSSDVGSYNLVSQYQHPGKAPKLMIEGNGRPSGVSNRFGSGSKSGNTASLTISGLQAEDEADYYCCSYAGSSAWMFGGGTKLTVL	46
PR194_00292_HC	S Non-RBD		QVQLQQWGAGLLKPSETLSLTCAVYGGSLSGYYWSWIRQPPGKGLEWIGEINHSNSTNHNPSLKSRSISVDTSKNQFSLKLSSVTAADTAVYYCARAWKYSSSWYSGGIYYGMDVWGQGTTLVTVSS	47
PR194_00292_LC	S Non-RBD		QSALTQPASVSGSPGQSITISCSGTSSDVGSYNLVSQYQHPGKAPKLMIEGNGRPSGVSNRFGSSSKSGNTASLTISGLQAEDEADYYCCSYAGFSTWVFGGGTKLTVL	48
PR194_00591_HC	S Non-S1		QVQLVESGGGVVQPGRSLRLSCAVSGFIFSSHGMHWVRQAPGKGLEWMTVISYDGSKKHYADSVQGRFIISRDNSKNMVYLQMNDLRAEDTAVYYCAKDATYCDSTITWCARYSHMDVWGRGTSVTVSS	49
PR194_00591_LC	S Non-S1		LRVWVSWTVDHHLTCSGASSDLGAYNYVSWYQHPGKAPNLMYDVNHRPSGVSNRFGSGSKSGNTASLTISGLQPEDEADYYCSSYTSRSTLVFGGGTRLTVL	50
PR196_00042_HC	S Non-S1		QVQLQESGPGLVKPSDTLSLICTVSGGSIKSYYSWIRQPPGKGLQWIGYIYYSGSTNYPNPSLKSRTISVDTSKNQFSLKLSVTAADTAVYYCASYSGYDWGGFDYWGQGTTLVTVSS	51
PR196_00042_LC	S Non-S1		QSVLTQPPSASGTPGQRATISCSGSRNIGSNTVNWYQQLPGTAPKLLIYSDNQRPSGVDPDRFGSGSKSGTSASLAVSGLQSEDEADYYCAAWDDSLNGPVFGGGTKLTVL	52
PR194_00448_HC	S Non-S1		QLQLQESGPGLVKPSDTLSLTCTVSGGSISNSNYWGWVRQPPGKGLEWIGSLYYTGSTYYTPSLKSRVAMAVDTSKNLFSLKLSSVTAADTALYYCARLFSSGYYSPLYSFYDWGQGTTLVTASS	53
PR194_00448_LC	S Non-S1		SVSGSPGQSITISCTGTTSSDVGGYNFVSWYQHPGKAPKLMYDVSNRPSGVSNRFGSGSKSGNTASLTISGLRAEDEADYYCSSYTSSSTLIFGGGTCLTVL	54
PR193_00018_HC		HCDR1 of IMM200184	SASGFTFSSFWMS	55
PR193_00018_HC		HCDR2 of IMM200184	TIREDGSEKYYVD	56

Sequence Name	Binds	Description	Amino acid sequence	SEQ ID No.
PR193_00018_HC		HCDR3 of IMM200184	ARSKWLRGSFDY	57
PR193_00018_LC		LCDR1 of IMM200184	TRRSGSIASNYVQ	58
PR193_00018_LC		LCDR2 of IMM200184	YEDNQRPS	59
PR193_00018_LC		LCDR3 of IMM200184	QSYDSSNPPGASWV	60
PR194_00232_HC		HCDR1 of IMM20190	SASGFTVSSNYMS	61
PR194_00232_HC		HCDR2 of IMM20190	VIYAGGSTF	62
PR194_00232_HC		HCDR3 of IMM20190	ARDRGGYLDY	63
PR194_00232_LC		LCDR1 of IMM20190	RASQGISNYLA	64
PR194_00232_LC		LCDR2 of IMM20190	YAASTLQS	65
PR194_00232_LC		LCDR3 of IMM20190	QKYNSAPGLT	66
PR200_00622_HC		HCDR1 of IMM20253	TASGFTFSTYGMH	67
PR200_00622_HC		HCDR2 of IMM20253	VISYDGSSKH	68
PR200_00622_HC		HCDR3 of IMM20253	ARDGQPPGWGNYFDY	69
PR200_00622_LC		LCDR1 of IMM20253	GGNGIGSKSVY	70
PR200_00622_LC		LCDR2 of IMM20253	YDDSDRPS	71
PR200_00622_LC		LCDR3 of IMM20253	QVWDSSSDPWV	72
PR194_00453_HC		HCDR1	TVSGGSISSSSSYWG	73

Sequence Name	Binds	Description	Amino acid sequence	SEQ ID No.
PR194_00453_HC		HCDR2	SIYYSGSTY	74
PR194_00453_HC		HCDR3	ARAKFSVWDNYRYPFDY	75
PR194_00453_LC		LCDR1	SGSSSNIGSNTVN	76
PR194_00453_LC		LCDR2	YSNNQRPS	77
PR194_00453_LC		LCDR3	AAWDDSLNGWV	78
PR196_00109_b_HC		HCDR1	AASGFTFSNYGMH	79
PR196_00109_b_HC		HCDR2	VIWYDGSNKY	80
PR196_00109_b_HC		HCDR3	ARERLEDTAMVNFLDY	81
PR196_00109_b_LC		LCDR1	SGDKLGHKYAS	82
PR196_00109_b_LC		LCDR2	YQDAKRPS	83
PR196_00109_b_LC		LCDR3	QAWDSSTVV	84
PR196_00413_a_HC		HCDR1	KASGGTFSSYAIT	85
PR196_00413_a_HC		HCDR2	GIIPIFGTAN	86
PR196_00413_a_HC		HCDR3	ASDYGDSPLGY	87
PR196_00413_a_LC		LCDR1	TSSQSVLYSSNNKNFLA	88
PR196_00413_a_LC		LCDR2	YWASTRES	89
PR196_00413_a_LC		LCDR3	QQYYSAPLT	90
PR194_00292_HC		HCDR1	AVYGGSLSGYYWS	91
PR194_00292_HC		HCDR2	EINHSGSTN	92
PR194_00292_HC		HCDR3	ARAWKYSSSWYSGGIYYGMDV	93
PR194_00292_LC		LCDR1	SGTSSDVGSYNLVS	94
PR194_00292_LC		LCDR2	YEGTKRPS	95
PR194_00292_LC		LCDR3	CSYAGFSTWV	96

Sequence Name	Binds	Description	Amino acid sequence	SEQ ID No.
PR194_00364_ b_HC		HCDR1	SASGFTFTTYTMN	97
PR194_00364_ b_HC		HCDR2	SISSTGLSIY	98
PR194_00364_ b_HC		HCDR3	ARDPSPTTIYYYYYMDV	99
PR194_00364_ b_LC		LCDR1	TGTSSDVGTYNLVS	100
PR194_00364_ b_LC		LCDR2	YEVSKRPS	101
PR194_00364_ b_LC		LCDR3	CSYAGSTTGYVV	102
PR197_00647_ HC		HCDR1	AASGFTFSSYAMH	103
PR197_00647_ HC		HCDR2	LISYDGGDKY	104
PR197_00647_ HC		HCDR3	ARDRPQTGDWFPPIPTGVLDV	105
PR197_00647_ LC		LCDR1	RASQGISNYLA	106
PR197_00647_ LC		LCDR2	YAASSLQS	107
PR197_00647_ LC		LCDR3	QQYHSYPIT	108
PR199_00255_ HC		HCDR1 of IMM20279	AASGFTFSTYGMH	109
PR199_00255_ HC		HCDR2 of IMM20279	VIWYNGINKH	110
PR199_00255_ HC		HCDR3 of IMM20279	ARDWGTLTTLFDF	111
PR199_00255_ LC		LCDR1 of IMM20279	RASQSISSHLN	112
PR199_00255_ LC		LCDR2 of IMM20279	YGASSLQS	113
PR199_00255_ LC		LCDR3 of IMM20279	QQSYSTPPWT	114
PR199_00255_ opt_HC		HCDR1	AASGFTFSTYGMH	115
PR199_00255_ opt_HC		HCDR2	VIWYNGINKY	116
PR199_00255_ opt_HC		HCDR3	ARDWGTLTTLFDF	117
PR199_00255_ opt_LC		LCDR1	RASQSISSHLN	118
PR199_00255_ opt_LC		LCDR2	YGASSLQS	119
PR199_00255_ opt_LC		LCDR3	QQSYSTPPWT	120

Sequence Name	Binds	Description	Amino acid sequence	SEQ ID No.
PR201_00151_HC		HCDR1	TFSGFSLNTSGMCVS	121
PR201_00151_HC		HCDR2	RIDWDDDKY	122
PR201_00151_HC		HCDR3	ARISIQSRGGGADY	123
PR201_00151_LC		LCDR1	RASQSISSYLH	124
PR201_00151_LC		LCDR2	FVASTLQS	125
PR201_00151_LC		LCDR3	QQSYSPWWT	126
PR194_00068_HC		HCDR1	SASGFTFTNYAMS	127
PR194_00068_HC		HCDR2	TISGSGGSTY	128
PR194_00068_HC		HCDR3	ANSGPTGDLDY	129
PR194_00068_LC		LCDR1	SGDKLGNKYVC	130
PR194_00068_LC		LCDR2	YQDTKRPS	131
PR194_00068_LC		LCDR3	QAWDSSTAV	132
PR198_00478_HC		HCDR1	TASGFTFNKAWMS	133
PR198_00478_HC		HCDR2	RIQSKTDDETTD	134
PR198_00478_HC		HCDR3	TSRAHYGSGTSYTPFDY	135
PR198_00478_LC		LCDR1	RSSQSLLYSNGYNYLD	136
PR198_00478_LC		LCDR2	YMGSNRAS	137
PR198_00478_LC		LCDR3	MQTLQTLFT	138
PR210_01029_λ_v1_HC		HCDR1	AVYGGSFSGYYWS	139
PR210_01029_λ_v1_HC		HCDR2	EIDHSGSTN	140
PR210_01029_λ_v1_HC		HCDR3	ARTTSITIFGILVAGGHNCFDS	141
PR210_01029_λ_v1_LC		LCDR1	SGTSSDVGNLYDLVS	142
PR210_01029_λ_v1_LC		LCDR2	MIYEVTKRPS	143
PR210_01029_λ_v1_LC		LCDR3	CSYTSSGTFWV	144
PR197_00350_HC		HCDR1	KASGGTFSNYAIN	145

Sequence Name	Binds	Description	Amino acid sequence	SEQ ID No.
PR197_00350_HC		HCDR2	GIIPFGTTN	146
PR197_00350_HC		HCDR3	ARAGYSSSWYRSTILSYYNYYGLDV	147
PR197_00350_LC		LCDR1	RSSQSLLHSNGYNYLD	148
PR197_00350_LC		LCDR2	YLGSNRAS	149
PR197_00350_LC		LCDR3	MQAQQTS	150
PR210_01524_HC		HCDR1	AASGFTFSDYGMH	151
PR210_01524_HC		HCDR2	VIWYDGSYKY	152
PR210_01524_HC		HCDR3	ARDGQWLRILDY	153
PR210_01524_LC		LCDR1	RASQSVRSSLG	154
PR210_01524_LC		LCDR2	FGASNRAT	155
PR210_01524_LC		LCDR3	QQSGSSLFT	156
PR210_00852_HC		HCDR1	TVSGASISSTTYWYG	157
PR210_00852_HC		HCDR2	SIHYVGSTY	158
PR210_00852_HC		HCDR3	TLSVAGTFYGLDV	159
PR210_00852_LC		LCDR1	RASQGISSWLA	160
PR210_00852_LC		LCDR2	YAASSLQS	161
PR210_00852_LC		LCDR3	QQANSFPLT	162
PR199_00106_b_λ_HC		HCDR1	AASGFTFRNVWMN	163
PR199_00106_b_λ_HC		HCDR2	RIKSKTDGGTID	164
PR199_00106_b_λ_HC		HCDR3	TTHSIRGFEI	165
PR199_00106_b_λ_LC		LCDR1	SGDALPKQYAY	166
PR199_00106_b_λ_LC		LCDR2	YKDSERPS	167
PR199_00106_b_λ_LC		LCDR3	QSADSSGAPLV	168
PR199_00179_κ_HC		HCDR1	AASGFTFSSYSMN	169
PR199_00179_κ_HC		HCDR2	SISSSSSYIY	170

Sequence Name	Binds	Description	Amino acid sequence	SEQ ID No.
PR199_00179_κ_HC		HCDR3	ARDRASGRVGSRFDY	171
PR199_00179_κ_LC		LCDR1	RASQSISSYLN	172
PR199_00179_κ_LC		LCDR2	YAASSLQS	173
PR199_00179_κ_LC		LCDR3	QQSYSTPRVT	174
PR197_00705_HC		HCDR1	TVSGDSVSSGDYYWG	175
PR197_00705_HC		HCDR2	YIYYTGRTF	176
PR197_00705_HC		HCDR3	ARARDSEGFSQYYFDY	177
PR197_00705_LC		LCDR1	QASEDIDVYLS	178
PR197_00705_LC		LCDR2	YDASNLET	179
PR197_00705_LC		LCDR3	QQYDNLPT	180
PR194_00547_r_HC		HCDR1	KASGYTFTSYGIS	181
PR194_00547_r_HC		HCDR2	WISAYNGNTN	182
PR194_00547_r_HC		HCDR3	AREVWGAGYYFDY	183
PR194_00547_r_LC		LCDR1	SGDALPKQYAY	184
PR194_00547_r_LC		LCDR2	YKDSERPS	185
PR194_00547_r_LC		LCDR3	QSADSSSGTYVV	186
PR194_00195_HC		HCDR1	KASGGTFSNYAIN	187
PR194_00195_HC		HCDR2	GIIPIFTAN	188
PR194_00195_HC		HCDR3	AREYSSSSGFYFDY	189
PR194_00195_LC		LCDR1	SGTSSDVGSYNLVS	190
PR194_00195_LC		LCDR2	YEGNKRPS	191
PR194_00195_LC		LCDR3	CSYAGSSAWM	192
PR194_00292_HC		HCDR1	AVYGGSLSGYYWS	193
PR194_00292_HC		HCDR2	EINHSGSTN	194
PR194_00292_HC		HCDR3	ARAWKYSSSWYSGGIYYGMDV	195

Sequence Name	Binds	Description	Amino acid sequence	SEQ ID No.
PR194_00292_LC		LCDR1	SGTSSDVGSYNLVS	196
PR194_00292_LC		LCDR2	YEGTKRPS	197
PR194_00292_LC		LCDR3	CSYAGFSTWV	198
PR194_00591_HC		HCDR1	AVSGFIFSSHGMH	199
PR194_00591_HC		HCDR2	VISYDGSKKH	200
PR194_00591_HC		HCDR3	AKDATYCDSTSWCARYSHMDV	201
PR194_00591_LC		LCDR1	SGASSDLGAYNYVS	202
PR194_00591_LC		LCDR2	YDVNHRPS	203
PR194_00591_LC		LCDR3	SSYTSRSTLV	204
PR196_00042_HC		HCDR1	TVSGGSIRSYYWS	205
PR196_00042_HC		HCDR2	YIYYSGSTN	206
PR196_00042_HC		HCDR3	ASYSGYDWGGFDY	207
PR196_00042_LC		LCDR1	SGSRSNIGSNTVN	208
PR196_00042_LC		LCDR2	YSDNQRP	209
PR196_00042_LC		LCDR3	AAWDDSLNGPV	210
PR194_00448_HC		HCDR1	TVSGGSISNSNYYWG	211
PR194_00448_HC		HCDR2	SLYYTGSTY	212
PR194_00448_HC		HCDR3	ARLFSSGYYSPLYSFDY	213
PR194_00448_LC		LCDR1	TGTTSSDVGGYNFVS	214
PR194_00448_LC		LCDR2	YDVSNRPS	215
PR194_00448_LC		LCDR3	SSYTSSSTLI	216
CD-2WNG loop epitope with border sequences			WESNGNELSDFKTT	217
CD-2WNG epitope			NGNELSDF	218
CD-4I2X:A epitope with border sequences			WEIDGSERQNGKTT	219

Sequence Name	Binds	Description	Amino acid sequence	SEQ ID No.
CD-4I2X:A epitope			IDGSERQNG	220
CD-TLK epitope with border sequences			WEDNPVYKTT	221
CD-TLK epitope			DNPVY	222
CD-CD2HV epitope with border sequences			WESNIAQPRNYKTT	223
CD-CD2HV epitope			SNIAQPRNY	224
CD-KRNE epitope with border sequences			WESNGQPEKRNENNYKTT	225
CD-KRNE epitope			SNGQPEKRNENNY	226
CD-LANE epitope with border sequences			WESNGQPELANENNYKTT	227
CD-LANE epitope			SNGQPELANENNY	228
CD-DRR epitope with border sequences			WESNGQPDRRYKTT	229
CD-DRR epitope			SNGQPDRRY	230
CD-DNF-derived epitope with border sequences			WESNGQPEDNFKTT	231
CD-DNF-derived epitope			SNGQPEDNF	232
CD-DQQ epitope with border sequences			WESNGQPDQQYKTT	233
CD-DQQ epitope			SNGQPDQQY	234
CD-OPN epitope with border sequences			WETWLNPDPSQKTT	235
CD-OPN epitope			TWLNPDPSQ	236

Sequence Name	Binds	Description	Amino acid sequence	SEQ ID No.
CD-Glu epitope with border sequences			WEYMPMENNYKTT	237
CD-Glu epitope			YMPMENNY	238
CD-Myc epitope with border sequences			WEQKLISEEDLKTT	239
CD-Myc epitope			QKLISEEDL	240
CD-FLAG epitope with border sequences			WEDYKDDDDKTT	241
CD-FLAG epitope			DYKDDDD	242
CD-HIS epitope with border sequences			WESNGHHHHHHYKTT	243
CD-HIS epitope			SNGHHHHHHY	244
EF-2WNG epitope with border sequences			DLTRWDVGNV	245
EF-2WNG epitope			LTRWDV	246
EF-4I2X:A epitope with border sequences			DKDRWERGNV	247
EF-4I2X:E epitope			KDRWER	248
EF-4I2X:E epitope with border sequences			WELDRWDVKTT	249
EF-4I2X:E epitope			LDRWDV	250
EF-ND epitope with border sequences			DNDRWQQGNV	251
EF-ND epitope			NDRWQQ	252

[0191] In some embodiments, provided herein is an antibody that binds to a SARS-CoV-2 Spike protein comprising a variable heavy chain (VH) and a variable light chain (VL), wherein the antibody comprises a HCDR1 comprising the amino acid sequence

SASGFTFSSFWMS (SEQ ID NO: 55); a HCDR2 comprising the amino acid sequence TIREDGSEKYYYVD (SEQ ID NO: 56); and a HCDR3 comprising the amino acid sequence ARSKWLRGSFDY (SEQ ID NO: 57); wherein the antibody comprises a LCDR1 comprising the amino acid sequence TRRSGSIASNYVQ (SEQ ID NO: 58); a LCDR2 comprising the amino acid sequence YEDNQRPS (SEQ ID NO: 59); and a LCDR3 comprising the amino acid sequence QSYDSSNPPGASWV (SEQ ID NO: 60). In some embodiments, the CDRs are defined according to North et al. In some embodiments, the VH comprises the amino acid set forth in SEQ ID NO: 1. In some embodiments, the VL comprises the amino acid sequence set forth in SEQ ID NO: 2. In some embodiments, the VH comprises the amino acid set forth in SEQ ID NO: 1 and the VL comprises the amino acid sequence set forth in SEQ ID NO: 2. In some embodiments, the antibody comprises a HCDR1, HCDR2, and HCDR3 of a heavy chain variable region (HCVR) comprising the amino acid sequence set forth in SEQ ID NO: 1, and a LCDR1, LCDR2, and LCDR3 of a light chain variable region (LCVR) comprising the amino acid sequence is set forth in SEQ ID NO: 2. In some embodiments the antibody comprises one or more CDRs or variable region sequences of IMM20184 (PR193_00018_HC). In some embodiments, the antibody binds to an epitope on the Spike protein outside of the ACE2 binding site. In some embodiments, the antibody neutralizes SARS-CoV-2 through an ACE2-dependent mechanism. In some embodiments, IMM20184 contacts one or more amino acids in the Spike protein selected from the group consisting of N370, A372, F374, K378, S383, and P384. In some embodiments, IMM20184 binds to a conserved epitope. In some embodiments, IMM20184 binds to an epitope of the Spike protein comprising one or more of N370, A372, F374, K378, S383, and P384.

[0192] In some embodiments, provided herein is an antibody that binds to a SARS-CoV-2 Spike protein comprising a variable heavy chain (VH) and a variable light chain (VL), wherein the antibody comprises a HCDR1 comprising the amino acid sequence SASGFTVSSNYMS (SEQ ID NO: 61); a HCDR2 comprising the amino acid sequence VIYAGGSTF (SEQ ID NO: 62); and a HCDR3 comprising the amino acid sequence ARDRGGYLDY (SEQ ID NO: 63); wherein the antibody comprises a LCDR1 comprising the amino acid sequence RASQGISNYLA (SEQ ID NO: 64); a LCDR2 comprising the amino acid sequence YAASTLQS (SEQ ID NO: 65); and a LCDR3 comprising the amino acid sequence QKYNSAPGLT (SEQ ID NO: 66). In some embodiments, the CDRs are defined according to North et al. In some embodiments, the VH comprises the amino acid set

forth in SEQ ID NO: 3. In some embodiments, the VL comprises the amino acid sequence set forth in SEQ ID NO: 4. In some embodiments, the VH comprises the amino acid set forth in SEQ ID NO: 3 and the VL comprises the amino acid sequence set forth in SEQ ID NO: 4. In some embodiments, the antibody comprises a HCDR1, HCDR2, and HCDR3 of a heavy chain variable region (HCVR) comprising the amino acid sequence set forth in SEQ ID NO: 3, and a LCDR1, LCDR2, and LCDR3 of a light chain variable region (LCVR) comprising the amino acid sequence is set forth in SEQ ID NO: 4. In some embodiments, the antibody comprises one or more CDRs or variable region sequences of IMM20190 (PR194_00232_HC). In some embodiments, the antibody binds to an epitope of the Spike protein in the ACE2 binding site and operates through an ACE2-dependent mechanism. In some embodiments, IMM20190 contacts one or more amino acids of the Spike protein selected from the group consisting of K417, D420, L455, F456, N460, Y473, N487, Y489, N501, and Y505. In some embodiments, IMM20190 binds to a non-conserved epitope. In some embodiments, IMM20190 binds to an epitope of the Spike protein comprising one or more of K417, D420, L455, F456, N460, Y473, N487, Y489, N501, and Y505.

[0193] In some embodiments, provided herein is an antibody that binds to a SARS-CoV-2 Spike protein comprising a variable heavy chain (VH) and a variable light chain (VL), wherein the antibody comprises a HCDR1 comprising the amino acid sequence TASGFTFSTYGMH (SEQ ID NO: 67); a HCDR2 comprising the amino acid sequence VISYDGSSKH (SEQ ID NO: 68); and a HCDR3 comprising the amino acid sequence ARDGQPPGWGNYFDY (SEQ ID NO: 69); wherein the antibody comprises a LCDR1 comprising the amino acid sequence GGNGIGSKSVY (SEQ ID NO: 70); a LCDR2 comprising the amino acid sequence YDDSDRPS (SEQ ID NO: 71); and a LCDR3 comprising the amino acid sequence QVWDSSSDPWV (SEQ ID NO: 72). In some embodiments, the CDRs are defined according to North et al. In some embodiments, the VH comprises the amino acid set forth in SEQ ID NO: 5. In some embodiments, the VL comprises the amino acid sequence set forth in SEQ ID NO: 6. In some embodiments, the VH comprises the amino acid set forth in SEQ ID NO: 5 and the VL comprises the amino acid sequence set forth in SEQ ID NO: 6. In some embodiments, the antibody comprises a HCDR1, HCDR2, and HCDR3 of a heavy chain variable region (HCVR) comprising the amino acid sequence set forth in SEQ ID NO: 5, and a LCDR1, LCDR2, and LCDR3 of a light chain variable region (LCVR) comprising the amino acid sequence is set forth in SEQ ID NO: 6. In some embodiments, the antibody comprises one or more CDR sequences or

variable region sequences of IMM20253 (PR200_00622_HC). In some embodiments, the antibody binds to a Spike protein with a mutation in the protease cleavage site. In some embodiments, the antibody binds with high affinity to pre-cleaved Spike proteins (i.e. Spike proteins that are cleaved prior to binding to the host cell surface). In some embodiments, the antibody binds with high affinity to Spike proteins with mutations that make a protease site more readily cleavable. In some embodiments, the antibody binds to a Spike protein at an epitope outside of the ACE2 binding site and operates through an ACE2 independent mechanism. In some embodiments, the antibody causes a conformation change in the Spike protein. In some embodiments, the antibody makes the Spike protein more susceptible to cleavage. In some embodiments IMM20253 contacts one or more amino acid of the Spike protein selected from the group consisting of K356 and R466. In some embodiments, IMM20253 binds to a conserved epitope. In some embodiments, IMM20253 binds to an epitope of the Spike protein comprising K356 and/or R466.

[0194] In some embodiments, provided herein is an antibody that binds to a SARS-CoV-2 Spike protein comprising a variable heavy chain (VH) and a variable light chain (VL), wherein the antibody comprises a HCDR1 comprising the amino acid sequence AASGFTFSTYGMH (SEQ ID NO: 109); a HCDR2 comprising the amino acid sequence VIWYNGINKH (SEQ ID NO: 110); and a HCDR3 comprising the amino acid sequence ARDWGTLTTLFDF (SEQ ID NO: 111); wherein the antibody comprises a LCDR1 comprising the amino acid sequence RASQSISSHLN (SEQ ID NO: 112); a LCDR2 comprising the amino acid sequence YGASSLQS (SEQ ID NO: 113); and a LCDR3 comprising the amino acid sequence QQSYSTPPWT (SEQ ID NO: 114). In some embodiments, the VH comprises the amino acid set forth in SEQ ID NO: 19. In some embodiments, the CDRs are defined according to North et al. In some embodiments, the VL comprises the amino acid sequence set forth in SEQ ID NO: 20. In some embodiments, the VH comprises the amino acid set forth in SEQ ID NO: 19 and the VL comprises the amino acid sequence set forth in SEQ ID NO: 20. In some embodiments, the antibody comprises a HCDR1, HCDR2, and HCDR3 of a heavy chain variable region (HCVR) comprising the amino acid sequence set forth in SEQ ID NO: 19, and a LCDR1, LCDR2, and LCDR3 of a light chain variable region (LCVR) comprising the amino acid sequence is set forth in SEQ ID NO: 20. In some embodiments, the antibody comprises one or more CDR sequences or variable region sequences of IMM20279 (PR199_00255_HC). In some embodiments, the antibody binds to an epitope of the Spike protein outside of the ACE2 binding site. In some

embodiments, the antibody comprising one or more CDR sequences or variable region sequences of IMM20279 cross-reacts with an antibody comprising one or more CDR sequences or variable region sequences of IMM20184. In some embodiments of the invention, an isolated antibody or antigen-binding fragment thereof binds a SARS-CoV-2 Spike protein, and contains one of the following combinations of a heavy chain variable region (HCVR) and a light chain variable region (LCVR): a HCVR comprising three heavy chain complementarity determining regions (CDRs), (HCDR1, HCDR2 and HCDR3), wherein the amino acid sequence of the HCVR is set forth in SEQ ID NO: 1, and a LCVR comprising three light chain complementarity determining regions (CDRs) (LCDR1, LCDR2 and LCDR3), wherein the amino acid sequence of the LCVR is set forth in any one of SEQ ID NO: 2; a HCVR comprising three CDRs, (HCDR1, HCDR2 and HCDR3), wherein the amino acid sequence of the HCVR is set forth in SEQ ID NO: 3, and a LCVR comprising three CDRs, (LCDR1, LCDR2 and LCDR3), wherein the amino acid sequence of the LCVR is set forth in SEQ ID NO: 4; a HCVR comprising three CDRs, (HCDR1, HCDR2 and HCDR3), wherein the amino acid sequence of the HCVR is set forth in SEQ ID NO: 19, and a LCVR comprising three CDRs, (LCDR1, LCDR2 and LCDR3), wherein the amino acid sequence of the LCVR is set forth in SEQ ID NO: 20; a HCVR comprising three CDRs, (HCDR1, HCDR2 and HCDR3), wherein the amino acid sequence of the HCVR is set forth in SEQ ID NO: 5, and a LCVR comprising three CDRs, (LCDR1, LCDR2 and LCDR3), wherein the amino acid sequence of the LCVR is set forth in SEQ ID NO: 6; a HCVR comprising three CDRs, (HCDR1, HCDR2 and HCDR3), wherein the amino acid sequence of the HCVR is set forth in SEQ ID NO: 7, and a LCVR comprising three CDRs, (LCDR1, LCDR2 and LCDR3), wherein the amino acid sequence of the LCVR is set forth in SEQ ID NO: 8; or a HCVR comprising three CDRs, (HCDR1, HCDR2 and HCDR3), wherein the amino acid sequence of the HCVR is set forth in SEQ ID NO: 23, and a LCVR comprising three CDRs, (LCDR1, LCDR2 and LCDR3), wherein the amino acid sequence of the LCVR is set forth in SEQ ID NO: 24.

[0195] As described above, some antibodies of the invention bind to highly-conserved epitopes, and, thus, are not affected by point mutations in the Spike protein associated with variants of SARS-Cov-2. A nonlimiting list of examples of antibodies or antigen-binding fragments of the invention which bind equivalently to the SARS-CoV-2 reference isolate, USA/WA_CDC-WA1/2020, and each of the aforementioned variant isolates, include: An antibody with a HCVR based on the amino acid sequence set forth in SEQ ID NO: 1 or

fragment thereof, and a LCVR based on the amino acid sequence set forth in SEQ ID NO: 2 or fragment thereof; An antibody with a HCVR based on the amino acid sequence set forth in SEQ ID NO: 3 or fragment thereof, and a LCVR based on the amino acid sequence set forth in SEQ ID NO: 4 or fragment thereof; An antibody with a HCVR based on the amino acid sequence set forth in SEQ ID NO: 5 or fragment thereof, and a LCVR based on the amino acid sequence set forth in SEQ ID NO: 6 or fragment thereof; and An antibody with a HCVR based on the amino acid sequence set forth in SEQ ID NO: 19 or fragment thereof, and a LCVR based on the amino acid sequence set forth in SEQ ID NO: 20 or fragment thereof.

[0196] The foregoing antibodies of the invention neutralize SARS-CoV-2 and SARS-CoV-2 variants, including variants Alpha (U.K./B.1.1.7), Beta (South African/B.1.351), Gamma (Brazil/P.1), Delta (India/B.1.617.2), B.1.617 (L452R/E484Q) and Epsilon (California/B.1.429/427), either alone, or in combination. In some embodiments, the virus neutralizes the Alpha (U.K./B.1.1.7) variant of SARS-CoV-2, the Beta (South African/B.1.351) variant of SARS-CoV-2, the Gamma (Brazilian/P.1) variant of SARS-CoV-2, the Delta (India/B.1.617.2), B.1.617 (L452R/E484Q)), the Epsilon (California/B.1.429/427, New York/B.1.526/526.1) variant of SARS-CoV-2, the UK/Nigeria (B.1.525) variant of SARS-CoV-2, the Brazilian (P.2) variant of SARS-CoV-2, the lambda (C.37) variant of SARS-CoV-2, or the Omicron (B.1.1.529) variant of SARS-CoV-2. More particularly, certain antibodies of the invention bind the SARS-CoV-2 RBD at epitopes, which contain residues that are conserved among variants. In some embodiments, binding to such conserved residues prevents viral escape. In some embodiments, binding to such conserved residues allows binding across variants. Accordingly, a RBD amino acid substitution at a non-conserved or poorly-conserved residue position will have limited or no impact on binding of an antibody of the invention. Such non conserved or poorly-conserved substitutions in the RBD are commonly associated with SARS-CoV-2 variants. Thus, an RBD epitope of some antibodies of the invention may contain at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or more residues at RBD positions 356 (K), 370 (N), 372 (A), 374 (F), 378 (K), 384 (P), 417 (K), 420 (D), 455 (L), 456 (F), 460 (N), 466 (R), 473 (Y), 487 (N), 489 (Y), 501 (N), and 505 (Y). For example, an antibody of the invention may bind an RBD epitope in which the binding energy is relatively higher at residues at 417 (K), 420 (D), 455 (L), 456 (F), 460 (N), 473 (Y), 487 (N), 489 (Y), 501 (N), and 505 (Y). Likewise, another antibody of the invention may bind an RBD epitope in which the binding energy is relatively higher at residues at 370 (N), 372 (A), 374 (F), 378 (K), 384 (P). And yet another antibody

of the invention may bind an RBD epitope in which the binding energy is relatively higher at residues at 356 (K) and 466 (R). In some embodiments, the antibody contacts one or more residues at RBD positions 356 (K), 370 (N), 372 (A), 374 (F), 378 (K), 384 (P), 417 (K), 420 (D), 455 (L), 456 (F), 460 (N), 466 (R), 473 (Y), 487 (N), 489 (Y), 501 (N), and 505 (Y). In some embodiments, the antibody contacts one or more of 417 (K), 420 (D), 455 (L), 456 (F), 460 (N), 473 (Y), 487 (N), 489 (Y), 501 (N), and 505 (Y). In some embodiments, the antibody contacts residues at 370 (N), 372 (A), 374 (F), 378 (K), 384 (P). In some embodiments, the epitope is identified using alanine scanning.

[0197] In some embodiments, the antibody binds the SARS-CoV-2 RBD at epitopes, which contain residues that are not conserved.

[0198] In certain embodiments of the invention, for example, a composition (i.e., a mixture) of two or more of: An antibody with a HCVR based on the amino acid sequence set forth in SEQ ID NO: 1 or fragment thereof, and a LCVR based on the amino acid sequence set forth in SEQ ID NO: 2 or fragment thereof; An antibody with a HCVR based on the amino acid sequence set forth in SEQ ID NO: 3 or fragment thereof, and a LCVR based on the amino acid sequence set forth in SEQ ID NO: 4 or fragment thereof; An antibody with a HCVR based on the amino acid sequence set forth in SEQ ID NO: 5 or fragment thereof, and a LCVR based on the amino acid sequence set forth in SEQ ID NO: 6 or fragment thereof; An antibody with a HCVR based on the amino acid sequence set forth in SEQ ID NO: 19 or fragment thereof, and a LCVR based on the amino acid sequence set forth in SEQ ID NO: 20 or fragment thereof; and An antibody with a HCVR based on the amino acid sequence set forth in SEQ ID NO: 21 or fragment thereof, and a LCVR based on the amino acid sequence set forth in SEQ ID NO: 22 or fragment thereof, additively or synergistically neutralizes SARS-CoV-2, or a variant thereof, such as the Alpha (U.K./B.1.1.7), Beta (South African/B.1.351), Gamma (Brazil/P.1), Delta (India/B.1.617.2), B.1.617 (L452R/E484Q) and Epsilon (California/B.1.429/427). In some embodiments, the antibodies neutralize the Omicron variant. In some embodiments, the antibodies neutralize Alpha (U.K./B.1.1.7) variant of SARS-CoV-2, the Beta (South African/B.1.351) variant of SARS-CoV-2, the Gamma (Brazilian/P.1) variant of SARS-CoV-2, the Delta (India/B.1.617.2), B.1.617 (L452R/E484Q)), the Epsilon (California/B.1.429/427, New York/B.1.526/526.1) variant of SARS-CoV-2, the UK/Nigeria (B.1.525) variant of SARS-CoV-2, the Brazilian (P.2) variant

of SARS-CoV-2, the lambda (C.37) variant of SARS-CoV-2, or the Omicron (B.1.1.529) variant of SARS-CoV-2.

[0199] In some embodiments, an antibody of the invention alters the conformation of Spike protein upon binding of the antibody to the Spike protein. More particularly, in certain embodiments, an antibody of the invention binds a Spike protein epitope located on the outside face of the RBD domain of the SARS-CoV-2 RBD. In such embodiments, the epitope may be in close proximity to the N-terminal domain of a second Spike protein within the Spike trimer, and binding of the antibody inactivates the virus' ability to bind cells. Consequently, certain antibodies of the invention neutralize SARS-CoV-2 by the foregoing mechanism. More specifically, binding of such antibodies to the outer face of the RBD imparts its intrinsic neutralization through induction of a conformational change in the Spike protein that prevents virus uptake into the cells without competing for ACE2 binding. An example of an embodiment of the invention that alters conformation of the Spike protein upon binding is an antibody with a heavy chain variable region (HCVR) or fragment thereof and/or a light chain variable region (LCVR) or a fragment thereof derived from an antibody described herein as IMM20253, which contains HCVR and LCVR with amino acid sequences of SEQ ID NOS. 5 and 6, respectively.

[0200] In certain embodiments, an antibody of the invention that alters the conformation of Spike protein upon binding of the antibody to the Spike protein as part of its intrinsic neutralization activity, acts additively, and more preferentially synergistically, with other antibodies that compete for ACE2 binding as part of their intrinsic neutralization mechanism. An example of an embodiment of the invention that alters conformation of the Spike protein upon binding and acts additively, and more preferentially synergistically, with antibodies that block ACE2 binding, is an antibody with a heavy chain variable region (HCVR) or fragment thereof and/or a light chain variable region (LCVR) or a fragment thereof derived from an antibody described herein as IMM20253, which contains HCVR and LCVR with amino acid sequences of SEQ ID NOS. 5 and 6, respectively.

[0201] As described above, an isolated antibody or antigen-binding fragment thereof of the invention may contain a CH3 scaffold "epitope tag", comprising at least one modification of the wild-type amino acid sequence of the CH3 domain derived from an immunoglobulin Fc region. Accordingly, any of the aforementioned antibodies may have been engineered to contain a CH3 scaffold. The CH3 scaffold of such an isolated antibody or antigen-binding

fragment thereof may possess at least one modification of the wild-type sequence occurs within the AB, EF, or CD loops of the CH3 scaffold, including an amino acid substitution, deletion or insertion, for example. In certain embodiments, the epitope tag amino acid sequence contains a sequence derived from SIRP α or Sip. Alternatively, the epitope tag amino acid sequence contains a sequence derived from a constant light chain of an antibody. More particularly, the antibody epitope amino acid sequence of an isolated antibody or antigen-binding fragment thereof that contains a CH3 scaffold with an amino acid sequence set forth in SEQ ID Nos. 3-30, SEQ ID Nos. 33-57, or SEQ ID Nos. 60-67 of International Patent Application No. PCT/US2019/032780.

Compositions

[0202] Also provided herein are compositions comprising one or more antibodies provided herein. In some embodiments, provided herein a composition comprising two or more antibodies that bind to a Spike protein, wherein the antibodies bind to different epitopes. In some embodiments, the composition comprises an antibody that operates in an ACE2 independent mechanism and an antibody that operates through an ACE2 independent mechanism. In some embodiments, the multiple antibodies in the composition act synergistically to treat a SARS-CoV-2 infection in a subject. In some embodiments, the presence of multiple antibodies binding to different epitopes of a SARS-CoV-2 protein allows treatment of variants with mutations in one or more SARS-CoV-2 proteins, such as the Spike protein.

[0203] In some embodiments, provided herein is a composition comprising a variable heavy chain (VH) and a variable light chain (VL), wherein the antibody comprises a HCDR1 comprising the amino acid sequence SASGFTFSSFWMS (SEQ ID NO: 55); a HCDR2 comprising the amino acid sequence TIREDGSEKYYVD (SEQ ID NO: 56); and a HCDR3 comprising the amino acid sequence ARSKWLRGSFDY (SEQ ID NO: 57); wherein the antibody comprises a LCDR1 comprising the amino acid sequence TRRSGSIASNYVQ (SEQ ID NO: 58); a LCDR2 comprising the amino acid sequence YEDNQRP (SEQ ID NO: 59); and a LCDR3 comprising the amino acid sequence QSYDSSNPPGASWV (SEQ ID NO: 60). In some embodiments, the CDRs are defined according to North et al.

[0204] In some embodiments, provided herein is a composition comprising a variable heavy chain (VH) and a variable light chain (VL), wherein the antibody comprises a HCDR1

comprising the amino acid sequence SASGFTVSSNYMS (SEQ ID NO: 61); a HCDR2 comprising the amino acid sequence VIYAGGSTF (SEQ ID NO: 62); and a HCDR3 comprising the amino acid sequence ARDRGGYLDY (SEQ ID NO: 63); wherein the antibody comprises a LCDR1 comprising the amino acid sequence RASQGISNYLA (SEQ ID NO: 64); a LCDR2 comprising the amino acid sequence YAASTLQS (SEQ ID NO: 65); and a LCDR3 comprising the amino acid sequence QKYNSAPGLT (SEQ ID NO: 66). In some embodiments, the CDRs are defined according to North et al.

[0205] In some embodiments, provided herein is a composition comprising a variable heavy chain (VH) and a variable light chain (VL), wherein the antibody comprises a HCDR1 comprising the amino acid sequence TASGFTFSTYGMH (SEQ ID NO: 67); a HCDR2 comprising the amino acid sequence VISYDGSSKH (SEQ ID NO: 68); and a HCDR3 comprising the amino acid sequence ARDGQPPGWGNYFDY (SEQ ID NO: 69); wherein the antibody comprises a LCDR1 comprising the amino acid sequence GGNGIGSKSVY (SEQ ID NO: 70); a LCDR2 comprising the amino acid sequence YDDSDRPS (SEQ ID NO: 71); and a LCDR3 comprising the amino acid sequence QVWDSSSDPWV (SEQ ID NO: 72). In some embodiments, the CDRs are defined according to North et al.

[0206] In some embodiments, provided herein is a composition comprising a variable heavy chain (VH) and a variable light chain (VL), wherein the antibody comprises a HCDR1 comprising the amino acid sequence AASGFTFSTYGMH (SEQ ID NO: 109); a HCDR2 comprising the amino acid sequence VIWYNGINKH (SEQ ID NO: 110); and a HCDR3 comprising the amino acid sequence ARDWGTLTTLFDF (SEQ ID NO: 111); wherein the antibody comprises a LCDR1 comprising the amino acid sequence RASQSISSHLN (SEQ ID NO: 112); a LCDR2 comprising the amino acid sequence YGASSLQS (SEQ ID NO: 113); and a LCDR3 comprising the amino acid sequence QQSYSTPPWT (SEQ ID NO: 114). In some embodiments, the CDRs are defined according to North et al.

[0207] In some embodiments, provided herein is a composition comprising a first antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SASGFTFSSFWMS (SEQ ID NO: 55), a HCDR2 comprising the amino acid sequence of TIREDGSEKYYVD (SEQ ID NO: 56), and a HCDR3 comprising the amino acid sequence of ARSKWLRGSFDY (SEQ ID NO: 57); and a VL comprising a LCDR1 comprising the amino acid sequence of TRRSGSIASNYVQ (SEQ ID NO: 58), a LCDR2 comprising the amino acid sequence of YEDNQRPS (SEQ ID NO: 59), and a LCDR3 comprising the amino

acid sequence of QSYDSSNPPGASWV (SEQ ID NO: 60); and a second antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SASGFTVSSNYMS (SEQ ID NO: 61), a HCDR2 comprising the amino acid sequence of VIYAGGSTF (SEQ ID NO: 62), and a HCDR3 comprising the amino acid sequence of ARDRGGYLDY (SEQ ID NO: 63); and a VL comprising a LCDR1 comprising the amino acid sequence of RASQGISNYLA (SEQ ID NO: 64), a LCDR2 comprising the amino acid sequence of YAASTLQS (SEQ ID NO: 65), and a LCDR3 comprising the amino acid sequence of QKYNSAPGLT (SEQ ID NO: 66).

[0208] In some embodiments, provided herein is a composition comprising a first antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SASGFTFSSFWMS (SEQ ID NO: 55), a HCDR2 comprising the amino acid sequence of TIREDGSEKYYYVD (SEQ ID NO: 56), and a HCDR3 comprising the amino acid sequence of ARSKWLRGSFYD (SEQ ID NO: 57); and a VL comprising a LCDR1 comprising the amino acid sequence of TRRSGSIASNYVQ (SEQ ID NO: 58), a LCDR2 comprising the amino acid sequence of YEDNQRPS (SEQ ID NO: 59), and a LCDR3 comprising the amino acid sequence of QSYDSSNPPGASWV (SEQ ID NO: 60); and a second antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of TASGFTFSTYGMH (SEQ ID NO: 67), a HCDR2 comprising the amino acid sequence of VISYDGSSKH (SEQ ID NO: 68), and a HCDR3 comprising the amino acid sequence of ARDGQPPGWGNYFDY (SEQ ID NO: 69), and a VL comprising a LCDR1 comprising the amino acid sequence of GGNGIGSKSVY (SEQ ID NO: 70), a LCDR2 comprising the amino acid sequence of YDDSDRPS (SEQ ID NO: 71), and a LCDR3 comprising the amino acid sequence of QVWDSSSDPWV (SEQ ID NO: 72).

[0209] In some embodiments, provided herein is a composition comprising a first antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SASGFTFSSFWMS (SEQ ID NO: 55), a HCDR2 comprising the amino acid sequence of TIREDGSEKYYYVD (SEQ ID NO: 56), and a HCDR3 comprising the amino acid sequence of ARSKWLRGSFYD (SEQ ID NO: 57); and a VL comprising a LCDR1 comprising the amino acid sequence of TRRSGSIASNYVQ (SEQ ID NO: 58), a LCDR2 comprising the amino acid sequence of YEDNQRPS (SEQ ID NO: 59), and a LCDR3 comprising the amino acid sequence of QSYDSSNPPGASWV (SEQ ID NO: 60); and a second antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of

AASGFTFSTYGMH (SEQ ID NO: 109), a HCDR2 comprising the amino acid sequence of VIWYNGINKH (SEQ ID NO: 110), and a HCDR3 comprising the amino acid sequence of ARDWGTLTTLFDF (SEQ ID NO: 111); and a VL comprising a LCDR1 comprising the amino acid sequence of RASQSISSHLN (SEQ ID NO: 112), a LCDR2 comprising the amino acid sequence of YGASSLQS (SEQ ID NO: 113), and a LCDR3 comprising the amino acid sequence of QQSYSTPPWT (SEQ ID NO: 114).

[0210] In some embodiments, provided herein is a composition comprising a first antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SASGFTVSSNYMS (SEQ ID NO: 61), a HCDR2 comprising the amino acid sequence of VIYAGGSTF (SEQ ID NO: 62), and a HCDR3 comprising the amino acid sequence of ARDRGGYLDY (SEQ ID NO: 63); and a VL comprising a LCDR1 comprising the amino acid sequence of RASQGISNYLA (SEQ ID NO: 64), a LCDR2 comprising the amino acid sequence of YAASTLQS (SEQ ID NO: 65), and a LCDR3 comprising the amino acid sequence of QKYNSAPGLT (SEQ ID NO: 66); and a second antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of TASGFTFSTYGMH (SEQ ID NO: 67), a HCDR2 comprising the amino acid sequence of VISYDGSSKH (SEQ ID NO: 68), and a HCDR3 comprising the amino acid sequence of ARDGQPPGWGNYFDY (SEQ ID NO: 69); and a VL comprising a LCDR1 comprising the amino acid sequence of GGNGIGSKSVY (SEQ ID NO: 70), a LCDR2 comprising the amino acid sequence of YDDSDRPS (SEQ ID NO: 71), and a LCDR3 comprising the amino acid sequence of QVWDSSSDPWV (SEQ ID NO: 72).

[0211] In some embodiments, provided herein is a composition comprising a first antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SASGFTVSSNYMS (SEQ ID NO: 61), a HCDR2 comprising the amino acid sequence of VIYAGGSTF (SEQ ID NO: 62), and a HCDR3 comprising the amino acid sequence of ARDRGGYLDY (SEQ ID NO: 63); and a VL comprising a LCDR1 comprising the amino acid sequence of RASQGISNYLA (SEQ ID NO: 64), a LCDR2 comprising the amino acid sequence of YAASTLQS (SEQ ID NO: 65), and a LCDR3 comprising the amino acid sequence of QKYNSAPGLT (SEQ ID NO: 66); and a second antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of AASGFTFSTYGMH (SEQ ID NO: 109), a HCDR2 comprising the amino acid sequence of VIWYNGINKH (SEQ ID NO: 110), and a HCDR3 comprising the amino acid sequence of ARDWGTLTTLFDF (SEQ ID

NO: 111); and a VL comprising a LCDR1 comprising the amino acid sequence of RASQSISSHLN (SEQ ID NO: 112), a LCDR2 comprising the amino acid sequence of YGASSLQS (SEQ ID NO: 113), and a LCDR3 comprising the amino acid sequence of QQSYSTPPWT (SEQ ID NO: 114).

[0212] In some embodiments, provided herein is a composition comprising a first antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of TASGFTFSTYGMH (SEQ ID NO: 67), a HCDR2 comprising the amino acid sequence of VISYDGSSKH (SEQ ID NO: 68), and a HCDR3 comprising the amino acid sequence of ARDGQPPGWGNYFDY (SEQ ID NO: 69); and a VL comprising a LCDR1 comprising the amino acid sequence of GGNGIGSKSVY (SEQ ID NO: 70), a LCDR2 comprising the amino acid sequence of YDDSDRPS (SEQ ID NO: 71), and a LCDR3 comprising the amino acid sequence of QVWDSSSDPWV (SEQ ID NO: 72); and a second antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of AASGFTFSTYGMH (SEQ ID NO: 109), a HCDR2 comprising the amino acid sequence of VIWYNGINKH (SEQ ID NO: 110), and a HCDR3 comprising the amino acid sequence of ARDWGTLTTLFDF (SEQ ID NO: 111); and a VL comprising a LCDR1 comprising the amino acid sequence of RASQSISSHLN (SEQ ID NO: 112), a LCDR2 comprising the amino acid sequence of YGASSLQS (SEQ ID NO: 113), and a LCDR3 comprising the amino acid sequence of QQSYSTPPWT (SEQ ID NO: 114).

[0213] In some embodiments, provided herein is a composition comprising a first antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SASGFTFSSFWMS (SEQ ID NO: 55), a HCDR2 comprising the amino acid sequence of TIREDGSEKYYVD (SEQ ID NO: 56), and a HCDR3 comprising the amino acid sequence of ARSKWLRGSFDY (SEQ ID NO: 57); and a VL comprising a LCDR1 comprising the amino acid sequence of TRRSGSIASNYVQ (SEQ ID NO: 58), a LCDR2 comprising the amino acid sequence of YEDNQRPS (SEQ ID NO: 59), and a LCDR3 comprising the amino acid sequence of QSYDSSNPPGASWV (SEQ ID NO: 60); a second antibody comprising the amino acid sequence of SASGFTVSSNYMS (SEQ ID NO: 61), a HCDR2 comprising the amino acid sequence of VIYAGGSTF (SEQ ID NO: 62), and a HCDR3 comprising the amino acid sequence of ARDRGGYLDY (SEQ ID NO: 63); and a VL comprising a LCDR1 comprising the amino acid sequence of RASQGISNYLA (SEQ ID NO: 64), a LCDR2 comprising the amino acid sequence of YAASTLQS (SEQ ID NO: 65), and a LCDR3

comprising the amino acid sequence of QKYNSAPGLT (SEQ ID NO: 66); and a third antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of TASGFTFSTYGMH (SEQ ID NO: 67), a HCDR2 comprising the amino acid sequence of VISYDGSSKH (SEQ ID NO: 68), and a HCDR3 comprising the amino acid sequence of ARDGQPPGWGNYFDY (SEQ ID NO: 69); and a VL comprising a LCDR1 comprising the amino acid sequence of GGNGIGSKSVY (SEQ ID NO: 70), a LCDR2 comprising the amino acid sequence of YDDSDRPS (SEQ ID NO: 71), and a LCDR3 comprising the amino acid sequence of QVWDSSSDPWV (SEQ ID NO: 72).

[0214] In some embodiments, provided herein is a composition comprising a first antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SASGFTFSSFWMS (SEQ ID NO: 55), a HCDR2 comprising the amino acid sequence of TIREDGSEKYYYVD (SEQ ID NO: 56), and a HCDR3 comprising the amino acid sequence of ARSKWLRGSFDY (SEQ ID NO: 57); and a VL comprising a LCDR1 comprising the amino acid sequence of TRRSGSIASNYVQ (SEQ ID NO: 58), a LCDR2 comprising the amino acid sequence of YEDNQRPS (SEQ ID NO: 59), and a LCDR3 comprising the amino acid sequence of QSYDSSNPPGASWV (SEQ ID NO: 60); a second antibody comprising the amino acid sequence of SASGFTVSSNYMS (SEQ ID NO: 61), a HCDR2 comprising the amino acid sequence of VIYAGGSTF (SEQ ID NO: 62), and a HCDR3 comprising the amino acid sequence of ARDRGGYLDY (SEQ ID NO: 63); and a VL comprising a LCDR1 comprising the amino acid sequence of RASQGISNYLA (SEQ ID NO: 64), a LCDR2 comprising the amino acid sequence of YAASTLQS (SEQ ID NO: 65), and a LCDR3 comprising the amino acid sequence of QKYNSAPGLT (SEQ ID NO: 66); and a third antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of AASGFTFSTYGMH (SEQ ID NO: 109), a HCDR2 comprising the amino acid sequence of VIWYNGINKH (SEQ ID NO: 110), and a HCDR3 comprising the amino acid sequence of ARDWGTLTTLFDF (SEQ ID NO: 111); and a VL comprising a LCDR1 comprising the amino acid sequence of RASQSISSHLN (SEQ ID NO: 112), a LCDR2 comprising the amino acid sequence of YGASSLQS (SEQ ID NO: 113), and a LCDR3 comprising the amino acid sequence of QQSYSTPPWT (SEQ ID NO: 114).

[0215] In some embodiments, provided herein is a composition comprising a first antibody comprising the amino acid sequence of SASGFTVSSNYMS (SEQ ID NO: 61), a HCDR2 comprising the amino acid sequence of VIYAGGSTF (SEQ ID NO: 62), and a

HCDR3 comprising the amino acid sequence of ARDRGGYLDY (SEQ ID NO: 63); and a VL comprising a LCDR1 comprising the amino acid sequence of RASQGISNYLA (SEQ ID NO: 64), a LCDR2 comprising the amino acid sequence of YAASTLQS (SEQ ID NO: 65), and a LCDR3 comprising the amino acid sequence of QKYNSAPGLT (SEQ ID NO: 66); a second antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of TASGFTFSTYGMH (SEQ ID NO: 67), a HCDR2 comprising the amino acid sequence of VISYDGSSKH (SEQ ID NO: 68), and a HCDR3 comprising the amino acid sequence of ARDGQPPGWGNYFDY (SEQ ID NO: 69); and a VL comprising a LCDR1 comprising the amino acid sequence of GGNGIGSKSVY (SEQ ID NO: 70), a LCDR2 comprising the amino acid sequence of YDDSDRPS (SEQ ID NO: 71), and a LCDR3 comprising the amino acid sequence of QVWDSSSDPWV (SEQ ID NO: 72); and a VL comprising a LCDR1 comprising the amino acid sequence of, a LCDR2 comprising the amino acid sequence of, and a LCDR3 comprising the amino acid sequence of ; and a third antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of AASGFTFSTYGMH (SEQ ID NO: 109), a HCDR2 comprising the amino acid sequence of VIWYNGINKH (SEQ ID NO: 110), and a HCDR3 comprising the amino acid sequence of ARDWGTLTTLFDF (SEQ ID NO: 111); and a VL comprising a LCDR1 comprising the amino acid sequence of RASQSISSHLN (SEQ ID NO: 112), a LCDR2 comprising the amino acid sequence of YGASSLQS (SEQ ID NO: 113), and a LCDR3 comprising the amino acid sequence of QQSYSTPPWT (SEQ ID NO: 114).

[0216] In some embodiments, provided herein is a composition comprising a first antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SASGFTFSSFWMS (SEQ ID NO: 55), a HCDR2 comprising the amino acid sequence of TIREDGSEKYYVD (SEQ ID NO: 56), and a HCDR3 comprising the amino acid sequence of ARSKWLRGSFDY (SEQ ID NO: 57); and a VL comprising a LCDR1 comprising the amino acid sequence of TRRSGSIASNYVQ (SEQ ID NO: 58), a LCDR2 comprising the amino acid sequence of YEDNQRPS (SEQ ID NO: 59), and a LCDR3 comprising the amino acid sequence of QSYDSSNPPGASWV (SEQ ID NO: 60); a second antibody comprising the amino acid sequence of SASGFTVSSNYMS (SEQ ID NO: 61), a HCDR2 comprising the amino acid sequence of VIYAGGSTF (SEQ ID NO: 62), and a HCDR3 comprising the amino acid sequence of ARDRGGYLDY (SEQ ID NO: 63); and a VL comprising a LCDR1 comprising the amino acid sequence of RASQGISNYLA (SEQ ID NO: 64), a LCDR2 comprising the amino acid sequence of YAASTLQS (SEQ ID NO: 65), and a LCDR3

comprising the amino acid sequence of QKYNSAPGLT (SEQ ID NO: 66); a third antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of TASGFTFSTYGMH (SEQ ID NO: 67), a HCDR2 comprising the amino acid sequence of VISYDGSSKH (SEQ ID NO: 68), and a HCDR3 comprising the amino acid sequence of ARDGQPPGWGNYFDY (SEQ ID NO: 69); and a VL comprising a LCDR1 comprising the amino acid sequence of GGNGIGSKSVY (SEQ ID NO: 70), a LCDR2 comprising the amino acid sequence of YDDSDRPS (SEQ ID NO: 71), and a LCDR3 comprising the amino acid sequence of QVWDSSSDPWV (SEQ ID NO: 72); and a fourth antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of AASGFTFSTYGMH (SEQ ID NO: 109), a HCDR2 comprising the amino acid sequence of VIWYNGINKH (SEQ ID NO: 110), and a HCDR3 comprising the amino acid sequence of ARDWGTLTTLFDF (SEQ ID NO: 111); and a VL comprising a LCDR1 comprising the amino acid sequence of RASQSISSHLN (SEQ ID NO: 112), a LCDR2 comprising the amino acid sequence of YGASSLQS (SEQ ID NO: 113), and a LCDR3 comprising the amino acid sequence of QQSYSTPPWT (SEQ ID NO: 114).

[0217] Pharmaceutical compositions of the invention contain one or more isolated antibodies or antigen-binding fragments thereof of the invention and a pharmaceutically acceptable carrier or diluent. In one embodiment of the invention, the pharmaceutical composition contains only one of the Spike-binding antibodies described herein. Other pharmaceutical composition of the invention contain a mixture of different Spike-binding antibodies which are described herein, such as, for example, at least 2, at least 3, at least 4, or at least 5, or at least 6 or more Spike-binding antibodies. For example, a pharmaceutical composition of two or more of: An antibody with a HCVR based on the amino acid sequence set forth in SEQ ID NO: 1 or fragment thereof, and a LCVR based on the amino acid sequence set forth in SEQ ID NO: 2 or fragment thereof; An antibody with a HCVR based on the amino acid sequence set forth in SEQ ID NO: 3 or fragment thereof, and a LCVR based on the amino acid sequence set forth in SEQ ID NO: 4 or fragment thereof; An antibody with a HCVR based on the amino acid sequence set forth in SEQ ID NO: 5 or fragment thereof, and a LCVR based on the amino acid sequence set forth in SEQ ID NO: 6 or fragment thereof; an antibody with a HCVR based on the amino acid sequence set forth in SEQ ID NO: 19 or fragment thereof, and a LCVR based on the amino acid sequence set forth in SEQ ID NO: 20 or fragment thereof, synergistically neutralizes SARS-CoV-2, or a variant thereof, and An antibody with a HCVR based on the amino acid sequence set forth in SEQ ID NO: 21

or fragment thereof, and a LCVR based on the amino acid sequence set forth in SEQ ID NO: 22 or fragment thereof, additively or synergistically neutralizes SARS-CoV-2, or a variant thereof, such as the Alpha (U.K./B.1.1.7), Beta (South African/B.1.351), Gamma (Brazil/P.1), Delta (India/B.1.617.2), B.1.617 (L452R/E484Q) and Epsilon (California/B.1.429/427). In some embodiments, the viruses neutralize Alpha (U.K./B.1.1.7) variant of SARS-CoV-2, the Beta (South African/B.1.351) variant of SARS-CoV-2, the Gamma (Brazilian/P.1) variant of SARS-CoV-2, the Delta (India/B.1.617.2), B.1.617 (L452R/E484Q)), the Epsilon (California/B.1.429/427, New York/B.1.526/526.1) variant of SARS-CoV-2, the UK/Nigeria (B.1.525) variant of SARS-CoV-2, the Brazilian (P.2) variant of SARS-CoV-2, the lambda (C.37) variant of SARS-CoV-2, or the Omicron (B.1.1.529) variant of SARS-CoV-2.

[0218] In some embodiments a pharmaceutical composition of the invention further contains a second therapeutic agent. For example, a pharmaceutical composition of the invention may also contain an anti-inflammatory agent or an antiviral agent.

[0219] In some embodiments, the second agent is an antibody. In some aspects, the second agent is casirivimab (REGN10933). In some aspects, the second agent is imdevimab (REGN10987). In some aspects, the second agent is a combination of the neutralizing antibodies, casirivimab and imdevimab (REGEN-COV, previously known as REGN-COV-2) (ClinicalTrials.gov number, NCT04452318 and NCT04425629). The two antibodies can simultaneously bind to two independent epitopes on the RBD (Hansen J. et.al., Studies in humanized mice and convalescent humans yield a SARS-CoV-2 antibody cocktail. 369(6506):1010-1014 (2020); Baum A. et.al, Antibody cocktail to SARS-CoV-2 Spike protein prevents rapid mutational escape seen with individual antibodies, Science 369(6506):1014-1018 (2020)). In some aspects, the second agent is bamlanivimab (LY3819253). In some aspects, the second agent is etesevimab (LY3832479). In some aspects, the second agent is a combination of the neutralizing antibodies, bamlanivimab and etesevimab (ClinicalTrials.gov number, NCT04427501, Dougan M. et.al., Bamlanivimab plus Etesevimab in Mild or Moderate Covid-19. N Engl J med 385(15):1382-1392 (2021)). In some aspects, the second agent is sotrovimab (ClinicalTrials.gov number, NCT04545060, Gupta A. et.al., Early Treatment for Covid-19 with SARS-CoV-2 Neutralizing antibody sotrovimab. N Engl J med 385:1941-1950 (2021)).

[0220] As stated above, antibodies and pharmaceutical compositions of the invention can be used in methods for preventing or treating, a SARS-CoV-2 infection in subject. Accordingly, antibodies and pharmaceutical compositions of the invention are useful for treating the disease caused by SARS-CoV-2, commonly referred to as COVID-19, or simply COVID. A pharmaceutical composition of the invention is typically administered to subject in need thereof by injecting the composition into the body of the subject subcutaneously, intravenously or intramuscularly.

Methods of Treatment

[0221] Provided herein is a method of treating or preventing a SARS-CoV-2 infection in a subject comprising administering an antibody provided herein to the subject. In some embodiments, the method comprises administering one antibody provided herein. In some embodiments, the method comprises administering two or more antibodies provided herein. In some embodiments, the method comprises administering three or more, or four or more antibodies provided herein.

[0222] In some embodiments, provided herein is a method of treating or preventing a SARS-CoV-2 infection in a subject comprising administering an antibody that binds to a Spike protein comprising a variable heavy chain (VH) and a variable light chain (VL), wherein the antibody comprises a HCDR1 comprising the amino acid sequence SASGFTFSSFWMS (SEQ ID NO: 55); a HCDR2 comprising the amino acid sequence TIREDGSEKYYVD (SEQ ID NO: 56); and a HCDR3 comprising the amino acid sequence ARSKWLRGSFDY (SEQ ID NO: 57); wherein the antibody comprises a LCDR1 comprising the amino acid sequence TRRSGSIASNYVQ (SEQ ID NO: 58); a LCDR2 comprising the amino acid sequence YEDNQRPS (SEQ ID NO: 59); and a LCDR3 comprising the amino acid sequence QSYDSSNPPGASWV (SEQ ID NO: 60).

[0223] In some embodiments, the method comprises administering an antibody comprising one or more CDR sequences and/or VH and VL sequences of IMM20184. In some embodiments, the method comprises administering an antibody comprising one or more CDR sequences and/or VH and VL sequences of IMM20184 as a monotherapy. In some embodiments, the method comprises administering an antibody comprising one or more CDR sequences and/or VH and VL sequences of IMM20184 as a combination therapy. In some embodiments, the method comprises administering an antibody comprising one or more CDR

sequences and/or VH and VL sequences of IMM20184 in combination with one or more additional antibodies provided herein. In some embodiments, the antibody comprising one or more CDR sequences and/or VH and VL sequences of IMM20184 is administered simultaneously with one or more additional antibodies provided herein. In some embodiments, the antibody comprising one or more CDR sequences and/or VH and VL sequences of IMM20184 is administered sequentially with one or more additional antibodies provided herein.

[0224] In some embodiments, provided herein is a method of treating or preventing a SARS-CoV-2 infection in a subject comprising administering an antibody that binds to a Spike protein comprising a variable heavy chain (VH) and a variable light chain (VL), wherein the antibody comprises a HCDR1 comprising the amino acid sequence SASGFTVSSNYMS (SEQ ID NO: 61); a HCDR2 comprising the amino acid sequence VIYAGGSTF (SEQ ID NO: 62); and a HCDR3 comprising the amino acid sequence ARDRGGYLDY (SEQ ID NO: 63); wherein the antibody comprises a LCDR1 comprising the amino acid sequence RASQGISNYLA (SEQ ID NO: 64); a LCDR2 comprising the amino acid sequence YAASTLQS (SEQ ID NO: 65); and a LCDR3 comprising the amino acid sequence QKYNSAPGLT (SEQ ID NO: 66).

[0225] In some embodiments, the method comprises administering an antibody comprising one or more CDR sequences and/or VH and VL sequences of IMM20190. In some embodiments, the method comprises administering an antibody comprising one or more CDR sequences and/or VH and VL sequences of IMM20190 as a monotherapy. In some embodiments, the method comprises administering an antibody comprising one or more CDR sequences and/or VH and VL sequences of IMM20190 as a combination therapy. In some embodiments, the method comprises administering an antibody comprising one or more CDR sequences and/or VH and VL sequences of IMM20190 in combination with one or more additional antibodies provided herein. In some embodiments, the antibody comprising one or more CDR sequences and/or VH and VL sequences of IMM20190 is administered simultaneously with one or more additional antibodies provided herein. In some embodiments, the antibody comprising one or more CDR sequences and/or VH and VL sequences of IMM20190 is administered sequentially with one or more additional antibodies provided herein.

[0226] In some embodiments, provided herein is a method of treating or preventing a SARS-CoV-2 infection in a subject comprising administering an antibody that binds to a Spike protein comprising a variable heavy chain (VH) and a variable light chain (VL), wherein the antibody comprises a HCDR1 comprising the amino acid sequence TASGFTFSTYGMH (SEQ ID NO: 67); a HCDR2 comprising the amino acid sequence VISYDGSSKH (SEQ ID NO: 68); and a HCDR3 comprising the amino acid sequence ARDGQPPGWGNYFDY (SEQ ID NO: 69); wherein the antibody comprises a LCDR1 comprising the amino acid sequence GGNGIGSKSVY (SEQ ID NO: 70); a LCDR2 comprising the amino acid sequence YDDSDRPS (SEQ ID NO: 71); and a LCDR3 comprising the amino acid sequence QVWDSSSDPWV (SEQ ID NO: 72).

[0227] In some embodiments, provided herein is a method of treating or preventing an infection with an Omicron variant of SARS-CoV-2 in a subject comprising administering an antibody that binds to a Spike protein comprising a variable heavy chain (VH) and a variable light chain (VL), wherein the antibody comprises a HCDR1 comprising the amino acid sequence TASGFTFSTYGMH (SEQ ID NO: 67); a HCDR2 comprising the amino acid sequence VISYDGSSKH (SEQ ID NO: 68); and a HCDR3 comprising the amino acid sequence ARDGQPPGWGNYFDY (SEQ ID NO: 69); wherein the antibody comprises a LCDR1 comprising the amino acid sequence GGNGIGSKSVY (SEQ ID NO: 70); a LCDR2 comprising the amino acid sequence YDDSDRPS (SEQ ID NO: 71); and a LCDR3 comprising the amino acid sequence QVWDSSSDPWV (SEQ ID NO: 72). In some embodiments, the method further comprises administering a second antibody.

[0228] In some embodiments, the method comprises administering an antibody comprising one or more CDR sequences and/or VH and VL sequences of IMM20253. In some embodiments, the method comprises administering an antibody comprising one or more CDR sequences and/or VH and VL sequences of IMM20253 as a monotherapy. In some embodiments, the method comprises administering an antibody comprising one or more CDR sequences and/or VH and VL sequences of IMM20253 as a combination therapy. In some embodiments, the method comprises administering an antibody comprising one or more CDR sequences and/or VH and VL sequences of IMM20253 in combination with one or more additional antibodies provided herein. In some embodiments, the antibody comprising one or more CDR sequences and/or VH and VL sequences of IMM20253 is administered simultaneously with one or more additional antibodies provided herein. In some

embodiments, the antibody comprising one or more CDR sequences and/or VH and VL sequences of IMM20253 is administered sequentially with one or more additional antibodies provided herein.

[0229] In some embodiments, provided herein is a method of treating or preventing a SARS-CoV-2 infection in a subject comprising administering an antibody that binds to a Spike protein comprising a variable heavy chain (VH) and a variable light chain (VL), wherein the antibody comprises a HCDR1 comprising the amino acid sequence AASGFTFSTYGMH (SEQ ID NO: 109); a HCDR2 comprising the amino acid sequence VIWYNGINKH (SEQ ID NO: 110); and a HCDR3 comprising the amino acid sequence ARDWGTLTTLFDF (SEQ ID NO: 111); wherein the antibody comprises a LCDR1 comprising the amino acid sequence RASQSISSHLN (SEQ ID NO: 112); a LCDR2 comprising the amino acid sequence YGASSLQS (SEQ ID NO: 113); and a LCDR3 comprising the amino acid sequence QQSYSTPPWT (SEQ ID NO: 114).

[0230] In some embodiments, provided herein is a method of treating or preventing an infection with an Omicron variant of SARS-CoV-2 a subject comprising administering an antibody that binds to a Spike protein comprising a variable heavy chain (VH) and a variable light chain (VL), wherein the antibody comprises a HCDR1 comprising the amino acid sequence AASGFTFSTYGMH (SEQ ID NO: 109); a HCDR2 comprising the amino acid sequence VIWYNGINKH (SEQ ID NO: 110); and a HCDR3 comprising the amino acid sequence ARDWGTLTTLFDF (SEQ ID NO: 111); wherein the antibody comprises a LCDR1 comprising the amino acid sequence RASQSISSHLN (SEQ ID NO: 112); a LCDR2 comprising the amino acid sequence YGASSLQS (SEQ ID NO: 113); and a LCDR3 comprising the amino acid sequence QQSYSTPPWT (SEQ ID NO: 114). In some embodiments, the method further comprises administering a second antibody.

[0231] In some embodiments, the method comprises administering an antibody comprising one or more CDR sequences and/or VH and VL sequences of IMM20279. In some embodiments, the method comprises administering an antibody comprising one or more CDR sequences and/or VH and VL sequences of IMM20279 as a monotherapy. In some embodiments, the method comprises administering an antibody comprising one or more CDR sequences and/or VH and VL sequences of IMM20279 as a combination therapy. In some embodiments, the method comprises administering an antibody comprising one or more CDR sequences and/or VH and VL sequences of IMM20279 in combination with one or more

additional antibodies provided herein. In some embodiments, the antibody comprising one or more CDR sequences and/or VH and VL sequences of IMM20279 is administered simultaneously with one or more additional antibodies provided herein. In some embodiments, the antibody comprising one or more CDR sequences and/or VH and VL sequences of IMM20279 is administered sequentially with one or more additional antibodies provided herein.

[0232] In some embodiments, provided herein is a method of treating or preventing a SARS-CoV-2 infection in a subject comprising administering a combination of two antibodies that bind to a Spike protein comprising a first antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SASGFTFSSFWMS (SEQ ID NO: 55), a HCDR2 comprising the amino acid sequence of TIREDGSEKYYVD (SEQ ID NO: 56), and a HCDR3 comprising the amino acid sequence of ARSKWLRGSFDY (SEQ ID NO: 57); and a VL comprising a LCDR1 comprising the amino acid sequence of TRRSGSIASNYVQ (SEQ ID NO: 58), a LCDR2 comprising the amino acid sequence of YEDNQRP (SEQ ID NO: 59), and a LCDR3 comprising the amino acid sequence of QSYDSSNPPGASWV (SEQ ID NO: 60); and a second antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SASGFTVSSNYMS (SEQ ID NO: 61), a HCDR2 comprising the amino acid sequence of VIYAGGSTF (SEQ ID NO: 62), and a HCDR3 comprising the amino acid sequence of ARDRGGYLDY (SEQ ID NO: 63); and a VL comprising a LCDR1 comprising the amino acid sequence of RASQGISNYLA (SEQ ID NO: 64), a LCDR2 comprising the amino acid sequence of YAASTLQS (SEQ ID NO: 65), and a LCDR3 comprising the amino acid sequence of QKYNSAPGLT (SEQ ID NO: 66).

[0233] In some embodiments, provided herein is a method of treating or preventing a SARS-CoV-2 infection in a subject comprising administering a combination of two antibodies that bind to a Spike protein comprising a first antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SASGFTFSSFWMS (SEQ ID NO: 55), a HCDR2 comprising the amino acid sequence of TIREDGSEKYYVD (SEQ ID NO: 56), and a HCDR3 comprising the amino acid sequence of ARSKWLRGSFDY (SEQ ID NO: 57); and a VL comprising a LCDR1 comprising the amino acid sequence of TRRSGSIASNYVQ (SEQ ID NO: 58), a LCDR2 comprising the amino acid sequence of YEDNQRP (SEQ ID NO: 59), and a LCDR3 comprising the amino acid sequence of

QSYDSSNPPGASWV (SEQ ID NO: 60); and a second antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of TASGFTFSTYGMH (SEQ ID NO: 67), a HCDR2 comprising the amino acid sequence of VISYDGSSKH (SEQ ID NO: 68), and a HCDR3 comprising the amino acid sequence of ARDGQPPGWGNYFDY (SEQ ID NO: 69), and a VL comprising a LCDR1 comprising the amino acid sequence of GGNGIGSKSVY (SEQ ID NO: 70), a LCDR2 comprising the amino acid sequence of YDDSDRPS (SEQ ID NO: 71), and a LCDR3 comprising the amino acid sequence of QVWDSSSDPWV (SEQ ID NO: 72).

[0234] In some embodiments, provided herein is a method of treating or preventing a SARS-CoV-2 infection in a subject comprising administering a combination of two antibodies that bind to a Spike protein comprising a first antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SASGFTFSSFWMS (SEQ ID NO: 55), a HCDR2 comprising the amino acid sequence of TIREDGSEKYYVD (SEQ ID NO: 56), and a HCDR3 comprising the amino acid sequence of ARSKWLGRGSFDY (SEQ ID NO: 57); and a VL comprising a LCDR1 comprising the amino acid sequence of TRRSGSIASNYVQ (SEQ ID NO: 58), a LCDR2 comprising the amino acid sequence of YEDNQRPS (SEQ ID NO: 59), and a LCDR3 comprising the amino acid sequence of QSYDSSNPPGASWV (SEQ ID NO: 60); and a second antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of AASGFTFSTYGMH (SEQ ID NO: 109), a HCDR2 comprising the amino acid sequence of VIWYNGINKH (SEQ ID NO: 110), and a HCDR3 comprising the amino acid sequence of ARDWGTLTTLFDF (SEQ ID NO: 111); and a VL comprising a LCDR1 comprising the amino acid sequence of RASQSISSHLN (SEQ ID NO: 112), a LCDR2 comprising the amino acid sequence of YGASSLQS (SEQ ID NO: 113), and a LCDR3 comprising the amino acid sequence of QQSYSTPPWT (SEQ ID NO: 114).

[0235] In some embodiments, provided herein is a method of treating or preventing a SARS-CoV-2 infection in a subject comprising administering a combination of two antibodies that bind to a Spike protein comprising a first antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SASGFTVSSNYMS (SEQ ID NO: 61), a HCDR2 comprising the amino acid sequence of VIYAGGSTF (SEQ ID NO: 62), and a HCDR3 comprising the amino acid sequence of ARDRGGYLDY (SEQ ID NO: 63); and a VL comprising a LCDR1 comprising the amino acid sequence of RASQGISNYLA

(SEQ ID NO: 64), a LCDR2 comprising the amino acid sequence of YAASTLQS (SEQ ID NO: 65), and a LCDR3 comprising the amino acid sequence of QKYNSAPGLT (SEQ ID NO: 66); and a second antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of TASGFTFSTYGMH (SEQ ID NO: 67), a HCDR2 comprising the amino acid sequence of VISYDGSSKH (SEQ ID NO: 68), and a HCDR3 comprising the amino acid sequence of ARDGQPPGWGNYFDY (SEQ ID NO: 69); and a VL comprising a LCDR1 comprising the amino acid sequence of GGNGIGSKSVY (SEQ ID NO: 70), a LCDR2 comprising the amino acid sequence of YDDSDRPS (SEQ ID NO: 71), and a LCDR3 comprising the amino acid sequence of QVWDSSSDPWV (SEQ ID NO: 72).

[0236] In some embodiments, provided herein is a method of treating or preventing a SARS-CoV-2 infection in a subject comprising administering a combination of two antibodies that bind to a Spike protein comprising a first antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SASGFTVSSNYMS (SEQ ID NO: 61), a HCDR2 comprising the amino acid sequence of VIYAGGSTF (SEQ ID NO: 62), and a HCDR3 comprising the amino acid sequence of ARDRGGYLDY (SEQ ID NO: 63); and a VL comprising a LCDR1 comprising the amino acid sequence of RASQGISNYLA (SEQ ID NO: 64), a LCDR2 comprising the amino acid sequence of YAASTLQS (SEQ ID NO: 65), and a LCDR3 comprising the amino acid sequence of QKYNSAPGLT (SEQ ID NO: 66); and a second antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of AASGFTFSTYGMH (SEQ ID NO: 109), a HCDR2 comprising the amino acid sequence of VIWYNGINKH (SEQ ID NO: 110), and a HCDR3 comprising the amino acid sequence of ARDWGTLTTLFDF (SEQ ID NO: 111); and a VL comprising a LCDR1 comprising the amino acid sequence of RASQSISSHLN (SEQ ID NO: 112), a LCDR2 comprising the amino acid sequence of YGASSLQS (SEQ ID NO: 113), and a LCDR3 comprising the amino acid sequence of QQSYSTPPWT (SEQ ID NO: 114).

[0237] In some embodiments, provided herein is a method of treating or preventing a SARS-CoV-2 infection in a subject comprising administering a combination of two antibodies that bind to a Spike protein comprising a first antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of TASGFTFSTYGMH (SEQ ID NO: 67), a HCDR2 comprising the amino acid sequence of VISYDGSSKH (SEQ ID NO: 68), and a HCDR3 comprising the amino acid sequence of ARDGQPPGWGNYFDY (SEQ ID NO: 69); and a VL comprising a LCDR1 comprising the amino acid sequence of

GGNGIGSKSVY (SEQ ID NO: 70), a LCDR2 comprising the amino acid sequence of YDDSDRPS (SEQ ID NO: 71), and a LCDR3 comprising the amino acid sequence of QVWDSSSDPWV (SEQ ID NO: 72); and a second antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of AASGFTFSTYGMH (SEQ ID NO: 109), a HCDR2 comprising the amino acid sequence of VIWYNGINKH (SEQ ID NO: 110), and a HCDR3 comprising the amino acid sequence of ARDWGTLTTLFDF (SEQ ID NO: 111); and a VL comprising a LCDR1 comprising the amino acid sequence of RASQSISSHLN (SEQ ID NO: 112), a LCDR2 comprising the amino acid sequence of YGASSLQS (SEQ ID NO: 113), and a LCDR3 comprising the amino acid sequence of QQSYSTPPWT (SEQ ID NO: 114).

[0238] In some embodiments, provided herein is a method of treating or preventing a SARS-CoV-2 infection in a subject comprising administering a combination of three antibodies that bind to a Spike protein comprising a first antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SASGFTFSSFWMS (SEQ ID NO: 55), a HCDR2 comprising the amino acid sequence of TIREDGSEKYYVD (SEQ ID NO: 56), and a HCDR3 comprising the amino acid sequence of ARSKWLRGSFDY (SEQ ID NO: 57); and a VL comprising a LCDR1 comprising the amino acid sequence of TRRSGSIASNYVQ (SEQ ID NO: 58), a LCDR2 comprising the amino acid sequence of YEDNQRPS (SEQ ID NO: 59), and a LCDR3 comprising the amino acid sequence of QSYDSSNPPGASWV (SEQ ID NO: 60); a second antibody comprising the amino acid sequence of SASGFTVSSNYMS (SEQ ID NO: 61), a HCDR2 comprising the amino acid sequence of VIYAGGSTF (SEQ ID NO: 62), and a HCDR3 comprising the amino acid sequence of ARDRGGYLDY (SEQ ID NO: 63); and a VL comprising a LCDR1 comprising the amino acid sequence of RASQGISNYLA (SEQ ID NO: 64), a LCDR2 comprising the amino acid sequence of YAASTLQS (SEQ ID NO: 65), and a LCDR3 comprising the amino acid sequence of QKYNSAPGLT (SEQ ID NO: 66); and a third antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of TASGFTFSTYGMH (SEQ ID NO: 67), a HCDR2 comprising the amino acid sequence of VISYDGSSKH (SEQ ID NO: 68), and a HCDR3 comprising the amino acid sequence of ARDGQPPGWGNYFDY (SEQ ID NO: 69); and a VL comprising a LCDR1 comprising the amino acid sequence of GGNGIGSKSVY (SEQ ID NO: 70), a LCDR2 comprising the amino acid sequence of YDDSDRPS (SEQ ID NO: 71), and a LCDR3 comprising the amino acid sequence of QVWDSSSDPWV (SEQ ID NO: 72).

[0239] In some embodiments, provided herein is a method of treating or preventing a SARS-CoV-2 infection in a subject comprising administering a combination of three antibodies that bind to a Spike protein comprising a first antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SASGFTFSSFWMS (SEQ ID NO: 55), a HCDR2 comprising the amino acid sequence of TIREDGSEKYYVD (SEQ ID NO: 56), and a HCDR3 comprising the amino acid sequence of ARSKWLRGSDY (SEQ ID NO: 57); and a VL comprising a LCDR1 comprising the amino acid sequence of TRRSGSIASNYVQ (SEQ ID NO: 58), a LCDR2 comprising the amino acid sequence of YEDNQRPS (SEQ ID NO: 59), and a LCDR3 comprising the amino acid sequence of QSYDSSNPPGASWV (SEQ ID NO: 60); a second antibody comprising the amino acid sequence of SASGFTVSSNYMS (SEQ ID NO: 61), a HCDR2 comprising the amino acid sequence of VIYAGGSTF (SEQ ID NO: 62), and a HCDR3 comprising the amino acid sequence of ARDRGGYLDY (SEQ ID NO: 63); and a VL comprising a LCDR1 comprising the amino acid sequence of RASQGISNYLA (SEQ ID NO: 64), a LCDR2 comprising the amino acid sequence of YAASTLQS (SEQ ID NO: 65), and a LCDR3 comprising the amino acid sequence of QKYNSAPGLT (SEQ ID NO: 66); and a third antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of AASGFTFSTYGMH (SEQ ID NO: 109), a HCDR2 comprising the amino acid sequence of VIWYNGINKH (SEQ ID NO: 110), and a HCDR3 comprising the amino acid sequence of ARDWGTLTTLFDF (SEQ ID NO: 111); and a VL comprising a LCDR1 comprising the amino acid sequence of RASQSISSHLN (SEQ ID NO: 112), a LCDR2 comprising the amino acid sequence of YGASSLQS (SEQ ID NO: 113), and a LCDR3 comprising the amino acid sequence of QQSYSTPPWT (SEQ ID NO: 114).

[0240] In some embodiments, provided herein is a method of treating or preventing a SARS-CoV-2 infection in a subject comprising administering a combination of three antibodies that bind to a Spike protein comprising a first antibody comprising the amino acid sequence of SASGFTVSSNYMS (SEQ ID NO: 61), a HCDR2 comprising the amino acid sequence of VIYAGGSTF (SEQ ID NO: 62), and a HCDR3 comprising the amino acid sequence of ARDRGGYLDY (SEQ ID NO: 63); and a VL comprising a LCDR1 comprising the amino acid sequence of RASQGISNYLA (SEQ ID NO: 64), a LCDR2 comprising the amino acid sequence of YAASTLQS (SEQ ID NO: 65), and a LCDR3 comprising the amino acid sequence of QKYNSAPGLT (SEQ ID NO: 66); a second antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of TASGFTFSTYGMH (SEQ ID

NO: 67), a HCDR2 comprising the amino acid sequence of VISYDGSSKH (SEQ ID NO: 68), and a HCDR3 comprising the amino acid sequence of ARDGQPPGWGNYFDY (SEQ ID NO: 69); and a VL comprising a LCDR1 comprising the amino acid sequence of GGNGIGSKSVY (SEQ ID NO: 70), a LCDR2 comprising the amino acid sequence of YDDSDRPS (SEQ ID NO: 71), and a LCDR3 comprising the amino acid sequence of QVWDSSSDPWV (SEQ ID NO: 72); and a VL comprising a LCDR1 comprising the amino acid sequence of, a LCDR2 comprising the amino acid sequence of, and a LCDR3 comprising the amino acid sequence of ; and a third antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of AASGFTFSTYGMH (SEQ ID NO: 109), a HCDR2 comprising the amino acid sequence of VIWYNGINKH (SEQ ID NO: 110), and a HCDR3 comprising the amino acid sequence of ARDWGTLTTLFDF (SEQ ID NO: 111); and a VL comprising a LCDR1 comprising the amino acid sequence of RASQSISSHLN (SEQ ID NO: 112), a LCDR2 comprising the amino acid sequence of YGASSLQS (SEQ ID NO: 113), and a LCDR3 comprising the amino acid sequence of QQSYSTPPWT (SEQ ID NO: 114).

[0241] In some embodiments, provided herein is a method of treating or preventing a SARS-CoV-2 infection in a subject comprising administering a combination of four antibodies that bind to a Spike protein comprising a first antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SASGFTFSSFWMS (SEQ ID NO: 55), a HCDR2 comprising the amino acid sequence of TIREDGSEKYYVD (SEQ ID NO: 56), and a HCDR3 comprising the amino acid sequence of ARSKWLRGSFDY (SEQ ID NO: 57); and a VL comprising a LCDR1 comprising the amino acid sequence of TRRSGSIASNYVQ (SEQ ID NO: 58), a LCDR2 comprising the amino acid sequence of YEDNQRPS (SEQ ID NO: 59), and a LCDR3 comprising the amino acid sequence of QSYDSSNPPGASWV (SEQ ID NO: 60); a second antibody comprising the amino acid sequence of SASGFTVSSNYMS (SEQ ID NO: 61), a HCDR2 comprising the amino acid sequence of VIYAGGSTF (SEQ ID NO: 62), and a HCDR3 comprising the amino acid sequence of ARDRGGYLDY (SEQ ID NO: 63); and a VL comprising a LCDR1 comprising the amino acid sequence of RASQGISNYLA (SEQ ID NO: 64), a LCDR2 comprising the amino acid sequence of YAASTLQS (SEQ ID NO: 65), and a LCDR3 comprising the amino acid sequence of QKYNSAPGLT (SEQ ID NO: 66); a third antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of TASGFTFSTYGMH (SEQ ID NO: 67), a HCDR2 comprising the amino acid sequence of VISYDGSSKH (SEQ ID NO:

68), and a HCDR3 comprising the amino acid sequence of ARDGQPPGWGNYFDY (SEQ ID NO: 69); and a VL comprising a LCDR1 comprising the amino acid sequence of GGNGIGSKSVY (SEQ ID NO: 70), a LCDR2 comprising the amino acid sequence of YDDSDRPS (SEQ ID NO: 71), and a LCDR3 comprising the amino acid sequence of QVWDSSSDPWV (SEQ ID NO: 72); and a fourth antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of AASGFTFSTYGMH (SEQ ID NO: 109), a HCDR2 comprising the amino acid sequence of VIWYNGINKH (SEQ ID NO: 110), and a HCDR3 comprising the amino acid sequence of ARDWGTLTTLFDF (SEQ ID NO: 111); and a VL comprising a LCDR1 comprising the amino acid sequence of RASQSISSHLN (SEQ ID NO: 112), a LCDR2 comprising the amino acid sequence of YGASSLQS (SEQ ID NO: 113), and a LCDR3 comprising the amino acid sequence of QQSYSTPPWT (SEQ ID NO: 114).

[0242] In some embodiments, the method comprises administering one or more of IMM20184, IMM20190, IMM20253, and/or IMM20279 and an additional agent selected from the group consisting of casirivimab, imdevimab, bamlanivimab, etesevimab and sotrovimab.

[0243] Also provided herein is a method of treating a SARS-CoV-2 infection in a subject comprising administering two or more antibodies provided herein to the subject. In some embodiments, the SARS-CoV-2 infection is caused by SARS-CoV-2 variant. In some embodiments, the SARS-CoV-2 is the Alpha (U.K./B.1.1.7) variant of SARS-CoV-2, the Beta (South African/B.1.351) variant of SARS-CoV-2, the Gamma (Brazilian/P.1) variant of SARS-CoV-2, the Delta (India/B.1.617.2), B.1.617 (L452R/E484Q)), the Episolon (California/B.1.429/427, New York/B.1.526/526.1) variant of SARS-CoV-2, the UK/Nigeria (B.1.525) variant of SARS-CoV-2, the Brazilian (P.2) variant of SARS-CoV-2, the lambda (C.37) variant of SARS-CoV-2, or the Omicron (B.1.1.529) variant of SARS-CoV-2. In some embodiments, the variant has one or more mutations in a Spike protein. In some embodiments, 3 or more, 4 or more, 5 or more, or 6 or more antibodies provided herein are administered to the subject. In some embodiments, the antibodies comprise a HCVR comprising three heavy chain complementarity determining regions (CDRs), (HCDR1, HCDR2 and HCDR3), wherein the amino acid sequence of the HCVR is set forth in SEQ ID NO: 1, and a LCVR comprising three light chain complementarity determining regions (CDRs) (LCDR1, LCDR2 and LCDR3), wherein the amino acid sequence of the LCVR is set

forth in any one of SEQ ID NO: 2; a HCVR comprising three CDRs, (HCDR1, HCDR2 and HCDR3), wherein the amino acid sequence of the HCVR is set forth in SEQ ID NO: 3, and a LCVR comprising three CDRs, (LCDR1, LCDR2 and LCDR3), wherein the amino acid sequence of the LCVR is set forth in SEQ ID NO: 4; a HCVR comprising three CDRs, (HCDR1, HCDR2 and HCDR3), wherein the amino acid sequence of the HCVR is set forth in SEQ ID NO: 19, and a LCVR comprising three CDRs, (LCDR1, LCDR2 and LCDR3), wherein the amino acid sequence of the LCVR is set forth in SEQ ID NO: 20; a HCVR comprising three CDRs, (HCDR1, HCDR2 and HCDR3), wherein the amino acid sequence of the HCVR is set forth in SEQ ID NO: 5, and a LCVR comprising three CDRs, (LCDR1, LCDR2 and LCDR3), wherein the amino acid sequence of the LCVR is set forth in SEQ ID NO: 6; a HCVR comprising three CDRs, (HCDR1, HCDR2 and HCDR3), wherein the amino acid sequence of the HCVR is set forth in SEQ ID NO: 7, and a LCVR comprising three CDRs, (LCDR1, LCDR2 and LCDR3), wherein the amino acid sequence of the LCVR is set forth in SEQ ID NO: 8; or a HCVR comprising three CDRs, (HCDR1, HCDR2 and HCDR3), wherein the amino acid sequence of the HCVR is set forth in SEQ ID NO: 23, and a LCVR comprising three CDRs, (LCDR1, LCDR2 and LCDR3), wherein the amino acid sequence of the LCVR is set forth in SEQ ID NO: 24.

[0244] In some embodiments, provided herein is a method of treating an Omicron variant of SARS-CoV-2 in an individual comprising administering two or antibodies provided herein. In some embodiments, the Omicron variant includes a combination of mutations in the Spike protein. In some embodiments, the mutations include a large number of changes that form a ring around the ACE2 binding site. Accordingly, in one aspect an advantage of the present methods is the ability to target epitopes within and outside of the ACE2 binding site such that the treatment is effective in variants, such as Omicron which harbor mutations within the Spike protein including in the ACE2 binding site. In some embodiments, the combinations of antibodies provided herein are especially effective for treating variants such as Omicron because they bind to non-overlapping epitopes. In some embodiments, the Omicron variant has one or more modifications that make the Spike protein more susceptible to cleavage and/or cause pre-cleavage of the Spike protein. In some embodiments, the antibodies provided herein, for example IMM20253, are able to bind to pre-cleaved Spike proteins, or Spike proteins that are more susceptible to cleavage with high affinity.

[0245] In some embodiments, provided herein is a method of treating a Delta variant of SARS-CoV-2 in an individual comprising administering two or antibodies provided herein. In some embodiments, the Omicron variant includes a combination of mutations in the Spike protein. In some embodiments, the mutations include a large number of changes that form a ring around the ACE2 binding site. Accordingly, in one aspect an advantage of the present methods is the ability to target epitopes within and outside of the ACE2 binding site such that the treatment is effective in variants, such as Omicron which harbor mutations within the Spike protein including in the ACE2 binding site. In some embodiments, the combinations of antibodies provided herein are especially effective for treating variants such as Delta because they bind to non-overlapping epitopes. In some embodiments, the Delta variant has one or more modifications that make the Spike protein more susceptible to cleavage and/or cause pre-cleavage of the Spike protein. In some embodiments, the antibodies provided herein, for example IMM20253, are able to bind to pre-cleaved Spike proteins, or Spike proteins that are more susceptible to cleavage with high affinity.

[0246] In some embodiments, provided herein is a method of treating a SARS-CoV-2 infection in an individual comprising administering antibody IMM20184 to the individual. In some embodiments the antibody comprises a HCVR comprising three heavy chain complementarity determining regions (CDRs), (HCDR1, HCDR2 and HCDR3), wherein the amino acid sequence of the HCVR is set forth in SEQ ID NO: 1, and a LCVR comprising three light chain complementarity determining regions (CDRs) (LCDR1, LCDR2 and LCDR3), wherein the amino acid sequence of the LCVR is set forth in any one of SEQ ID NO: 2. In some embodiments, the antibody comprise a HCDR1, a HCDR2, and anHCDR3 of the HCVR amino acid sequence set forth in SEQ ID NO:1 and a LCDR1, a LCDR2, and a LCDR3 of the LCVR amino acid sequence set forth in SEQ ID NO: 2. In some embodiments, the method comprises administering 2 or more antibodies. In some embodiments, IMM20184 targets an epitope outside the ACE2 binding site and operates via an ACE2 dependent mechanism of action.

[0247] In some embodiments, provided herein is a method of treating an Omicron variant of SARS-CoV-2 in an individual comprising administering antibody IMM20253 to the individual. In some embodiments the antibody comprises a HCVR comprising three CDRs, (HCDR1, HCDR2 and HCDR3), wherein the amino acid sequence of the HCVR is set forth in SEQ ID NO: 5, and a LCVR comprising three CDRs, (LCDR1, LCDR2 and

LCDR3), wherein the amino acid sequence of the LCVR is set forth in SEQ ID NO: 6. In some embodiments, the antibody comprises a HCDR1, a HCDR2 and a HCDR3 of the HCVR amino acid sequence set forth in SEQ ID NO:5 and a LCDR1, a LCDR2, and a LCDR3 of the LCVR amino acid sequence set forth in SEQ ID NO:6. In some embodiments, IMM20253 targets an epitope outside the ACE2 binding site and operates via an ACE2 independent mechanism of action. In some embodiments, IMM20253 has high affinity for virus comprising pre-cleaved Spike proteins or Spike proteins that are more susceptible to cleavage, such as Omicron.

[0248] In some embodiments, provided herein is a method of treating a Delta variant of SARS-CoV-2 in an individual comprising administering antibody IMM20253 to the individual. In some embodiments the antibody comprises a HCVR comprising three CDRs, (HCDR1, HCDR2 and HCDR3), wherein the amino acid sequence of the HCVR is set forth in SEQ ID NO: 5, and a LCVR comprising three CDRs, (LCDR1, LCDR2 and LCDR3), wherein the amino acid sequence of the LCVR is set forth in SEQ ID NO: 6. In some embodiments, the antibody comprises a HCDR1, a HCDR2 and a HCDR3 of the HCVR amino acid sequence set forth in SEQ ID NO:5 and a LCDR1, a LCDR2, and a LCDR3 of the LCVR amino acid sequence set forth in SEQ ID NO:6. In some embodiments, IMM20253 targets an epitope outside the ACE2 binding site and operates via an ACE2 independent mechanism of action. In some embodiments, IMM20253 targets an epitope outside the ACE2 binding site and operates via an ACE2 independent mechanism of action. In some embodiments, IMM20253 has high affinity for virus comprising pre-cleaved Spike proteins or Spike proteins that are more susceptible to cleavage, such as Delta.

[0249] In some embodiments, provided herein is a method of treating an Omicron variant of SARS-CoV-2 comprising administering antibody MM20190 to the individual. In some embodiments, the antibody comprises a HCVR comprising three CDRs, (HCDR1, HCDR2 and HCDR3), wherein the amino acid sequence of the HCVR is set forth in SEQ ID NO: 3, and a LCVR comprising three CDRs, (LCDR1, LCDR2 and LCDR3), wherein the amino acid sequence of the LCVR is set forth in SEQ ID NO: 4. In some embodiments, the antibody comprises a HCDR1, a HCDR2, and a HCDR3 of the HCVR amino acid sequence set forth in SEQ ID NO: 3 and a LCDR1, a LCDR2, and a LCDR3 of the LCVR amino acid sequence set forth in SEQ ID NO:4. In some embodiments, IMM20190, targets an epitope within the ACE2 binding site and operates via an ACE2 dependent mechanism of action.

[0250] In some embodiments, provided herein is a method of treating a Delta variant of SARS-CoV-2 comprising administering antibody MM20190 to the individual. In some embodiments, the antibody comprises a HCVR comprising three CDRs, (HCDR1, HCDR2 and HCDR3), wherein the amino acid sequence of the HCVR is set forth in SEQ ID NO: 3, and a LCVR comprising three CDRs, (LCDR1, LCDR2 and LCDR3), wherein the amino acid sequence of the LCVR is set forth in SEQ ID NO: 4. In some embodiments, the antibody comprises a HCDR1, a HCDR2, and a HCDR3 of the HCVR amino acid sequence set forth in SEQ ID NO: 3 and a LCDR1, a LCDR2, and a LCDR3 of the LCVR amino acid sequence set forth in SEQ ID NO:4. In some embodiments, IMM20190, targets an epitope within the ACE2 binding site and operates via an ACE2 dependent mechanism of action.

[0251] In some embodiments, provided herein is a method of treating an Omicron variant of SARS-CoV-2 in an individual comprising administering antibody IMM20184 and IMM20253 to the individual. In some embodiments, the method comprises administering i) an antibody comprising a HCVR comprising three CDRs, (HCDR1, HCDR2 and HCDR3), wherein the amino acid sequence of the HCVR is set forth in SEQ ID NO: 5, and a LCVR comprising three CDRs, (LCDR1, LCDR2 and LCDR3), wherein the amino acid sequence of the LCVR is set forth in SEQ ID NO: 6 and ii) an antibody comprising a HCVR comprising three CDRs, (HCDR1, HCDR2 and HCDR3), wherein the amino acid sequence of the HCVR is set forth in SEQ ID NO: 5, and a LCVR comprising three CDRs, (LCDR1, LCDR2 and LCDR3), wherein the amino acid sequence of the LCVR is set forth in SEQ ID NO: 6. In some embodiments, the method comprises administering i) an antibody comprising a HCDR1, a HCDR2, and a HCDR3 of the HCVR amino acid sequence set forth in SEQ ID NO:1 and a LCDR1, a LCDR2, and LCDR3 of the LCVR amino acid sequence set forth in SEQ ID NO: 2 and ii) a HCDR1, a HCDR2 and a HCDR3 of the HCVR amino acid sequence set forth in SEQ ID NO:5 and a LCDR1, a LCDR2, and a LCDR3 of the LCVR amino acid sequence set forth in SEQ ID NO:6.

[0252] In some embodiments, provided herein is a method of treating a Delta variant of SARS-CoV-2 in an individual comprising administering antibody IMM20184 and IMM20253 to the individual. In some embodiments, the method comprises administering i) an antibody comprising a HCVR comprising three CDRs, (HCDR1, HCDR2 and HCDR3), wherein the amino acid sequence of the HCVR is set forth in SEQ ID NO: 5, and a LCVR comprising three CDRs, (LCDR1, LCDR2 and LCDR3), wherein the amino acid sequence of

the LCVR is set forth in SEQ ID NO: 6 and ii) an antibody comprising a HCVR comprising three CDRs, (HCDR1, HCDR2 and HCDR3), wherein the amino acid sequence of the HCVR is set forth in SEQ ID NO: 5, and a LCVR comprising three CDRs, (LCDR1, LCDR2 and LCDR3), wherein the amino acid sequence of the LCVR is set forth in SEQ ID NO: 6. In some embodiments, the method comprises administering i) an antibody comprising a HCDR1, a HCDR2, and a HCDR3 of the HCVR amino acid sequence set forth in SEQ ID NO:1 and a LCDR1, a LCDR2, and LCDR3 of the LCVR amino acid sequence set forth in SEQ ID NO: 2 and ii) a HCDR1, a HCDR2 and a HCDR3 of the HCVR amino acid sequence set forth in SEQ ID NO:5 and a LCDR1, a LCDR2, and a LCDR3 of the LCVR amino acid sequence set forth in SEQ ID NO:6.

[0253] In some embodiments, provided herein is a method of treating an Omicron variant of SARS-CoV-2 in an individual comprising administering antibody IMM20184, IMM20253, and IMM20190. In some embodiments, the method comprises administering i) an antibody comprising a HCVR comprising three CDRs, (HCDR1, HCDR2 and HCDR3), wherein the amino acid sequence of the HCVR is set forth in SEQ ID NO: 5, and a LCVR comprising three CDRs, (LCDR1, LCDR2 and LCDR3), wherein the amino acid sequence of the LCVR is set forth in SEQ ID NO: 6 ii) an antibody comprising a HCVR comprising three CDRs, (HCDR1, HCDR2 and HCDR3), wherein the amino acid sequence of the HCVR is set forth in SEQ ID NO: 5, and a LCVR comprising three CDRs, (LCDR1, LCDR2 and LCDR3), wherein the amino acid sequence of the LCVR is set forth in SEQ ID NO: 6; and iii) an antibody comprising a HCVR comprising three CDRs, (HCDR1, HCDR2 and HCDR3), wherein the amino acid sequence of the HCVR is set forth in SEQ ID NO: 3, and a LCVR comprising three CDRs, (LCDR1, LCDR2 and LCDR3), wherein the amino acid sequence of the LCVR is set forth in SEQ ID NO: 4. In some embodiments, the method comprises administering i) an antibody comprising a HCDR1, a HCDR2, and a HCDR3 of the HCVR amino acid sequence set forth in SEQ ID NO:1 and a LCDR1, a LCDR2, and a LCDR3 of the LCVR amino acid sequence set forth in SEQ ID NO: 2 ii) an antibody comprising a HCDR1, a HCDR2 and a HCDR3 of the HCVR amino acid sequence set forth in SEQ ID NO:5 and a LCDR1, a LCDR2, and a LCDR3 of the LCVR amino acid sequence set forth in SEQ ID NO:6, and iii) an antibody comprising a HCDR1, a HCDR2, and a HCDR3 of the HCVR amino acid sequence set forth in SEQ ID NO: 3 and a LCDR1, a LCDR2, and a LCDR3 of the LCVR amino acid sequence set forth in SEQ ID NO:4.

[0254] In some embodiments, provided herein is a method of treating a Delta variant of SARS-CoV-2 in an individual comprising administering antibody IMM20184, IMM20253, and IMM20190. In some embodiments, the method comprises administering i) an antibody comprising a HCVR comprising three CDRs, (HCDR1, HCDR2 and HCDR3), wherein the amino acid sequence of the HCVR is set forth in SEQ ID NO: 5, and a LCVR comprising three CDRs, (LCDR1, LCDR2 and LCDR3), wherein the amino acid sequence of the LCVR is set forth in SEQ ID NO: 6 ii) an antibody comprising a HCVR comprising three CDRs, (HCDR1, HCDR2 and HCDR3), wherein the amino acid sequence of the HCVR is set forth in SEQ ID NO: 5, and a LCVR comprising three CDRs, (LCDR1, LCDR2 and LCDR3), wherein the amino acid sequence of the LCVR is set forth in SEQ ID NO: 6; and iii) an antibody comprising a HCVR comprising three CDRs, (HCDR1, HCDR2 and HCDR3), wherein the amino acid sequence of the HCVR is set forth in SEQ ID NO: 3, and a LCVR comprising three CDRs, (LCDR1, LCDR2 and LCDR3), wherein the amino acid sequence of the LCVR is set forth in SEQ ID NO: 4. In some embodiments, the method comprises administering i) an antibody comprising a HCDR1, a HCDR2, and a HCDR3 of the HCVR amino acid sequence set forth in SEQ ID NO:1 and a LCDR1, a LCDR2, and a LCDR3 of the LCVR amino acid sequence set forth in SEQ ID NO: 2 ii) an antibody comprising a HCDR1, a HCDR2 and a HCDR3 of the HCVR amino acid sequence set forth in SEQ ID NO:5 and a LCDR1, a LCDR2, and a LCDR3 of the LCVR amino acid sequence set forth in SEQ ID NO:6, and iii) an antibody comprising a HCDR1, a HCDR2, and a HCDR3 of the HCVR amino acid sequence set forth in SEQ ID NO: 3 and a LCDR1, a LCDR2, and a LCDR3 of the LCVR amino acid sequence set forth in SEQ ID NO:4.

[0255] "Subjects" refers to any person who has been infected with, or has the potential to be infected with the SARS-CoV-2 virus. In some embodiments of the invention those subjects may be of high risk for contracting the virus as a result of being immunocompromised through genetic mutation or drug treatment. For example, subjects may be being treated with immunosuppressive medications as a result of being a solid organ transplant recipient or having a chronic inflammatory disease (e.g. rheumatoid arthritis, psoriasis, chrohn's disease). They may be being treated with chemotherapeutic, radiation, or targeted agents that suppress immune function for treatment of diseases such as cancer. Subjects may also have conditions that place them into high-risk categories for developing severe COVID-19, such as diabetes, chronic pulmonary conditions, chronic cardiovascular conditions, obesity, or pregnancy.

[0256] "Preventing" a disease refers to inhibiting the full development of a disease. Other terms, such as "prophylaxis", are also understood to refer to the concept of preventing a disease.

[0257] "Treating" refers to a therapeutic intervention that ameliorates, (i.e., reduces the severity), a sign or symptom of a disease or pathological condition after it has begun to develop. In some embodiments of the invention, the antibodies or antigen-binding fragments thereof contained in the pharmaceutical composition treat or prevent the a SARS-CoV-2 infection by neutralizing SARS-CoV-2 virus and/or a SARS-CoV-2 variant. Examples of SARS-CoV-2 variants that are responsive to a method of treatment of the invention include the: Alpha (U.K./B.1.1.7), Beta (South African/B.1.351), Gamma (Brazil/P.1), Delta (India/B.1.617.2), B.1.617 (L452R/E484Q) and Epsilon (California/B.1.429/427). Other examples of SARS-CoV-2 variants that are responsive to a method of treatment of the invention include the CDC Variants of Interest, including the Alpha (U.K./B.1.1.7) variant of SARS-CoV-2, the Beta (South African/B.1.351) variant of SARS-CoV-2, the Gamma (Brazilian/P.1) variant of SARS-CoV-2, the Delta (India/B.1.617.2), B.1.617 (L452R/E484Q)), the Epsilon (California/B.1.429/427, New York/B.1.526/526.1) variant of SARS-CoV-2, the UK/Nigeria (B.1.525) variant of SARS-CoV-2, the Brazilian (P.2) variant of SARS-CoV-2, the lambda (C.37) variant of SARS-CoV-2, or the Omicron (B.1.1.529) variant of SARS-CoV-2.

[0258] In certain embodiments, an effective amount of an antibody or antibody composition of the invention to prevent or treat SARS-CoV-2 infection does not result in complete protection from a SARS-CoV-2 disease but results in a lower titer or reduced number of SARS-CoV-2 viruses compared to an untreated subject. In certain embodiments, the effective amount results in a 0.5-fold, 1-fold, 2-fold, 4-fold, 6-fold, 8-fold, 10-fold, 15-fold, 20-fold, 25-fold, 50-fold, 75-fold, 100-fold, 125-fold, 150-fold, 175-fold, 200-fold, 300-fold, 400-fold, 500-fold, 750-fold, or 1,000-fold or greater reduction in titer of SARS-CoV-2 virus relative to an untreated subject. In some embodiments, the effective amount results in a reduction in titer of SARS-CoV-2 virus relative to an untreated subject of approximately 1 log or more, approximately 2 logs or more, approximately 3 logs or more, approximately 4 logs or more, approximately 5 logs or more, approximately 6 logs or more, approximately 7 logs or more, approximately 8 logs or more, approximately 9 logs or more, approximately 10 logs or more, 1 to 5 logs, 2 to 10 logs, 2 to 5 logs, or 2 to 10 logs. Benefits of a reduction in

the titer, number or total burden of SARS-CoV-2 virus include, but are not limited to, less severe symptoms of the infection, fewer symptoms of the infection, reduction in the length of the disease associated with the infection, reduction in the length of viral shedding, and prevention of the onset or diminution of severity of diseases occurring secondary to SARS-CoV-2 virus infections.

Kits

[0259] Also, provided herein are kits for treating or preventing a SARS-CoV-2 infection in a subject comprising one or more antibodies provided herein. In some embodiments, the kit comprises two antibodies that bind to a Spike protein. In some embodiments, the kit comprises three or more antibodies that bind to a Spike protein. In some embodiments, the kit comprises four or more antibodies that bind to a Spike protein. In some embodiments, the anti-Spike antibodies are in different compositions in the kit. In some embodiments, the anti-Spike antibodies are in the same composition.

[0260] In some embodiments, the kit comprises one or more of IMM20184, IMM20190, IMM20253, and/or IMM20279 and an additional agent. In some embodiments, the kit comprises one or more of IMM20184, IMM20190, IMM20253, and/or IMM20279 and an additional agent selected from the group consisting of casirivimab, imdevimab, bamlanivimab, etesevimab and sotrovimab. In some embodiments, the kit comprises an anti-Spike antibody comprising a variable heavy chain (VH) and a variable light chain (VL), wherein the antibody comprises a HCDR1 comprising the amino acid sequence SASGFTFSSFWMS (SEQ ID NO: 55); a HCDR2 comprising the amino acid sequence TIREDGSEKYYVD (SEQ ID NO: 56); and a HCDR3 comprising the amino acid sequence ARSKWLRGSFDY (SEQ ID NO: 57); wherein the antibody comprises a LCDR1 comprising the amino acid sequence TRRSGSIASNYVQ (SEQ ID NO: 58); a LCDR2 comprising the amino acid sequence YEDNQRP (SEQ ID NO: 59); and a LCDR3 comprising the amino acid sequence QSYDSSNPPGASWV (SEQ ID NO: 60). In some embodiments, the CDRs are defined according to North et al.

[0261] In some embodiments, the kit comprises an anti-Spike antibody comprising a variable heavy chain (VH) and a variable light chain (VL), wherein the antibody comprises a HCDR1 comprising the amino acid sequence SASGFTVSSNYMS (SEQ ID NO: 61); a HCDR2 comprising the amino acid sequence VIYAGGSTF (SEQ ID NO: 62); and a HCDR3 comprising the amino acid sequence ARDRGGYLDY (SEQ ID NO: 63); wherein the

antibody comprises a LCDR1 comprising the amino acid sequence RASQGISNYLA (SEQ ID NO: 64); a LCDR2 comprising the amino acid sequence YAASTLQS (SEQ ID NO: 65); and a LCDR3 comprising the amino acid sequence QKYNSAPGLT (SEQ ID NO: 66). In some embodiments, the CDRs are defined according to North et al.

[0262] In some embodiments, the kit comprises an anti-Spike antibody comprising a variable heavy chain (VH) and a variable light chain (VL), wherein the antibody comprises a HCDR1 comprising the amino acid sequence TASGFTFSTYGMH (SEQ ID NO: 67); a HCDR2 comprising the amino acid sequence VISYDGSSKH (SEQ ID NO: 68); and a HCDR3 comprising the amino acid sequence ARDGQPPGWGNYFDY (SEQ ID NO: 69); wherein the antibody comprises a LCDR1 comprising the amino acid sequence GGNGIGSKSVY (SEQ ID NO: 70); a LCDR2 comprising the amino acid sequence YDDSDRPS (SEQ ID NO: 71); and a LCDR3 comprising the amino acid sequence QVWDSSSDPWV (SEQ ID NO: 72). In some embodiments, the CDRs are defined according to North et al.

[0263] In some embodiments, the kit comprises an anti-Spike antibody comprising a variable heavy chain (VH) and a variable light chain (VL), wherein the antibody comprises a HCDR1 comprising the amino acid sequence AASGFTFSTYGMH (SEQ ID NO: 109); a HCDR2 comprising the amino acid sequence VIWYNGINKH (SEQ ID NO: 110); and a HCDR3 comprising the amino acid sequence ARDWGTLTTLFDF (SEQ ID NO: 111); wherein the antibody comprises a LCDR1 comprising the amino acid sequence RASQSISSHLN (SEQ ID NO: 112); a LCDR2 comprising the amino acid sequence YGASSLQS (SEQ ID NO: 113); and a LCDR3 comprising the amino acid sequence QQSYSTPPWT (SEQ ID NO: 114). In some embodiments, the CDRs are defined according to North et al.

[0264] In some embodiments, the kit comprises an anti-Spike antibody comprising a first antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SASGFTFSSFWMS (SEQ ID NO: 55), a HCDR2 comprising the amino acid sequence of TIREDGSEKYYVD (SEQ ID NO: 56), and a HCDR3 comprising the amino acid sequence of ARSKWLGRGSDY (SEQ ID NO: 57); and a VL comprising a LCDR1 comprising the amino acid sequence of TRRSGSIASNYVQ (SEQ ID NO: 58), a LCDR2 comprising the amino acid sequence of YEDNQRPS (SEQ ID NO: 59), and a LCDR3 comprising the amino acid sequence of QSYDSSNPPGASWV (SEQ ID NO: 60); and a second antibody

comprising a VH comprising a HCDR1 comprising the amino acid sequence of SASGFTVSSNYMS (SEQ ID NO: 61), a HCDR2 comprising the amino acid sequence of VIYAGGSTF (SEQ ID NO: 62), and a HCDR3 comprising the amino acid sequence of ARDRGGYLDY (SEQ ID NO: 63); and a VL comprising a LCDR1 comprising the amino acid sequence of RASQGISNYLA (SEQ ID NO: 64), a LCDR2 comprising the amino acid sequence of YAASTLQS (SEQ ID NO: 65), and a LCDR3 comprising the amino acid sequence of QKYNSAPGLT (SEQ ID NO: 66).

[0265] In some embodiments, the kit comprises a combination of two anti-Spike antibodies comprising a first antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SASGFTFSSFWMS (SEQ ID NO: 55), a HCDR2 comprising the amino acid sequence of TIREDGSEKYYVD (SEQ ID NO: 56), and a HCDR3 comprising the amino acid sequence of ARSKWLRGSFDY (SEQ ID NO: 57); and a VL comprising a LCDR1 comprising the amino acid sequence of TRRSGSIASNYVQ (SEQ ID NO: 58), a LCDR2 comprising the amino acid sequence of YEDNQRPS (SEQ ID NO: 59), and a LCDR3 comprising the amino acid sequence of QSYDSSNPPGASWV (SEQ ID NO: 60); and a second antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of TASGFTFSTYGMH (SEQ ID NO: 67), a HCDR2 comprising the amino acid sequence of VISYDGSSKH (SEQ ID NO: 68), and a HCDR3 comprising the amino acid sequence of ARDGQPPGWGNYFDY (SEQ ID NO: 69), and a VL comprising a LCDR1 comprising the amino acid sequence of GGNGIGSKSVY (SEQ ID NO: 70), a LCDR2 comprising the amino acid sequence of YDDSDRPS (SEQ ID NO: 71), and a LCDR3 comprising the amino acid sequence of QVWDSSSDPWV (SEQ ID NO: 72).

[0266] In some embodiments, the kit comprises a combination of two anti-Spike antibodies comprising a first antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SASGFTFSSFWMS (SEQ ID NO: 55), a HCDR2 comprising the amino acid sequence of TIREDGSEKYYVD (SEQ ID NO: 56), and a HCDR3 comprising the amino acid sequence of ARSKWLRGSFDY (SEQ ID NO: 57); and a VL comprising a LCDR1 comprising the amino acid sequence of TRRSGSIASNYVQ (SEQ ID NO: 58), a LCDR2 comprising the amino acid sequence of YEDNQRPS (SEQ ID NO: 59), and a LCDR3 comprising the amino acid sequence of QSYDSSNPPGASWV (SEQ ID NO: 60); and a second antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of AASGFTFSTYGMH (SEQ ID NO: 109), a HCDR2 comprising the amino acid

sequence of VIWYNGINKH (SEQ ID NO: 110), and a HCDR3 comprising the amino acid sequence of ARDWGTLTTLFDF (SEQ ID NO: 111); and a VL comprising a LCDR1 comprising the amino acid sequence of RASQSISSHLN (SEQ ID NO: 112), a LCDR2 comprising the amino acid sequence of YGASSLQS (SEQ ID NO: 113), and a LCDR3 comprising the amino acid sequence of QQSYSTPPWT (SEQ ID NO: 114).

[0267] In some embodiments, the kit comprises a combination of two anti-Spike antibodies comprising a first antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SASGFTVSSNYMS (SEQ ID NO: 61), a HCDR2 comprising the amino acid sequence of VIYAGGSTF (SEQ ID NO: 62), and a HCDR3 comprising the amino acid sequence of ARDRGGYLDY (SEQ ID NO: 63); and a VL comprising a LCDR1 comprising the amino acid sequence of RASQGISNYLA (SEQ ID NO: 64), a LCDR2 comprising the amino acid sequence of YAASTLQS (SEQ ID NO: 65), and a LCDR3 comprising the amino acid sequence of QKYNSAPGLT (SEQ ID NO: 66); and a second antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of TASGFTFSTYGMH (SEQ ID NO: 67), a HCDR2 comprising the amino acid sequence of VISYDGSSKH (SEQ ID NO: 68), and a HCDR3 comprising the amino acid sequence of ARDGQPPGWGNYFDY (SEQ ID NO: 69); and a VL comprising a LCDR1 comprising the amino acid sequence of GGNGIGSKSVY (SEQ ID NO: 70), a LCDR2 comprising the amino acid sequence of YDDSDRPS (SEQ ID NO: 71), and a LCDR3 comprising the amino acid sequence of QVWDSSSDPWV (SEQ ID NO: 72).

[0268] In some embodiments, the kit comprises a combination of two anti-Spike antibodies comprising a first antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SASGFTVSSNYMS (SEQ ID NO: 61), a HCDR2 comprising the amino acid sequence of VIYAGGSTF (SEQ ID NO: 62), and a HCDR3 comprising the amino acid sequence of ARDRGGYLDY (SEQ ID NO: 63); and a VL comprising a LCDR1 comprising the amino acid sequence of RASQGISNYLA (SEQ ID NO: 64), a LCDR2 comprising the amino acid sequence of YAASTLQS (SEQ ID NO: 65), and a LCDR3 comprising the amino acid sequence of QKYNSAPGLT (SEQ ID NO: 66); and a second antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of AASGFTFSTYGMH (SEQ ID NO: 109), a HCDR2 comprising the amino acid sequence of VIWYNGINKH (SEQ ID NO: 110), and a HCDR3 comprising the amino acid sequence of ARDWGTLTTLFDF (SEQ ID NO: 111); and a VL comprising a LCDR1 comprising the

amino acid sequence of RASQSISSHLN (SEQ ID NO: 112), a LCDR2 comprising the amino acid sequence of YGASSLQS (SEQ ID NO: 113), and a LCDR3 comprising the amino acid sequence of QQSYSTPPWT (SEQ ID NO: 114).

[0269] In some embodiments, the kit comprises a combination of two anti-Spike antibodies comprising a first antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of TASGFTFSTYGMH (SEQ ID NO: 67), a HCDR2 comprising the amino acid sequence of VISYDGSSKH (SEQ ID NO: 68), and a HCDR3 comprising the amino acid sequence of ARDGQPPGWGNYFDY (SEQ ID NO: 69); and a VL comprising a LCDR1 comprising the amino acid sequence of GGNGIGSKSVY (SEQ ID NO: 70), a LCDR2 comprising the amino acid sequence of YDDSDRPS (SEQ ID NO: 71), and a LCDR3 comprising the amino acid sequence of QVWDSSSDPWV (SEQ ID NO: 72); and a second antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of AASGFTFSTYGMH (SEQ ID NO: 109), a HCDR2 comprising the amino acid sequence of VIWYNGINKH (SEQ ID NO: 110), and a HCDR3 comprising the amino acid sequence of ARDWGTLTTLFDF (SEQ ID NO: 111); and a VL comprising a LCDR1 comprising the amino acid sequence of RASQSISSHLN (SEQ ID NO: 112), a LCDR2 comprising the amino acid sequence of YGASSLQS (SEQ ID NO: 113), and a LCDR3 comprising the amino acid sequence of QQSYSTPPWT (SEQ ID NO: 114).

[0270] In some embodiments, the kit comprises a combination of three anti-Spike antibodies comprising a first antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SASGFTFSSFWMS (SEQ ID NO: 55), a HCDR2 comprising the amino acid sequence of TIREDGSEKYYVD (SEQ ID NO: 56), and a HCDR3 comprising the amino acid sequence of ARSKWLRGSFDY (SEQ ID NO: 57); and a VL comprising a LCDR1 comprising the amino acid sequence of TRRSGSIASNYVQ (SEQ ID NO: 58), a LCDR2 comprising the amino acid sequence of YEDNQRPS (SEQ ID NO: 59), and a LCDR3 comprising the amino acid sequence of QSYDSSNPPGASWV (SEQ ID NO: 60); a second antibody comprising the amino acid sequence of SASGFTVSSNYMS (SEQ ID NO: 61), a HCDR2 comprising the amino acid sequence of VIYAGGSTF (SEQ ID NO: 62), and a HCDR3 comprising the amino acid sequence of ARDRGGYLDY (SEQ ID NO: 63); and a VL comprising a LCDR1 comprising the amino acid sequence of RASQGISNYLA (SEQ ID NO: 64), a LCDR2 comprising the amino acid sequence of YAASTLQS (SEQ ID NO: 65), and a LCDR3 comprising the amino acid sequence of QKYNSAPGLT (SEQ ID NO: 66);

and a third antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of TASGFTFSTYGMH (SEQ ID NO: 67), a HCDR2 comprising the amino acid sequence of VISYDGSSKH (SEQ ID NO: 68), and a HCDR3 comprising the amino acid sequence of ARDGQPPGWGNYFDY (SEQ ID NO: 69); and a VL comprising a LCDR1 comprising the amino acid sequence of GGNGIGSKSVY (SEQ ID NO: 70), a LCDR2 comprising the amino acid sequence of YDDSDRPS (SEQ ID NO: 71), and a LCDR3 comprising the amino acid sequence of QVWDSSSDPWV (SEQ ID NO: 72).

[0271] In some embodiments, the kit comprises a combination of three anti-Spike antibodies comprising a first antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SASGFTFSSFWMS (SEQ ID NO: 55), a HCDR2 comprising the amino acid sequence of TIREDGSEKYYVD (SEQ ID NO: 56), and a HCDR3 comprising the amino acid sequence of ARSKWLRGSFDY (SEQ ID NO: 57); and a VL comprising a LCDR1 comprising the amino acid sequence of TRRSGSIASNYVQ (SEQ ID NO: 58), a LCDR2 comprising the amino acid sequence of YEDNQRPS (SEQ ID NO: 59), and a LCDR3 comprising the amino acid sequence of QSYDSSNPPGASWV (SEQ ID NO: 60); a second antibody comprising the amino acid sequence of SASGFTVSSNYMS (SEQ ID NO: 61), a HCDR2 comprising the amino acid sequence of VIYAGGSTF (SEQ ID NO: 62), and a HCDR3 comprising the amino acid sequence of ARDRGGYLDY (SEQ ID NO: 63); and a VL comprising a LCDR1 comprising the amino acid sequence of RASQGISNYLA (SEQ ID NO: 64), a LCDR2 comprising the amino acid sequence of YAASTLQS (SEQ ID NO: 65), and a LCDR3 comprising the amino acid sequence of QKYNSAPGLT (SEQ ID NO: 66); and a third antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of AASGFTFSTYGMH (SEQ ID NO: 109), a HCDR2 comprising the amino acid sequence of VIWYNGINKH (SEQ ID NO: 110), and a HCDR3 comprising the amino acid sequence of ARDWGTLTTLFDF (SEQ ID NO: 111); and a VL comprising a LCDR1 comprising the amino acid sequence of RASQSISSHLN (SEQ ID NO: 112), a LCDR2 comprising the amino acid sequence of YGASSLQS (SEQ ID NO: 113), and a LCDR3 comprising the amino acid sequence of QQSYSTPPWT (SEQ ID NO: 114).

[0272] In some embodiments, the kit comprises a combination of three anti-Spike antibodies comprising a first antibody comprising the amino acid sequence of SASGFTVSSNYMS (SEQ ID NO: 61), a HCDR2 comprising the amino acid sequence of VIYAGGSTF (SEQ ID NO: 62), and a HCDR3 comprising the amino acid sequence of

ARDRGGYLDY (SEQ ID NO: 63); and a VL comprising a LCDR1 comprising the amino acid sequence of RASQGISNYLA (SEQ ID NO: 64), a LCDR2 comprising the amino acid sequence of YAASTLQS (SEQ ID NO: 65), and a LCDR3 comprising the amino acid sequence of QKYNSAPGLT (SEQ ID NO: 66); a second antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of TASGFTFSTYGMH (SEQ ID NO: 67), a HCDR2 comprising the amino acid sequence of VISYDGSSKH (SEQ ID NO: 68), and a HCDR3 comprising the amino acid sequence of ARDGQPPGWGNYFDY (SEQ ID NO: 69); and a VL comprising a LCDR1 comprising the amino acid sequence of GGNGIGSKSVY (SEQ ID NO: 70), a LCDR2 comprising the amino acid sequence of YDDSDRPS (SEQ ID NO: 71), and a LCDR3 comprising the amino acid sequence of QVWDSSSDPWV (SEQ ID NO: 72); and a VL comprising a LCDR1 comprising the amino acid sequence of, a LCDR2 comprising the amino acid sequence of, and a LCDR3 comprising the amino acid sequence of ; and a third antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of AASGFTFSTYGMH (SEQ ID NO: 109), a HCDR2 comprising the amino acid sequence of VIWYNGINKH (SEQ ID NO: 110), and a HCDR3 comprising the amino acid sequence of ARDWGTLTTLFDF (SEQ ID NO: 111); and a VL comprising a LCDR1 comprising the amino acid sequence of RASQSISSHLN (SEQ ID NO: 112), a LCDR2 comprising the amino acid sequence of YGASSLQS (SEQ ID NO: 113), and a LCDR3 comprising the amino acid sequence of QQSYSTPPWT (SEQ ID NO: 114).

[0273] In some embodiments, the kit comprises a combination of four anti-Spike antibodies comprising a first antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SASGFTFSSFWMS (SEQ ID NO: 55), a HCDR2 comprising the amino acid sequence of TIREDGSEKYYVD (SEQ ID NO: 56), and a HCDR3 comprising the amino acid sequence of ARSKWLRGSFDY (SEQ ID NO: 57); and a VL comprising a LCDR1 comprising the amino acid sequence of TRRSGLIASNYVQ (SEQ ID NO: 58), a LCDR2 comprising the amino acid sequence of YEDNQRPS (SEQ ID NO: 59), and a LCDR3 comprising the amino acid sequence of QSYDSSNPPGASWV (SEQ ID NO: 60); a second antibody comprising the amino acid sequence of SASGFTVSSNYMS (SEQ ID NO: 61), a HCDR2 comprising the amino acid sequence of VIYAGGSTF (SEQ ID NO: 62), and a HCDR3 comprising the amino acid sequence of ARDRGGYLDY (SEQ ID NO: 63); and a VL comprising a LCDR1 comprising the amino acid sequence of RASQGISNYLA (SEQ ID NO: 64), a LCDR2 comprising the amino acid sequence of YAASTLQS (SEQ ID NO: 65),

and a LCDR3 comprising the amino acid sequence of QKYNSAPGLT (SEQ ID NO: 66); a third antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of TASGFTFSTYGMH (SEQ ID NO: 67), a HCDR2 comprising the amino acid sequence of VISYDGSSKH (SEQ ID NO: 68), and a HCDR3 comprising the amino acid sequence of ARDGQPPGWGNYFDY (SEQ ID NO: 69); and a VL comprising a LCDR1 comprising the amino acid sequence of GGNGIGSKSVY (SEQ ID NO: 70), a LCDR2 comprising the amino acid sequence of YDDSDRPS (SEQ ID NO: 71), and a LCDR3 comprising the amino acid sequence of QVWDSSSDPWV (SEQ ID NO: 72); and a fourth antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of AASGFTFSTYGMH (SEQ ID NO: 109), a HCDR2 comprising the amino acid sequence of VIWYNGINKH (SEQ ID NO: 110), and a HCDR3 comprising the amino acid sequence of ARDWGTLTTLFDF (SEQ ID NO: 111); and a VL comprising a LCDR1 comprising the amino acid sequence of RASQSISSHLN (SEQ ID NO: 112), a LCDR2 comprising the amino acid sequence of YGASSLQS (SEQ ID NO: 113), and a LCDR3 comprising the amino acid sequence of QQSYSTPPWT (SEQ ID NO: 114). In some embodiments, the kit comprises an anti-Spike antibody provided in Table 1 and one or more additional antibodies. In some embodiments, the kit comprises a combination of casirivimab and imdevimab (REGEN-COV, previously known as REGN-COV-2). In some embodiments, the kit comprises a combination of bamlanivimab and etesevimab. In some embodiments, the kit comprises sotrovimab.

Embodiments

Embodiment 1. An antibody composition comprising at least first and second recombinant anti-SARS-CoV-2 antibodies that bind distinct epitopes of SARS-CoV-2, wherein at least one of the antibodies is selected from the group consisting of:

- (a) an anti-Spike antibody comprising
 - a heavy chain variable region (HCVR) as set forth in the amino acid sequence set forth in SEQ ID NO: 5 or fragment thereof, and
 - a light chain variable region (LCVR) as set forth in the amino acid sequence set forth in SEQ ID NO: 6 or fragment thereof;
- (b) an anti-Spike antibody comprising
 - a HCVR as set forth in the amino acid sequence set forth in SEQ ID NO: 3 or fragment thereof, and

a LCVR as set forth in the amino acid sequence set forth in SEQ ID NO: 4 or fragment thereof;

(c) an anti-Spike antibody comprising

a HCVR as set forth in the amino acid sequence set forth in SEQ ID NO: 1 or fragment thereof, and

a LCVR as set forth in the amino acid sequence set forth in SEQ ID NO: 2 or fragment thereof;

(d) an anti-Spike antibody comprising

a HCVR as set forth in the amino acid sequence set forth in SEQ ID NO: 7 or fragment thereof, and

a LCVR as set forth in the amino acid sequence set forth in SEQ ID NO: 8 or fragment thereof;

(e) an anti-Spike antibody comprising

a HCVR as set forth in the amino acid sequence set forth in SEQ ID NO: 9 or fragment thereof, and

a LCVR as set forth in the amino acid sequence set forth in SEQ ID NO: 10 or fragment thereof;

(f) an anti-Spike antibody comprising

a HCVR as set forth in the amino acid sequence set forth in SEQ ID NO: 11 or fragment thereof, and

a LCVR as set forth in the amino acid sequence set forth in SEQ ID NO: 12 or fragment thereof;

(g) an anti-Spike antibody comprising

a HCVR as set forth in the amino acid sequence set forth in SEQ ID NO: 13 or fragment thereof, and

a LCVR as set forth in the amino acid sequence set forth in SEQ ID NO: 14 or fragment thereof;

(h) an anti-Spike antibody comprising

a HCVR as set forth in the amino acid sequence set forth in SEQ ID NO: 15 or fragment thereof, and

a LCVR as set forth in the amino acid sequence set forth in SEQ ID NO: 16 or fragment thereof;

(i) an anti-Spike antibody comprising

a HCVR as set forth in the amino acid sequence set forth in SEQ ID NO: 17 or fragment thereof, and

a LCVR as set forth in the amino acid sequence set forth in SEQ ID NO: 18 or fragment thereof;

(j) an anti-Spike antibody comprising

a HCVR as set forth in the amino acid sequence set forth in SEQ ID NO: 19 or fragment thereof, and

a LCVR as set forth in the amino acid sequence set forth in SEQ ID NO: 20 or fragment thereof;

(k) an anti-Spike antibody comprising

a HCVR as set forth in the amino acid sequence set forth in SEQ ID NO: 21 or fragment thereof, and

a LCVR as set forth in the amino acid sequence set forth in SEQ ID NO: 22 or fragment thereof;

(l) an anti-Spike antibody comprising

a HCVR as set forth in the amino acid sequence set forth in SEQ ID NO: 23 or fragment thereof, and

a LCVR as set forth in the amino acid sequence set forth in SEQ ID NO: 24 or fragment thereof;

(m) an anti-Spike antibody comprising

a HCVR as set forth in the amino acid sequence set forth in SEQ ID NO: 25 or fragment thereof, and

a LCVR as set forth in the amino acid sequence set forth in SEQ ID NO: 26 or fragment thereof;

(n) an anti-ORF3a antibody comprising

a HCVR as set forth in the amino acid sequence set forth in SEQ ID NO: 27 or fragment thereof, and

a LCVR as set forth in the amino acid sequence set forth in SEQ ID NO: 28 or fragment thereof;

(o) an anti-Membrane antibody comprising

a HCVR as set forth in the amino acid sequence set forth in SEQ ID NO: 29 or fragment thereof, and

a LCVR as set forth in the amino acid sequence set forth in SEQ ID NO: 30 or fragment thereof;

- (p) an anti-Nucleocapsid antibody comprising
a HCVR as set forth in the amino acid sequence set forth in SEQ ID NO: 31 or
fragment thereof, and
a LCVR as set forth in the amino acid sequence set forth in SEQ ID NO: 32 or
fragment thereof;
- (q) an anti-Nucleocapsid antibody comprising
a HCVR as set forth in the amino acid sequence set forth in SEQ ID NO: 33 or
fragment thereof, and
a LCVR as set forth in the amino acid sequence set forth in SEQ ID NO: 34 or
fragment thereof;
- (r) an anti-Nucleocapsid antibody comprising
a HCVR as set forth in the amino acid sequence set forth in SEQ ID NO: 35 or
fragment thereof, and
a LCVR as set forth in the amino acid sequence set forth in SEQ ID NO: 36 or
fragment thereof;
- (s) an anti-ORF8 antibody comprising
a HCVR as set forth in the amino acid sequence set forth in SEQ ID NO: 37 or
fragment thereof, and
a LCVR as set forth in the amino acid sequence set forth in SEQ ID NO: 38 or
fragment thereof; and
- (t) an anti-ORF8 antibody comprising
a HCVR as set forth in the amino acid sequence set forth in SEQ ID NO: 39 or
fragment thereof, and
a LCVR as set forth in the amino acid sequence set forth in SEQ ID NO: 40 or
fragment thereof.

Embodiment 2. The antibody composition of embodiment 1, comprising first and second antibodies selected from the group consisting of:

- (a) the anti-Spike antibody comprising
a heavy chain variable region (HCVR) as set forth in the amino acid sequence set
forth in SEQ ID NO: 5 or fragment thereof, and
a light chain variable region (LCVR) as set forth in the amino acid sequence set forth in SEQ
ID NO: 6 or fragment thereof;
- (b) the anti-Spike antibody comprising

a HCVR as set forth in the amino acid sequence set forth in SEQ ID NO: 3 or fragment thereof, and

a LCVR as set forth in the amino acid sequence set forth in SEQ ID NO: 4 or fragment thereof;

(c) the anti-Spike antibody comprising

a HCVR as set forth in the amino acid sequence set forth in SEQ ID NO: 1 or fragment thereof, and

a LCVR as set forth in the amino acid sequence set forth in SEQ ID NO: 2 or fragment thereof; and

(d) the anti-Spike antibody comprising

a HCVR as set forth in the amino acid sequence set forth in SEQ ID NO: 19 or fragment thereof, and

a LCVR as set forth in the amino acid sequence set forth in SEQ ID NO: 20 or fragment thereof.

Embodiment 3. The antibody composition of embodiment 2, wherein the ratio between the first and the second antibodies is about 1 : 1.

Embodiment 4. The antibody composition of embodiment 1, comprising first, second, and third recombinant anti-SARS-CoV-2 antibodies, wherein:

(a) the first recombinant antibody is the anti-Spike antibody comprising

a heavy chain variable region (HCVR) as set forth in the amino acid sequence set forth in SEQ ID NO: 5 or fragment thereof, and

a light chain variable region (LCVR) as set forth in the amino acid sequence set forth in SEQ ID NO: 6 or fragment thereof;

(b) the second recombinant antibody is the anti-Spike antibody comprising

a HCVR as set forth in the amino acid sequence set forth in SEQ ID NO: 3 or fragment thereof, and

a LCVR as set forth in the amino acid sequence set forth in SEQ ID NO: 4 or fragment thereof; and

(c) the third recombinant antibody is the anti-Spike antibody comprising

a HCVR as set forth in the amino acid sequence set forth in SEQ ID NO: 1 or fragment thereof, and

a LCVR as set forth in the amino acid sequence set forth in SEQ ID NO: 2 or fragment thereof.

Embodiment 5. The antibody composition of embodiment 1, comprising first, second, and third recombinant anti-SARS-CoV-2 antibodies, wherein:

- (a) the first recombinant antibody is the anti-Spike antibody comprising
a heavy chain variable region (HCVR) as set forth in the amino acid sequence set forth in SEQ ID NO: 19 or fragment thereof, and
a light chain variable region (LCVR) as set forth in the amino acid sequence set forth in SEQ ID NO: 20 or fragment thereof;
- (b) the second recombinant antibody is the anti-Spike antibody comprising
a HCVR as set forth in the amino acid sequence set forth in SEQ ID NO: 3 or fragment thereof, and
a LCVR as set forth in the amino acid sequence set forth in SEQ ID NO: 4 or fragment thereof; and
- (c) the third recombinant antibody is the anti-Spike antibody comprising
a HCVR as set forth in the amino acid sequence set forth in SEQ ID NO: 1 or fragment thereof, and
a LCVR as set forth in the amino acid sequence set forth in SEQ ID NO: 2 or fragment thereof.

Embodiment 6. The antibody composition of embodiment 4 or 5, wherein the ratios between the first, second, and third antibodies are about 1 : 1 : 1.

Embodiment 7. The antibody composition of embodiment 1, comprising first, second, third, and fourth antibodies selected from the group consisting of:

- (a) the anti-Spike antibody comprising
a heavy chain variable region (HCVR) as set forth in the amino acid sequence set forth in SEQ ID NO: 5 or fragment thereof, and
a light chain variable region (LCVR) as set forth in the amino acid sequence set forth in SEQ ID NO: 6 or fragment thereof;
- (b) the anti-Spike antibody comprising
a HCVR as set forth in the amino acid sequence set forth in SEQ ID NO: 3 or fragment thereof, and

a LCVR as set forth in the amino acid sequence set forth in SEQ ID NO: 4 or fragment thereof;

(c) the anti-Spike antibody comprising

a HCVR as set forth in the amino acid sequence set forth in SEQ ID NO: 1 or fragment thereof, and

a LCVR as set forth in the amino acid sequence set forth in SEQ ID NO: 2 or fragment thereof; and

(d) the anti-Spike antibody comprising

a HCVR as set forth in the amino acid sequence set forth in SEQ ID NO: 19 or fragment thereof, and

a LCVR as set forth in the amino acid sequence set forth in SEQ ID NO: 20 or fragment thereof.

Embodiment 8. The antibody composition of embodiment 7, wherein the ratio between the first, second, third, and fourth antibodies is about 1 : 1 : 1 : 1.

Embodiment 9. The antibody composition of any one of claims 1-8, wherein the antibody composition neutralizes at least 50% of one or more of the following variants of SARS-CoV-2: U.K. B.1.1.7; South African B.1.351; Brazil P.1; and California B.1.429/427 relative to the neutralization of the USA/WA_CDC-WA1/2020 SARS-CoV-2 by the composition.

Embodiment 10. The antibody composition of any one of embodiments 1-8, wherein the antibody composition neutralizes about 100% of one or more of the following variants of SARS-CoV-2: U.K. B.1.1.7; South African B.1.351; Brazil P.1; and California B.1.429/427 relative to the neutralization of the USA/WA_CDC-WA1/2020 SARS-CoV-2 by the composition.

Embodiment 11. The antibody composition of any one of embodiments 1-10, wherein the epitopes of the antibodies in the composition are non-overlapping.

Embodiment 12. A method of treating or preventing a SARS-CoV-2 infection in a subject in need thereof, comprising administering an amount of the antibody composition of any one of embodiments 1-11 sufficient to treat the SARS-CoV-2 infection.

Embodiment 13. The method of claim 12, wherein antibodies or antigen-binding fragments thereof in the antibody composition treat the SARS-CoV-2 infection by effecting at least one of the following actions:

- inhibiting binding of SARS-CoV-2 viruses to host ACE2 receptors;
- inducing clearance of SARS-CoV-2 viruses by fixing complement to the viruses;
- and
- inducing phagocytosis of the of SARS-CoV-2 viruses virus.

Embodiment 14. An isolated antibody or antigen-binding fragment thereof that binds a SARS-CoV-2 Spike protein comprising one of the following combinations of a heavy chain variable region (HCVR) and a light chain variable region (LCVR):

a HCVR comprising three heavy chain complementarity determining regions (CDRs), (HCDR1, HCDR2 and HCDR3), wherein the amino acid sequence of the HCVR is set forth in SEQ ID NO: 1, and a LCVR comprising three light chain complementarity determining regions (CDRs) (LCDR1, LCDR2 and LCDR3), wherein the amino acid sequence of the LCVR is set forth in any one of SEQ ID NO: 2;

a HCVR comprising three CDRs, (HCDR1, HCDR2 and HCDR3), wherein the amino acid sequence of the HCVR is set forth in SEQ ID NO: 3, and a LCVR comprising three CDRs, (LCDR1, LCDR2 and LCDR3), wherein the amino acid sequence of the LCVR is set forth in SEQ ID NO: 4;

a HCVR comprising three CDRs, (HCDR1, HCDR2 and HCDR3), wherein the amino acid sequence of the HCVR is set forth in SEQ ID NO: 5, and a LCVR comprising three CDRs, (LCDR1, LCDR2 and LCDR3), wherein the amino acid sequence of the LCVR is set forth in SEQ ID NO: 6;

a HCVR comprising three CDRs, (HCDR1, HCDR2 and HCDR3), wherein the amino acid sequence of the HCVR is set forth in SEQ ID NO: 7, and a LCVR comprising three CDRs, (LCDR1, LCDR2 and LCDR3), wherein the amino acid sequence of the LCVR is set forth in SEQ ID NO: 8;

a HCVR comprising three CDRs, (HCDR1, HCDR2 and HCDR3), wherein the amino acid sequence of the HCVR is set forth in SEQ ID NO: 9, and a LCVR comprising three CDRs, (LCDR1, LCDR2 and LCDR3), wherein the amino acid sequence of the LCVR is set forth in SEQ ID NO: 10;

a HCVR comprising three CDRs, (HCDR1, HCDR2 and HCDR3), wherein the amino acid sequence of the HCVR is set forth in SEQ ID NO: 11, and a LCVR comprising three CDRs, (LCDR1, LCDR2 and LCDR3), wherein the amino acid sequence of the LCVR is set forth in SEQ ID NO: 12;

a HCVR comprising three CDRs, (HCDR1, HCDR2 and HCDR3), wherein the amino acid sequence of the HCVR is set forth in SEQ ID NO: 13, and a LCVR comprising three CDRs, (LCDR1, LCDR2 and LCDR3), wherein the amino acid sequence of the LCVR is set forth in SEQ ID NO: 14

a HCVR comprising three CDRs, (HCDR1, HCDR2 and HCDR3), wherein the amino acid sequence of the HCVR is set forth in SEQ ID NO: 15, and a LCVR comprising three CDRs, (LCDR1, LCDR2 and LCDR3), wherein the amino acid sequence of the LCVR is set forth in SEQ ID NO: 16

a HCVR comprising three CDRs, (HCDR1, HCDR2 and HCDR3), wherein the amino acid sequence of the HCVR is set forth in SEQ ID NO: 17, and a LCVR comprising three CDRs, (LCDR1, LCDR2 and LCDR3), wherein the amino acid sequence of the LCVR is set forth in SEQ ID NO: 18

a HCVR comprising three CDRs, (HCDR1, HCDR2 and HCDR3), wherein the amino acid sequence of the HCVR is set forth in SEQ ID NO: 19, and a LCVR comprising three CDRs, (LCDR1, LCDR2 and LCDR3), wherein the amino acid sequence of the LCVR is set forth in SEQ ID NO: 20;

a HCVR comprising three CDRs, (HCDR1, HCDR2 and HCDR3), wherein the amino acid sequence of the HCVR is set forth in SEQ ID NO: 21, and a LCVR comprising three CDRs, (LCDR1, LCDR2 and LCDR3), wherein the amino acid sequence of the LCVR is set forth in SEQ ID NO: 22;

a HCVR comprising three CDRs, (HCDR1, HCDR2 and HCDR3), wherein the amino acid sequence of the HCVR is set forth in SEQ ID NO: 23, and a LCVR comprising three CDRs, (LCDR1, LCDR2 and LCDR3), wherein the amino acid sequence of the LCVR is set forth in SEQ ID NO: 24; or

a HCVR comprising three CDRs, (HCDR1, HCDR2 and HCDR3), wherein the amino acid sequence of the HCVR is set forth in SEQ ID NO: 25 and a LCVR comprising three CDRs, (LCDR1, LCDR2 and LCDR3), wherein the amino acid sequence of the LCVR is set forth in SEQ ID NO: 26.

Embodiment 15. An isolated antibody or antigen-binding fragment thereof that binds a SARS-CoV-2 nucleocapsid protein comprising one of the following combinations of a heavy chain variable region (HCVR) and a light chain variable region (LCVR):

a HCVR comprising three CDRs, HCDR1, HCDR2 and HCDR3, wherein the amino acid sequence of the HCVR is set forth in SEQ ID NO: 31; and

a LCVR comprising three CDRs, LCDR1, LCDR2 and LCDR3, wherein the amino acid sequence of the LCVR is set forth in SEQ ID NO: 32;

a HCVR comprising three CDRs, HCDR1, HCDR2 and HCDR3, wherein the amino acid sequence of the HCVR is set forth in SEQ ID NO: 33; and

a LCVR comprising three CDRs, LCDR1, LCDR2 and LCDR3, wherein the amino acid sequence of the LCVR is set forth in SEQ ID NO: 34; and

a HCVR comprising three CDRs, HCDR1, HCDR2 and HCDR3, wherein the amino acid sequence of the HCVR is set forth in SEQ ID NO: 35 and

a LCVR comprising three CDRs, LCDR1, LCDR2 and LCDR3, wherein the amino acid sequence of the LCVR is set forth in SEQ ID NO: 36.

Embodiment 16. An isolated antibody or antigen-binding fragment thereof that binds a SARS-CoV-2 membrane protein comprising:

a heavy chain variable region (HCVR) comprising three CDRs, HCDR1, HCDR2 and HCDR3, wherein the amino acid sequence of the HCVR is set forth in SEQ ID NO: 29; and

a light chain variable region (LCVR) comprising three CDRs, LCDR1, LCDR2 and LCDR3, wherein the amino acid sequence of the LCVR is set forth in SEQ ID NO: 30.

Embodiment 17. An isolated antibody or antigen-binding fragment thereof that binds a SARS-CoV-2 open reading frame protein (ORF)3a protein comprising:

a HCVR comprising three CDRs, HCDR1, HCDR2 and HCDR3, wherein the amino acid sequence of the HCVR is set forth in SEQ ID NO: 27; and

a LCVR comprising three CDRs, LCDR1, LCDR2 and LCDR3, wherein the amino acid sequence of the LCVR is set forth in SEQ ID NO: 28.

Embodiment 18. An isolated antibody or antigen-binding fragment thereof that binds a SARS-CoV-2 open reading frame protein (ORF)8 protein comprising one of the following combinations of a heavy chain variable region (HCVR) and a light chain variable region (LCVR):

a HCVR comprising three CDRs, HCDR1, HCDR2 and HCDR3, wherein the amino acid sequence of the HCVR is set forth in SEQ ID NO: 37; and

a LCVR comprising three CDRs, LCDR1, LCDR2 and LCDR3, wherein the amino acid sequence of the LCVR is set forth in SEQ ID NO: 38; and

a HCVR comprising three CDRs, HCDR1, HCDR2 and HCDR3, wherein the amino acid sequence of the HCVR is set forth in SEQ ID NO: 39 and

a LCVR comprising three CDRs, LCDR1, LCDR2 and LCDR3, wherein the amino acid sequence of the LCVR is set forth in SEQ ID NO: 40.

Embodiment 19. The isolated antibody or antigen-binding fragment thereof of any one of embodiments 13-18, wherein the antibody comprises a CH3 scaffold, comprising at least one modification of the wild-type amino acid sequence of the CH3 domain derived from an immunoglobulin Fc region.

Embodiment 20. The isolated antibody or antigen-binding fragment thereof of embodiment 19, wherein at least one modification of the wild-type sequence occurs within the AB, EF, or CD loops of the CH3 scaffold.

Embodiment 21. The isolated antibody or antigen-binding fragment thereof of embodiment 20, wherein the at least one modification is an amino acid substitution, deletion or insertion.

Embodiment 22. The isolated antibody or antigen-binding fragment thereof of embodiment 21, wherein the at least one antibody epitope amino acid sequence is located within the AB loop.

Embodiment 23. The isolated antibody or antigen-binding fragment thereof of embodiment 22, wherein the antibody epitope amino acid sequence comprises a sequence derived from SIRP α or SIRP γ .

Embodiment 24. The isolated antibody or antigen-binding fragment thereof of embodiment 23, wherein the antibody epitope amino acid sequence comprises a sequence derived from a constant light chain of an antibody.

Embodiment 25. The isolated antibody or antigen-binding fragment thereof of embodiments 24, wherein the antibody epitope amino acid sequence comprises a sequence selected from the group consisting of SEQ ID Nos. 33-57 of International Patent Application No. PCT/US2019/032780.

Embodiment 26 The isolated antibody or antigen-binding fragment thereof of any one of embodiments 19-25, wherein the EF and CD loops comprise only wild-type amino acid sequences.

Embodiment 27. The isolated antibody or antigen-binding fragment thereof of embodiment 26, wherein the at least one antibody epitope amino acid sequence is located within the EF loop.

Embodiment 28. The isolated antibody or antigen-binding fragment thereof of embodiment 27, wherein the antibody epitope amino acid sequence comprises a sequence derived from SIRP α or SIRP γ .

Embodiment 29. The isolated antibody or antigen-binding fragment thereof of embodiment 28, wherein the antibody epitope amino acid sequence comprises a sequence derived from a constant light chain of an antibody.

Embodiment 30. The isolated antibody or antigen-binding fragment thereof of embodiment 27, wherein the antibody epitope amino acid sequence comprises a sequence selected from the group consisting of SEQ ID Nos. 60-67 of International Patent Application No: PCT/US2019/032780.

Embodiment 31. The isolated antibody or antigen-binding fragment thereof of any one of embodiment 25-30, wherein the AB and CD loops comprise only the wild-type amino acid sequences.

Embodiment 32. The isolated antibody or antigen-binding fragment thereof of embodiment 20, wherein the antibody epitope amino acid sequence is located within the CD loop.

Embodiment 33. The isolated antibody or antigen-binding fragment thereof of embodiment 32, wherein the antibody epitope amino acid sequence comprises a sequence derived from SIRP α or SIRP γ .

Embodiment 34. The isolated antibody or antigen-binding fragment thereof of embodiment 32, wherein the antibody epitope amino acid sequence comprises a sequence derived from a constant light chain of an antibody.

Embodiment 35. The isolated antibody or antigen-binding fragment thereof of embodiment 32, wherein the antibody epitope amino acid sequence comprises a sequence selected from the group consisting of SEQ ID Nos. 3-30 of International Patent Application No: PCT/US2019/032780.

Embodiment 36. The isolated antibody or antigen-binding fragment thereof of any one of embodiments 32-35, wherein the AB and EF loops comprise only the wild-type amino acid sequences of the immunoglobulin heavy chain.

Embodiment 37. The isolated antibody or antigen-binding fragment thereof of any one of embodiments 19-36, wherein the CH3 scaffold is derived from a human immunoglobulin Fc region.

Embodiment 38. The isolated antibody or antigen-binding fragment thereof of embodiment 37, wherein the immunoglobulin Fc region is an IgG1, IgG2, IgG3, or IgG4.

Embodiment 39. The isolated antibody or antigen-binding fragment thereof of embodiment 38, wherein the human antibody is an IgG1.

Embodiment 40. The isolated antibody or antigen-binding fragment thereof of embodiment 39, wherein the IgG1 is a G1m1 or nG1m1 allotype.

Embodiment 41. The isolated antibody or antigen-binding fragment thereof of any one of embodiments 14-40, comprises an immunoglobulin Fc region or fragment thereof of a human IgG1, IgG2, IgG3, IgG4, IgM, IgD, IgA1, IgA2 or IgE.

Embodiment 42. An isolated antigen-binding fragment of any one of embodiments 14-18, wherein the antigen-binding fragment is a variable heavy (VH) single domain monoclonal antibody.

Embodiment 43. An isolated antigen-binding fragment of any one of embodiments 14-18, wherein the antigen-binding fragment is a single chain (sc)Fv-Fc fragment.

Embodiment 44. An isolated antigen-binding fragment of any one of embodiments 14-18, wherein the isolated antigen-binding fragment comprises an Fv, scFv, Fab, F(ab')₂, or Fab' fragment, diabody, or any fragment whose half-life has been increased.

Embodiment 45. The isolated antibody or antigen-binding fragment thereof of any one of embodiments 14-44, wherein binding of the antibody or antigen-binding fragment thereof:

- inhibits binding of a SARS-CoV-2 virus to a host ACE2 receptor;
- fixes complement to a SARS-CoV-2 virus;
- induces phagocytosis of a SARS-CoV-2 virus; or
- any combination thereof.

Embodiment 46. The isolated antibody or antigen-binding fragment of any one of embodiments 14-44, wherein the binding of the antibody or antigen-binding fragment thereof neutralizes a SARS-CoV-2 virus by blocking binding of the receptor binding domain (RBD) of the virus with an ACE2 receptor.

Embodiment 47. The isolated antibody or antigen-binding fragment thereof of any one of embodiments 14-46, wherein the SARS-CoV-2 virus is a SARS-CoV-2 variant.

Embodiment 48. The isolated antibody or antigen-binding fragment thereof of embodiment 47, wherein the SARS-CoV-2 variant is the U.K. (B.1.1.7) variant of SARS-CoV-2, the South African (B.1.351) variant of SARS-CoV-2, the California (B.1.429) variant of SARS-CoV-2, the California (B.1.427) variant of SARS-CoV-2, the Brazilian (P.1) variant of SARS-CoV-2, the New York (B.1.526) variant of SARS-CoV-2, the New York (B.1.526.1) variant of SARS-CoV-2, the UK/Nigeria (B.1.525) variant of SARS-CoV-2, or the Brazilian (P.2) variant of SARS-CoV-2.

Embodiment 49. A pharmaceutical composition comprising an isolated antibody or antigen-binding fragment thereof of embodiment 14 and a pharmaceutically acceptable carrier or diluent.

Embodiment 50. The pharmaceutical composition of embodiment 49, further comprising at least 1, at least 2, at least 3, at least 4, or at least 5 additional isolated antibodies or antigen-binding fragments thereof of embodiment 14.

Embodiment 51. The pharmaceutical composition of embodiment 49 or 50, further comprising at least 1, at least 2, or at least 3 additional isolated antibodies or antigen-binding fragments thereof of claim 15.

Embodiment 52. The pharmaceutical composition of any one of embodiments 49-51, further comprising the isolated antibody or antigen-binding fragment thereof of claim 16.

Embodiment 53. The pharmaceutical composition of any one of embodiments 49-52, further comprising the isolated antibody or antigen-binding fragment thereof of claim 17.

Embodiment 54. The pharmaceutical composition of any one of embodiments 49-53, wherein at least one antibody or antigen-binding fragment thereof comprises an immunoglobulin Fc region or fragment thereof of a human IgG1, IgG2, IgG3, or IgG4.

Embodiment 55. The pharmaceutical composition of any one of embodiments 49-53, wherein at least one antibody or antigen-binding fragment thereof comprises an immunoglobulin Fc region or fragment thereof of a human IgM.

Embodiment 56. The pharmaceutical composition of any one of embodiments 49-53, wherein at least one antibody or antigen-binding fragment thereof comprises an immunoglobulin Fc region or fragment thereof of a human IgD.

Embodiment 57. The pharmaceutical composition of any one of embodiments 49-53, wherein at least one antibody or antigen-binding fragment thereof comprises an immunoglobulin Fc region or fragment thereof of a human IgA1 or IgA2.

Embodiment 58. The pharmaceutical composition of any one of embodiments 49-53, wherein at least one antibody or antigen-binding fragment thereof comprises an immunoglobulin Fc region or fragment thereof of a human IgE.

Embodiment 59. The pharmaceutical composition of any one of embodiments 49-58, wherein at least one antibody or antigen-binding fragment thereof is a polyreactive antibody.

Embodiment 60. The pharmaceutical composition of any one of embodiments 49-59, further comprising a second therapeutic agent.

Embodiment 61. The pharmaceutical composition of embodiment 60, wherein the second therapeutic agent is selected from the group consisting of: an anti-inflammatory agent, and an antiviral agent.

Embodiment 62. A method for treating or preventing a SARS-CoV-2 infection in a subject in need thereof, comprising administering an effective amount of any one of the pharmaceutical compositions of embodiments 49-61.

Embodiment 63. The method of embodiment 62, wherein the one or more antibodies or antigen-binding fragments thereof contained in the pharmaceutical composition treat or prevent the a SARS-CoV-2 infection by neutralizing the SARS-CoV-2 virus.

Embodiment 64. The method of embodiment 63, wherein the SARS-CoV-2 virus is a SARS-CoV-2 variant.

Embodiment 65. The method of embodiment 64, wherein the SARS-CoV-2 variant is the U.K. (B.1.1.7) variant of SARS-CoV-2, the South African (B.1.351) variant of SARS-CoV-2, the California (B.1.429) variant of SARS-CoV-2, the California (B.1.427) variant of SARS-CoV-2, the Brazilian (P.1) variant of SARS-CoV-2, the New York (B.1.526) variant of SARS-CoV-2, the New York (B.1.526.1) variant of SARS-CoV-2, the UK/Nigeria (B.1.525) variant of SARS-CoV-2, the Brazilian (P.2) variant of SARS-CoV-2, or the Omicron (B.1.1.529) variant.

Embodiment 66. The method of embodiments 64 or 65, wherein the pharmaceutical composition treats or prevents SARS-CoV-2 variant and nonvariant infections with equivalent efficacies.

Embodiment 67. The method of treatment of any one of embodiments 62-66, wherein the administering of the pharmaceutical composition to the subject in need thereof comprises injecting the composition into the body of the subject subcutaneously, intravenously or intramuscularly.

Examples

[0274] **Example 1. Evaluation of the breadth of patients' humoral responses against SARS-CoV-2.** The overall spectrum of the productive antibody response to SARS-CoV-2 was examined using an automated, high-throughput hybridoma library generation and screening platform [Puligedda et al. 2014] after isolating memory B cells acquired from blood samples of COVID-19 convalescent patients who demonstrated a high antibody titer to N and/or S proteins.

[0275] **Collection of patient samples.** Blood samples were drawn from convalescing COVID-19 patient volunteers deemed eligible for donating convalescent plasma as set forth

in the U.S. Food and Drug Administration (FDA)'s Recommendations [FDA 2020]. Patients displayed no PCR-detectable viremia and maximal IgG (2880) titer of class switched, virus-specific antibodies.

[0276] Generation of hybridoma libraries. Hybridomas were generated from the memory B cells isolated from the donors by following protocols for isolating and expanding primary B cells as well as electrofusion methods described in U.S. patents [Dessain & Weinberg 2002, Dessain & Adekar 2009]. Hybridomas stably expressing human mAbs were generated by electrofusion of expanded B-cells to the B5-6T myeloma cell line, which expresses an ectopic human telomerase gene that stabilizes human chromosomes in the hybrid cells created. Fused hybridomas were plated into 96-well plates in growth medium with HAT selection of stable hybridomas for 7 days. After 7 days, growth media were switched to media with HT for stable selected hybridoma growth. Hybridomas were cultured in a 37°C incubator for 14-21 days during which time they were imaged for monoclonality and monitored for isotype-and sub-class-specific Ig secretion. Supernatants from monoclonal wells expressing measurable levels of Ig were cherry-picked and submitted for target-based screening.

[0277] Screening Assays For Antiviral Antibodies. The naturally occurring human antibodies (IgM, IgG, and IgA isotypes) secreted by those hybridomas were screened for reactivity against a panel of SARS-CoV-2 proteins. Antibody screening assays were developed for three SARS-CoV-2 structural proteins (S, N, M) and a panel of accessory ORF proteins of SARS-CoV-2. In addition to the reference Spike (S) protein corresponding to that found on the USA/WA_CDC-WA1/2020 virus, counterscreening was carried out on Spike proteins, or Spike protein domains, corresponding to the Spike proteins present on the surface of viral variants. The breadth of variants tested are described in Table 2.

Table 2. SARS-CoV-2 Spike Screening Proteins

SARS-CoV-2 Viral Target		Assay System		Variants Tested
Spike (S)		HTRF	Cell-based	
1	Trimer-stabilized FL (non-S1)	√		A352S, E406Q, K417N, N439K, K444R, L452R, Y453F, A475V, E484Q, E484K, F486S, N501Y, D614G, S. African partial (K417N, E484K, N501Y); Brazilian (K417T, E484K, N501Y); S. African (K417N, E484K, N501Y, D614G); Spanish (A222S, D614G); U.K. partial (ΔHV69/70, N501Y D614G); U.K. (ΔHV69/70, ΔY144, N501Y, A570D, D614G, P681H); Denmark (ΔHV69/70, Y453F, D614G), Californian (S13I, W152C, L452R, D614G), and USA/WA_CDC-WA1/2020
2	S1 domain (non-RBD)	√		
3	Receptor binding domain (RBD)	√		
4	FL Δ19aa		√	USA/WA_CDC-WA1/2020

[0278] The screening assays included a rapid and sensitive homogeneous time resolved fluorescence (hTRF) assay that used soluble recombinant viral proteins, as well as a selective, cell-based flow cytometry assay that allowed probing of antibodies to transiently transfected viral antigens expressed within the context of human cells. Viral protein expression in the cell-based assay was additionally confirmed by Western blot. For cell-based assays, using commercially available controls, the localization of the C-terminus truncated Spike protein (SΔ19aa) was confirmed to be on the surface of the transfected cells. Commercially available antibodies specific for SARS-CoV-2 targets, and more specifically the Spike protein, demonstrated selective and saturable binding in both assays. Screening led to the isolation of antibodies specific for eight different viral proteins (Fig. 1).

[0279] *HTRF Screening Assays.* A homogeneous time-resolved fluorescence (hTRF) assay [Degorce et al. 2009] comprised of terbium labeled anti-human IgG (H+L) (Cisbio, custom label) donor and AF488-labeled anti-HIS (Cell Signaling, Cat # 14930S) acceptor antibodies was used to screen patient-derived antibodies for their binding to recombinantly produced SARS-CoV-2 antigens, and more specifically to the SARS-CoV-2 Spike protein. The assay, adapted for high-throughput screening, was optimized so that a number of recombinant, HIS-tagged SARS-CoV-2 target proteins could be substituted interchangeably. This recombinant target panel consisted of a full-length S (FL, trimer-stabilized, LakePharma) and two truncated S protein domains, S1 (GenScript, Cat # Z03485-1) and RBD (aa 319-591, LakePharma). Commercially available antibodies specific for the individual structural viral proteins, SARS-CoV/SARS-CoV-2 Spike S1 (RBD) chimeric mAb (Sino Biological, Cat # 40150-D001), SARS CoV-2 Nucleocapsid human chimeric mAb (GenScript, Cat # A02039-100 served as controls. Assay background was determined by averaging the signal of wells containing only the donor and acceptor cocktail. Hybridoma

supernatants exhibiting signals greater than 2-fold over background were reported as positive HITs and are submitted for Ig sequence analysis.

[0280] *Flow cytometry-based cellular screens for antiviral antibodies.* SARS-CoV-2 antigen sequences were cloned into pcDNA3.4 plasmids and transfected into 293F cells utilizing the Expi293 Expression System (Life Technologies, Inc.) per manufacturer's instructions. Cells transiently expressing SARS-CoV-2 S (SΔ19aa) were used for screening. Optimal protein expression was achieved three days post-transfection for S proteins.

[0281] For the cell-surface binding assays cells were incubated with LIVE/DEAD Cell Stain (Life Technologies, Inc.) per the manufacturer's instructions. Live cells expressing SΔ19aa were suspended in QSol Buffer (IntelliCyt Corporation) to which a cocktail of Fc-specific secondary antibodies was added: AF647 goat anti-human IgG (Jackson ImmunoResearch, Inc.), AF488 goat anti-human IgA (Jackson ImmunoResearch, Inc.) and BV650 mouse anti-human IgM (BioLegend, Inc.).

[0282] For each assay, the cell suspensions were dispensed into 384-well plates, followed by the addition of hybridoma supernatant at a 1:10 final dilution. The reaction was allowed to incubate for 90 minutes at room temperature. Cells for each assay were fixed with a final concentration of 1% paraformaldehyde and analyzed with IntelliCyt iQue Screener (IntelliCyt Corporation). Positive binding gates for detection of each secondary antibody were established using cells plus secondary antibody cocktail as a negative control. Binding of hybridoma supernatant antibodies to specific SARS-CoV-2 proteins, and more specifically the SΔ19a, were quantified as percent positive relative to the secondary only control. To calculate percent positive, live events that shifted into detection channels were divided by the total live events.

[0283] **Example 2.** *Immunoglobulin gene usage in convalescent COVID-19 patients.* Ig gene usage in memory B cells of six COVID-19 patients was evaluated using an NGS analysis of identified and sequenced 134 hybridoma hits.

RNA isolation and Next Generation Sequencing (NGS). Hybridoma RNA was isolated using Invitrogen RNAqueous-96 Total RNA Isolation Kit (Cat. #AM1920). Isolated RNA samples were submitted to iRepertoire (Huntsville, AL) for NGS. Hybridoma-derived RNA samples were sequenced using the Illumina MiSeq system at iRepertoire (Huntsville, AL). Sequencing runs were performed using the

MiSeq Nano Kit V2 following bead-based cleanup of RNA. Immunoglobulin sequences containing CDR1, 2 and 3 and framework regions were amplified using IgG and IgA-specific mixes for IgH, and kappa and lambda-specific primers for IgL. IgM-expressing hybridoma samples, from which IgG or IgA heavy chains were not amplified using this approach, were sequenced using the iRepertoire iPair system. Final sequences were exported using iPair software.

[0284] Immunoglobulin sequences were analyzed for predicted CDR sequences, % identity to appropriate germlines, isotype of the constant regions and read counts. Sequence pairing was performed based on the read count information. In the event more than one LC:HC pair was discovered in a single well, each LC:HC combination was analyzed as a separate antibody. In all cases, sequencing method resulted in 5' truncation in the VH and VL regions, the germline sequence for the closest related V gene was used to generate a full-length version of each gene. The gene sequences were codon optimized to create expression constructs for recombinant production and testing of antibodies. Final sequences were translated and analyzed for potential stop codons and frame shifts.

[0285] **Example 3. Recombinant production of antibodies.** Heavy and light chain pairs from 103 clones, from which productive immunoglobulin RNA sequences were determined, were expressed as recombinant antibodies.

[0286] Production of paired light and heavy chains. Variable domains yielding productive uninterrupted protein sequences were analyzed for number of reads and the degree of somatic hypermutations (SHM) in comparison to the closest immunoglobulin germline. Hybridoma hit sequences with at least one chain that had more than 2% of SHM were advanced to HC/LC pairing and the recombinant production of antibodies. Immunoglobulin expression fragments were cloned into the pcDNA3.4-based vectors and expressed in 293F cells. Affinity and binding pattern of recombinant antibodies were compared to the original antibody-containing hybridoma supernatants in BLI, HTRF and cell-based assay. Antibody-containing supernatants or purified antibodies were advanced to downstream assays. If multiple heavy or light chain sequences were detected within one well, their CDRs were aligned and compared for potential PCR errors. In cases where multiple sequences within a well were different, i.e., originated from separate clones, all potential combinations of light and heavy chains were recombinantly produced and tested in downstream assays. Wells that yielded a single HC/LC pair were advanced to recombinant expression and downstream assays. 5' fragments of the constant regions were sequenced to identify the isotype of the antibody and compared to the experimentally identified isotype of hybridoma supernatants.

The resulting isotype of the heavy or light chain was assigned based on two or more positive readings from experimental (ex. ELISA and FACS) assays and sequencing.

[0287] A combined analysis of Ig isotype and their level of SHM of virus-specific antibodies revealed several key properties of the productive antiviral response. First, among all “mutated” immunoglobulins that had more than 2% of their nucleotide sequence deviated from the closest germline, there was an unusually high (26.4%) proportion of mutated IgMs, having a mean SHM rate of 5.73%. The functional basis of this phenomenon is not known, but one could speculate that these IgMs came from non-switched memory B cells that had undergone affinity maturation. Second, a subset of such somatically hypermutated IgMs recognized full-length Spike, but not the soluble RBD or S1 subunit of Spike protein. And third, while the predominant isotype among class-switched antibodies was, as expected, IgG it was possible to capture a panel of fairly mutated virus-specific IgAs. It is plausible that these antibodies play a major role in mucosal neutralization of the incoming virus and may be of particular use for prophylaxis of viral infection and for vaccine design.

[0288] **Example 4.** *Identified anti-Spike antibodies from convalescent COVID-19 patients exhibit potent binding to Spike proteins mimicking a range of different viral variants.* Purified recombinant antibodies were assessed, in the HTRF assay described above, using either soluble RBD or S1 domains containing mutations found in naturally occurring viral variants, as well as mutations predicted to decrease binding of neutralizing antibodies. Table 3 depicts the binding of identified anti-Spike antibodies, expressed as fold-binding over background. As anticipated, binding of some antibodies, such as PR201_00151 and PR194_00232, are negatively affected by specific mutations within the Spike domain (e.g. K417N). In contrast, binding by antibodies like PR199_00255, PR193_00018, and PR200_00622 are unaffected by the range of mutations analyzed, including variants containing single point mutations, as well as multiple point mutations that mimic the naturally occurring Spike proteins found on the B.1.1.7 and B.1.351 virus isolates. A subset of antibodies, such as PR199_00255 and PR200_00622, also bind to Spike protein found on SARS-CoV-1, suggesting that they bind to a highly conserved epitope.

[0289] **Binding of the antibodies PR913_00018, PR194_00232, and PR200_00622 were further** characterized in the HTRF assay to determine EC₅₀ of binding to a wide range of single and multi-point mutations, including to the B.1.1.7, B.1.429, P.1, and B.1.351 variants. Each of the antibodies bound to the Wuhan/Washington reference Spike RBD

protein with EC₅₀s in the HTRF assay of between 45 – 68 pM. Mutations that mapped to the ACE2 binding site on the RBD appear to disrupt the binding affinity of PR199_00232, whereas no mutation, or combination of mutations, tested disrupted the ability of either PR193_00018 or PR200_00622 to bind to the RBD. The ability of these two antibodies to bind to the wide range of variants suggests that their epitopes are maintained even in the face of the viral drift that has occurred to date.

[0290] The impact of mutational drift on the binding of each of PR193_0018, PR194_00232, and PR200_00622 antibodies was evaluated using a series of Spike proteins containing either single point mutations or complex point mutations that recapitulate the spectrum of mutations in naturally occurring variants that have emerged across the globe. PR194_00232 is the most sensitive of the three antibodies to mutational drift within the Spike protein. Mutations, such as K417N and N501Y, mutations known to exist in naturally occurring variants, and consistent with the alanine scanning data, significantly decrease the ability of PR194_00232 to bind the Spike protein. Whereas other naturally occurring mutations, such as L452R, E484Q, or D614G do not impact binding relative to binding to the Washington reference Spike protein. In contrast, binding of PR193_0018 and PR200_00622 are not significantly impacted by any of the single point mutations tested. In fact, binding by PR193_0018 and PR200_00622 to specific variant Spike proteins (e.g., E484K and E484Q) appears to be modestly enhanced over the reference Spike. Similar observations were made when binding of PR193_0018, PR194_00232, and PR200_00622 was tested against RBD domain proteins containing the full complement of mutations known to exist in four different variants. Of particular interest is the binding to RBDs corresponding to the South African (B.1.351) and U.K. (B.1.1.7) variants. As predicted by the K417N and N501Y single point mutation data, binding of PR194_00232 to both the U.K. and S.A. variants is weaker than observed against the reference strain Spike protein.

Table 3. Binding of Antibodies to Variant Forms of Recombinant Spike Protein

Ab #	Epitope	D614G	N439K	E406Q	K417N	N501Y	Y453F	A352S	A475V	DHV69/ 70,DY14 4, N501Y, A570D, D614G, P681H	DHV69/ 70, Y453F, D614G	A222S, D614G	K417N, E484K, N501Y, D614G
PR193_00018	RBD	4.930	4.427	6.581	3.637	4.921	4.737	4.616	4.419	4.150	5.613	5.429	4.637
PR194_00068	Non-RD	1.119	1.064	1.002	1.056	0.932	1.005	0.894	0.989	1.198	1.224	1.186	1.230
PR194_00232	RBD	4.837	5.952	8.811	2.252	4.303	5.943	6.749	7.474	3.910	8.180	8.470	1.123
PR194_00292	Non-RBD	1.064	1.057	0.967	1.028	0.996	0.974	0.940	1.023	2.372	2.594	1.017	2.257
PR194_00364_b	Non-RBD	2.469	1.016	0.918	1.060	0.948	0.977	0.917	1.019	3.631	3.054	3.052	4.546
PR194_00453	RBD	9.552	1.052	0.990	1.099	1.034	0.987	1.111	1.064	9.059	9.447	9.212	9.574
PR196_00413_a	Non-RBD	9.921	1.070	1.023	1.059	1.079	1.061	1.073	1.007	6.394	9.676	8.740	9.002
PR197_00647	Non-RBD	8.299	1.036	1.032	1.033	1.056	1.106	1.038	0.999	1.103	1.072	9.539	7.725
PR199_00255	RBD	11.231	6.087	10.864	7.286	6.150	1.032	8.258	7.645	7.291	9.631	9.296	9.477
PR200_00622	RBD	6.100	5.049	7.598	4.680	5.113	4.670	5.142	5.222	5.922	7.003	6.644	6.278
PR201_00151	RBD	7.246	6.027	8.298	1.089	6.156	5.479	7.058	5.700	4.220	6.531	7.294	1.049

Antibodies were evaluated for ability to bind to recombinant Spike protein in an HTRF assay, binding was expressed as a fold over background. Single point mutations (except D614G) were expressed in the context of soluble RBD domain, all others were expressed in context of soluble S1 domain. No binding was anticipated to RBD domain constructs by antibodies that bind to epitopes outside the RBD domain.

Table 4. EC50 of Binding to Variant Forms of Recombinant Spike Protein.

Mutation	Location	EC50 (pM) HTRF assay (relative to RBD)		
		PR194_00232 IMM20190	PR200_00622 IMM20253	PR193_00018 IMM20184
REF	RBD	68.2	52.7	44.8
N439K	RBD	68.9	53.4	51.0
E406Q	RBD	67.7	40.6	26.1
K417N	RBD	>500	67.4	43.7
N501Y	RBD	279	58.5	39.8
Y453F	RBD	64.6	62.6	49.4
A352S	RBD	21.9	31.7	26.3
A475V	RBD	72.4	33.0	27.9
E484Q	RBD	52.4	23.8	21.6
E484K	RBD	33.4	31.6	20.5
L452R	RBD	31.8	34.0	43.6
K444R	RBD	25.8	26.1	19.4
F486S	RBD	33.4	25.9	22.1

K417N, E484K, N501Y	RBD	Inactive	19.7	14.5
K417T, E484K, N501Y	RBD	Inactive	23.6	18.3
REF	S1	56.0	49.1	31.8
D614G	S1	62.7	62.4	39.7
A222S, D614G	S1	49.1	44.9	26.9
K417N, E484K, N501Y, D614G	S1	230	24.8	26.7
Δ HV69/70, N501Y, D614G	S1	396	21.6	14.3
Δ H69/70, Δ Y144, N501Y, A570D, D614G, P681H	S1, RBD	>500	62.4	45.5
Δ H69/70, Y453F, D614G	S1, RBD	47.2	66.4	31.6

[0291] **Example 5.** *Identified anti-Spike antibodies bind to non-overlapping epitopes within the RBD of SARS-CoV-2 Spike.* Purified recombinant forms of the PR193_00018, PR194_00232, and PR200_00622, failed to compete with each other for binding to the SARS-CoV-2 RBD when assessed via biolayer interferometry on an Octet QKe instrument. These data suggested the three antibodies bind to non-overlapping epitopes on the SARS-CoV-2 RBD. Alanine scanning of the RBD was performed to identify residues critical for binding of each of the antibodies. Consistent with each of the antibodies binding to non-overlapping epitopes, non-overlapping sets of residues were identified as being critical for binding of the antibodies (Table 5). Those residues map to unique regions of three dimensional structure of the RBD, consistent with the ability of the antibodies to fail to compete with each other for binding (Fig. 2)

Table 5. *Identification of critical residues for Ab binding.*

Binding Reactivity (% WT)					
Mutation	IMM20190 Fab	IMM20184 Fab	IMM20253 Fab HS	COV010 MAb	COV003 MAb
K356A	82.2 (6)	61.5 (6)	7.1 (4)	86.3 (4)	45.7 (8)
N370A	63.4 (5)	7.5 (3)	72.4 (4)	65.9 (12)	66.4 (2)

A372S	127.3 (42)	3 (2)	99.9 (16)	97.1 (8)	72.6 (4)
F374A	64.8 (7)	7.4 (1)	70.8 (8)	87.4 (4)	53 (1)
K378A	87.9 (3)	6.7 (0)	66.9 (17)	57.7 (10)	64.6 (2)
S383A	110.8 (1)	0.4 (2)	86.3 (2)	41 (2)	94.7 (9)
P384A	111.5 (1)	2.1 (1)	112 (12)	54 (7)	107.9 (11)
K417A	5.6 (6)	96.2 (32)	113 (20)	120 (2)	116.1 (7)
D420A	4.6 (2)	65.5 (14)	69 (6)	76.5 (7)	48.1 (5)
L455A	4.5 (7)	170.6 (27)	114 (13)	175.3 (15)	119.3 (50)
F456A	2.3 (2)	79.7 (2)	64.8 (4)	97.4 (8)	84.8 (2)
N460A	9.4 (6)	76.3 (20)	89 (12)	117.2 (24)	112.4 (1)
R466A	70.8 (19)	78.7 (15)	5 (1)	57.8 (10)	26 (3)
Y473A	1 (7)	83.5 (26)	65.3 (7)	92.1 (14)	35.4 (19)
N487A	12.6 (6)	84.5 (7)	67 (31)	83.8 (2)	65.8 (0)
Y489A	3.1 (4)	73 (6)	65 (12)	99.3 (21)	73.9 (1)
N501A	12.9 (1)	93.4 (5)	80.1 (14)	94.1 (8)	84.7 (1)
Y505A	0.3 (4)	130 (9)	108.2 (11)	131.9 (13)	119.9 (6)

Mean binding reactivities (and ranges) are listed for all identified critical residues. Critical residues for Ab binding (boxed) were residues whose mutations were negative for binding to test Abs, but positive for binding to control Ab

[0292] **Example 6. Identified anti-Spike antibodies neutralize SARS-CoV-2 pseudovirus.**

The functional consequence of antibodies binding to Spike was assessed in assays using pseudotyped replication-incompetent lentivirus which were used to infect HEK293 cells overexpressing Angiotensin converting enzyme 2 (ACE2). Spike-expressing pseudovirus was generated with System Bioscience's pPACK-SPIKE packaging system (System Biosciences, Cat #CVD19-500A-1) as per manufacturer's protocol. Briefly, 8×10^6 293TN Producer cells (System Biosciences, LV900A-1) were plated in T150 flasks overnight. Plasmids encoding lentiviral packaging proteins and Spike were added 1 mL of plain DMEM for each T150 being transfected. 55 mL of PureFection reagent (System Biosciences; Cat #LV750A-1) was added to each 1 mL tube, vortexed for 10 seconds, and incubated at room temperature for 15 minutes. The plasmid and PureFection mixture were added to a T150 flask containing 293TN cells and placed in a 37°C incubator containing 5% CO₂ for 48 hours. Pseudovirus-containing supernatants were harvested at 48 hours and passed through a 0.45 micron PVDF filter to remove cellular debris. 5x PEG-it Virus Precipitation Solution (System Biosciences, Cat #LV810A-1) was added to supernatants and incubated 4°C overnight. Pseudovirus-containing supernatants with 1x PEG-it Virus Precipitation Solution were then spun at 1500 x g for 30 minutes. Pseudovirus-containing pellets were resuspended in plain DMEM to achieve at 10x concentration and frozen at -80°C in single use aliquots.

[0293] Pseudovirus infection and neutralization assays were performed by using standard methods. Pseudoviruses were produced with the pPACK-SPIKE packaging kit, 10^4 ACE2-293T cells were plated in the inner 60 wells of a white opaque 96 well flat bottom plate (Corning; Cat #3917) in 100 μ L of ACE2-293T media overnight in a 37°C incubator containing 5% CO₂. To determine infectivity of each lot of pseudovirus, pseudovirus-containing supernatants were thawed from -80°C and two-fold dilutions were performed. 100 μ L of pseudovirus at various dilutions was added to ACE2-293T cells. To test neutralization activity of antibodies, indicated antibody concentrations were pre-incubated with pseudovirus for 1 hour in a 37°C incubator containing 5% CO₂. Then, 100 μ L of antibody/pseudovirus mixture was added to ACE2-293T cells. After 72 hours, cells and media were equilibrated to room temperature for 20 minutes. 100 μ L of media was removed and replaced with 100 μ L of Bright-Glo Luciferase Assay Reagent (Promega, Cat #E2620). Luminescence was measured on the EnSpire Plate Reader (PerkinElmer).

[0294] Initial testing with pseudovirus was performed using antibody-containing supernatants, 3-4 log dilutions of 26 unique anti-Spike antibodies were tested for their ability to block infection in comparison to an anti-RSV negative control and a commercially available anti-Spike positive control.

[0295] Neutralization activity of a subset of antibodies (Fig. 3) was confirmed using SARS-CoV-2 luciferase reporter virus particles (RVP's) (Integral Molecular) based on the manufacturer's instructions. In brief, RVP's were thawed for 2-3 minutes in a 37°C water bath. The recommended amount of RVP's was added to the inner wells of a white opaque 96 well plate (Corning; Cat #3917) or 384 well plate (Greiner Bio-One; Cat #781080). Media containing the indicated amount of antibody was added to each well, resulting in a final volume of 100 μ L per well (96 well plate) or 25 μ L per well (384 well plate). The antibody/RVP mixture was pre-incubated for 1 hour in a 37°C incubator containing 5% CO₂. ACE2-293T target cells were added to each well (2×10^4 cells in 100 μ L for a 96 well plate or 0.9×10^4 cells for a 384 well plate) and incubated for 72 hours. Media was removed from all wells, equal volumes of PBS and Renilla-Glo Luciferase Assay Reagent (Promega; Cat #E2720) were added to each well (60 μ L total for a 96 well plate or 30 μ L total for a 384 well plate). After 10 minutes, luminescence was measured on the EnSpire Plate Reader (PerkinElmer). Percent neutralization was calculated with the following equation: [(RLU of

Virus + cells) – (RLU of Experimental Sample)] / [(RLU of Virus + cells) – (RLU of cells only)].

[0296] The PR194_00232 antibody that exhibited potent neutralization against pseudovirus expressing both the reference (SARS-CoV-2/human/USA/WA_CDC-WA1/2020) and D614G (SARS-CoV-2/human/Germany/BavPat 1/2020) were also assessed in neutralization assays using live virus of each of the isolates (Figs 4A and 4B).

[0297] Full dose response of purified antibodies confirmed strong neutralizing activity by antibodies such as PR194_00232. The D614G variant is a widespread mutation [Plante et al. 2020] found in a number of different isolates. Antibodies such as PR194_00232, that bound to the soluble protein and neutralized pseudovirus expressing the D614G Spike, were also able to neutralize the live virus with comparable IC₅₀ values (Fig. 4B).

[0298] Pseudovirus particles expressing Spike proteins that mimic the U.K. (B.1.1.7) and South African (B.1.351) isolates are neutralized by antibodies which retain binding to the mutated Spikes (Tables 3 & 4). This is exemplified by the antibodies PR193_00018 and PR200_00622 (Fig. 5). In contrast, antibodies that lose binding affinity for the mutated Spikes have a decreased neutralization potency; PR193_00232 retains neutralization activity against the UK variant pseudovirus but is unable to effectively neutralize the S. African pseudovirus.

[0299] **Example 7.** *A cocktail of three anti-SARS-CoV-2 anti-Spike antibodies elicit combinatorial effects.* With the objective of producing an antibody composition that is able to neutralize both current, and future, variants, including, but not limited to, CDC Variants of Concern/Interest (alpha/B.1.1.7; beta/B.1.351; gamma/P.1; delta/B.1.617.2; epsilon/B.1.429/427), antibodies selective for non-overlapping epitopes on the SARS-CoV-2 Spike protein were assessed in pair-wise, and three-way combinations to identify additive, or preferably synergistic, neutralization.

[0300] More specifically, the antibodies PR194_00232 (IMM20190), PR193_00018 (IMM20184), and PR200_00622 (IMM20253) were assessed in combinations to evaluate the combinatorial impact on neutralization of pseudovirus expressing a range of different variations of the Spike protein (Fig. 6). IC₅₀ values for the triple combination and double combination comprising IMM20184 and IMM20253 were determined using RVPs, as described above.

[0301] As depicted in Fig. 6 the triple combination of antibodies neutralized pseudoviruses corresponding to the USA/WA_CDC-WA1/2020 (reference sequence) and the CDC variants of concern (alpha/U.K./B.1.1.7, beta/South African/B.1.351, gamma/Brazil/P.1 and epsilon/California/B.1.429/427). In these pseudovirus assays, the IC₅₀s for neutralization of the reference and California variants were not determined due to the potency exhibited against those variants; concentrations sufficiently low enough to obtain below 50% neutralization were not tested. Neutralization of the U.K., Brazilian, and South African were achieved with IC₅₀s of 0.7 nM, 31 nM, and 23 nM, respectively, in these assays. The impact of IMM20190 on neutralization of the reference, CA, and UK variants can be observed by comparing the IC₅₀s achieved with the double combination of IMM20184/IMM20253 against the same pseudoviruses. In the absence of IMM20190, the reference California and U.K. variant pseudoviruses are neutralized with higher IC₅₀s, corresponding to 37 nM, 15 nM, and 25 nM respectively. In the case of the S. African and Brazilian, the lack of IMM20190 does not dramatically alter the IC₅₀s, consistent with IMM20184/IMM20253 providing the majority of the neutralization activity.

[0302] To determine combinatorial impact of the antibodies pseudovirus neutralization experiments were set up as described above, except that for combinations of two antibodies, one test article was titrated in the background of each concentration in a serial dilution of the other test article. Single antibody titrations were included as controls. For combinations of three antibodies, one test article was titrated in the background of each concentration in a serial dilution of a 1:1 mixture of the other two test articles. To evaluate antibody synergy in the combinations, the observed combination response matrix of pseudovirus neutralization was used as input for the online SynergyFinder platform (4), where quadruplicate data points were input separately. The highest single agent (HSA) reference model was applied, which quantifies synergy as the excess over the maximum response of a single drug in the combination. Synergy between antibodies in each combination is reported as an overall synergy score (the average of observed synergy across the dose combination matrix) as well as a peak HSA score (the highest synergy score calculated across the dose combination matrix). Synergy scores of less than -10, between -10 and 10, and greater than 10 indicate antagonistic, additive, and synergistic antibody combinations, respectively. While peak HSA scores report on synergy at the most optimal combination concentrations, the overall synergy score is less affected by outlier data points.

[0303] As depicted in Fig. 7, the triple antibody combination of IMM20184/IMM20190/IMM20253, also known as IMM-BCP-01, synergized with each other to neutralize pseudovirus expressing the WA1/2020 reference, alpha/UK/B.1.1.7, Beta/S.African/B.1.351, Gamma/Brazil/P.1, and epsilon/Californian/B.1.429 spike proteins. Peak synergy scores ranged from 19.8 against the gamma variant to 61.1 against the alpha variant. Synergy was maintained against the alpha/UK variant across the entire concentration range tested. Overall additivity was observed against the other pseudoviruses. Synergy was observed against the live virus isolate Germany BavPat 1/2020 at defined ratios, with overall additivity being observed across the concentrations tested (Fig. 7B).

[0304] **Example 8. Predicted activity against new variants.** As the SARS-CoV-2 virus continues to mutate it will be imperative to predict, and confirm, the ability of antibodies to neutralize newly arising variants. As depicted in Fig. 8 the residues critical for binding of IMM20184, IMM20190, and IMM20253 are spatially distinct from the residues mutated in the RBD of the B.1.617.2 (delta), B.1.617.3 (kappa), and C.37 (lambda) variants. Based upon the location of the L452R T478K mutations in the B.1.617.2 variant, the L452R E484Q mutations in the B.1.617.3 variant, and the L452Q F490S mutations in the lambda variant, it was predicted that the triple antibody combination would be able to neutralize those variants in a manner at least equivalent to the reference WA1/2020 strain.

[0305] Pseudovirus neutralization assays were performed with RVPs, as described above, that express the B.1.617.2, B.1.617.3, or C.37 variants. Consistent with the prediction, IMM-BCP-01 neutralized the pseudoviruses in a manner that was at least equivalent to the reference WA1/2020 variant (Table 6). Neutralization curves (Fig. 9).

[0306] Activity of the triple antibody cocktail against the B.1.617.2 and B.1.617.3 variants is depicted in the context of other variants in Fig. 10. Consistent with the known epitopes of the antibodies, and positions of RBD-localized mutations in the different variants, the triple antibody cocktail exhibits neutralizing activity across all variants tested.

[0307] IMM20190 binds to a large epitope that encompasses two distinct regions on the RBD (Fig. 2). K417 and N501, residues known to be mutated in different variants, represent residues in each of the two binding sites. Mutation of one of those sites (N501Y), as observed in the alpha/B.1.1.7 variant, is sufficient to maintain IMM20190 activity (Fig. 5) and provides for improved synergy with IMM20184/IMM20253. The delta

plus/B.1.617.2.ay1/2 variant contains a K417N mutation. As predicted by our understanding of the IMM20190 epitope, and borne out by the results depicted in Table 6, the K417N mutation causes a partial loss of neutralization potential, the magnitude of the effect is in line with that observed against the alpha. Mutation of both K417 and N501, as observed in the beta/B.1.351 and gamma/P.1 variants, more fully abrogates IMM20190 activity, and neutralization is achieved through the IMM20184/IMM20253 antibodies. Those are reflected in the results depicted Fig. 10 and the IC50/90 values derived from those data (Table 6).

Table 6. IC50 & IC90 Values (nM) for IMM-BCP-01 Against Reference and Variants

	Pseudovirus		Live Virus	
	IC50	IC90	IC50	IC90
REF (WA1/2020)	1.0	5.2	1.1	3.4
D614G	0.9	4.2	NT	NT
Alpha	3.4	16.1	3.1	8.7
Beta	13.5	87.4	7.4	41.7
Gamma	24.8	129	NT	NT
Delta	0.4	2.3	NT	NT
Delta plus	3.0	15.2	NT	NT
Epsilon	0.6	3.4	NT	NT
Lambda	0.4	1.5	NT	NT
Kappa (L452/E484Q/D614G)	1.0	5.7	NT	NT

NT = Not Tested

[0308] The broad panel of neutralization data, combined with our understanding of the IMM-BCP-01 epitopes, provides us with confidence on predicting the impact of any newly emerging variants on the efficacy of the IMM-BCP-01 cocktail.

[0309] **Example 9.** *Triple combination is active against live virus* To confirm results obtained with pseudovirus testing we performed neutralization assays on four different live virus variants under BSL3 conditions: USA/WA_CDC-WA1/2020 (reference sequence), Germany/BavPat 1/2020 (D614G), UK (B.1.1.7), and South African (B.1.351). In all cases, neutralization of the live virus recapitulated data obtained in pseudovirus neutralization assays (Fig. 11 and Table 6). Assays using the Germany/BavPat1/2020 strain were performed in a manner sufficient to assess combinatorial effects via the HSA algorithm. Data demonstrated an overall additive effect, with peak HSA scores reaching levels of synergy (Fig. 7B)

[0310] **Example 10.** *Abs neutralize virus in a hamster model of SARS-CoV-2.* Antibodies capable of neutralizing live virus in vitro were assessed for the ability to neutralize virus in vivo using a hamster model of SARS-CoV-2 infection. Hamsters treated with increasing

doses of PR194_00232 were infected with SARS-CoV-2 (SARS-CoV-2/human/USA/WA_CDC-WA1/2020) and viral load in the lungs were assessed at Day 4 post inoculation of the virus using standard tissue culture infectivity assays and plaque counting. PR194_00232 was able to neutralize virus, relative to no-treatment controls, in a dose-dependent manner when dosed in the prophylactic setting (Fig. 12). Consistent with PR193_00018 and PR200_00622 working combinatorially with PR194_00232 to clear the virus, combinations consisting of PR194_00232/PR193_00018 and PR194_00232/PR200_00622 appear more effective at clearing the virus than PR194_00232 alone.

[0311] When dosed in the therapeutic setting (Fig. 13), a roughly 3-log clearance of virus, relative to no treatment, was observed in 5 out of 6 animals treated with this antibody cocktail. In contrast, other dose groups exhibited a more variable response with only three animals in any other group ever reaching maximal clearance. These data suggest that optimal viral clearance requires all three antibodies to be part of the cocktail.

[0312] In a follow-up study, the triple combination dosed at equimolar ratios (0.25 mg each) resulted in a statistically significant decrease in viral load in the lungs at day 4 post-inoculation, as measured with TCID50 assays (Fig. 14). To that end, in the same study doses of IMM20184 and IMM20253 were decreased to 0.125 mg each and we observed an increase in the median level of viral load in the lung compared to the cohort treated with the 1:1:1 ratio. These data provide additional support that IMM20184 and IMM20253 are contributing to in vivo efficacy, even in the context of the USA/WA_CDC-WA1/2020 viral isolate which is highly sensitive to neutralization by IMM20190 in vitro.

[0313] Variability observed in the efficacy of IMM-BCP-01 in various studies led to retrospective correlation of systemic exposure post-intraperitoneal injection with overall viral clearance (Fig. 15). Syrian golden Hamsters were inoculated with 3.3×10^5 TCID50 doses of WA1/2020 live virus in the nasal turbinates (1.65×10^5 per nare). IMM-BCP-01 was administered i.p. 6 hours post-inoculation at three different dose levels. Dose levels were 0.1mg each (0.3mg total), 0.2mg each (0.6 mg total), or 0.3 mg each (0.9mg total). Animals were euthanized at Day 4 and viral titers in lung determined by TCID50 assays. Levels of IgG in serum at time of euthanasia were determined by anti-huIgG ELISA to correlate IgG exposure with overall viral clearance. Data support the idea that i.p. injections led to variable levels of exposure and correlated with viral clearance. Serum levels of approximately 3 – 5

ug/mL at day 4 were sufficient to achieve viral clearance and were obtained by all three dose levels tested.

[0314] IMM-BCP-01 is able to clear virus from the lungs of hamsters infected with variants of concern. Hamsters were dosed prophylactically with IMM-BCP-01 one day prior to inoculation with either the Alpha (Fig 16A) or Beta (Fig 16B) variant and lung titers were determined on day 4 post-inoculation. IMM-BCP-01 at the lowest doses tested provided levels of viral clearance that match, or exceed, those obtained by antibodies with demonstrated clinical efficacy. In addition, increased doses of IMM-BCP-01 led to a dose-dependent improvement in viral clearance, with $\geq$ four-log clearance of WA1/2020 and 2.5 log clearance of Beta at the highest doses tested. All doses tested represent clinically relevant doses.

[0315] Robust activity of the cocktail was observed regardless of inoculation titer used (Fig 17). Syrian hamsters were inoculated with either 3.3×10^5 TCID₅₀ doses of WA1/2020 live virus in the nasal turbinates (1.65×10^5 per nare) or 3.3×10^4 TCID₅₀ doses of WA1/2020 live virus in the nasal turbinates (1.65×10^4 per nare). Animals were then treated 6 hours post-inoculation with either vehicle or IMM-BCP-01 at 0.1mg each dose level. Robust viral clearance was observed, relative to the vehicle control, for both inoculation levels.

Table 7. Binding Constants of IMM20184, IMM20190, & IMM20253 for Isolated RBD and Trimer

Ligand	Analyte	Kon (1/ms)	Koff (1/s)	KD (M)
IMM20184	Trimer	3.12E+04	2.29E-04	7.35E-09
	RBD	5.95E+04	1.31E-03	2.20E-09
IMM20190	Trimer	2.95E+04	1.95E-04	6.59E-09
	RBD	2.02E+05	3.76E-04	1.87E-09
IMM20253	Trimer	8.13E+04	1.17E-04	1.44E-09
	RBD	1.39E+06	2.18E-04	1.57E-10

Table 8. Phagocytosis Scores of Various anti-RBD Abs

IMM #	Target	Score at 0.6 nM
IMM20184	Spike (RBD)	56.6
IMM20190	Spike (RBD)	48.1
IMM20198	Spike (RBD)	37.9
IMM20242	Spike (RBD)	1.26
IMM20253	Spike (RBD)	49.5
IMM20254	Spike (RBD)	48.9
IMM20279	Spike (RBD)	43.3
COM00035	Positive Control	50.1

Anti-RSV	Negative Control	1.38
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[0316] **Example 11. Antibodies Elicit Mechanisms that Could Enhance Viral Neutralization and Clearance.** Each of the antibodies comprising IMM-BCP-01 (IMM20184, IMM20190, and IMM20253) bind to both isolated RBD and Spike trimer when assessed by surface plasmon resonance (Fig. 18). These data suggest that IMM20184 can bind avidly to the Spike trimer, as signified by the decrease off-rate (Table 7), and crosslink two Spike monomers.

[0317] Consistent with its epitope overlapping with the ACE2 binding site, IMM20190 is able to compete binding of ACE2 to isolated RBD protein from the REF and Alpha variant (Fig. 19A and Fig. 19B), but its ability to compete ACE2 binding to the Beta variant is decreased (Fig. 19C), consistent with its known decreased binding and neutralization potency. IMM20184 effectively competes binding of ACE2 to all three isolated RBD (Fig. 19A – C), despite binding to an epitope that is outside of known ACE2 binding site (Fig. 2). Despite exhibiting neutralization activity against both pseudovirus and live virus, IMM20253 is unable to effectively compete for ACE2 binding (Fig. 19A-C). This suggests the neutralization is due to a mechanism distinct from direct ACE2 competition.

[0318] IMM20184, IMM20190 and IMM20253 were assessed for the ability to fix complement using standard assays [Nikitin et al., 2019]. As depicted in Figs. 20A & B, all three antibodies comprising IMM-BCP-01 were able to fix complement, albeit to different levels when assessed at defined concentrations. All three antibodies demonstrated a preference for fixing complement upon binding to the stabilized trimer as compared to the isolated RBD. When assessed in a concentration-dependent manner (Fig. 20C), the combination of IMM20184 and IMM20253 induced an enhanced level of complement fixation beyond what was observed by either antibody alone. That activity was further enhanced by addition of IMM20190 to the antibody cocktail. These data suggesting the antibodies comprising IMM-BCP-01 elicit a combinatorial, or synergistic, activation of complement fixation upon binding Spike.

[0319] Select antibodies were also assessed for the ability to phagocytosis at a defined concentration and using methods described previously [Shi et al., 2014]. As listed in Table 8, antibodies elicited a range of phagocytosis scores, with higher values representing a more robust ability to induce phagocytosis. Each of the antibodies comprising IMM-BCP-01 was

further evaluated in the ability to induce phagocytosis in a concentration-dependent manner against the full-length trimer, both as individual antibodies and as cocktails of two or three antibodies (Fig. 21). All three antibodies induce phagocytosis of the full-length trimer in concentration-dependent manners, with IMM20253 inducing the most robust activation of phagocytosis as assessed in vitro. IMM-BCP-01 exhibited enhanced activity, over a wider concentration range, as compared to any of the individual antibodies and the IMM20184/IMM20253 two antibody combination.

[0320] IMM-BCP-01 induces a more robust antibody-dependent cellular cytotoxicity than any of the individual component antibodies when assessed in vitro using Promega's ADCC Reporter Bioassay and S-expressing CHO-K1 target cells at a 2:1 effector:target cell ratio and manufacturer protocols.

[0321] Taken together these data suggest that the IMM-BCP-01 cocktail robustly induces multiple effector functions in a manner that is enhanced by the presence of two or more of its constituent antibodies as compared to the individual antibodies alone.

[0322] **Example 12.** *IMM20253 may neutralize SARS-CoV-2 through a mechanism that alters Spike protein conformation.* As depicted in Fig. 2, IMM20253 binds to an epitope that is on the outside face of the RBD domain of the SARS-CoV-2 RBD. When in the closed conformation, the epitope is in close proximity to the N-terminal domain of a second Spike protein within the Spike trimer. A recent paper [Sun et al, 2021] describes the isolation of nanobodies (Nb), defined as class III Nb, that bind to epitopes that appear to overlap with the IMM20253 epitope. Biochemical characterization the Class III Nb demonstrates that binding of the Nb to the Spike protein induces a conformational change to the post-fusion conformation. This presumably inactivates the virus' ability to bind cells and provides a mechanism for the neutralization observed in vitro. Like the Class III Nbs, IMM20253 is unable to directly compete for ACE2 binding (Fig. 20), but is able to neutralize both reference and alpha variant live virus as a single agent when measured as a function of virus internalization (Table 9). Together, these data suggest that IMM20253 binding to the outer face of the RBD may impart its intrinsic neutralization through induction of a conformational change in the Spike protein that prevents virus uptake into the cells without competing for ACE2 binding. Interestingly, IMM20253 appears to be approximately 30-times more potent against the alpha strain than the delta strain. This may be a function of the internalization kinetics of the two different variants. This difference may also underlie the strong synergy

observed between the IMM20184/IMM20190/IMM20253 in the context of neutralizing the alpha variant (Fig. 7). It should be noted that like Greaney et al [Greaney et al], Sun et al describe the region around the IMM20253 epitope as being of therapeutic interest, one to which antibodies are not known to exist [Greaney et al] and one that is going to be difficult for antibodies to access [Sun et al]. Consistent with these assertions, the CoVIC consortium analyzed over 300 antibodies that bind to the RBD domain of the SARS-CoV-2 Spike protein and failed to identify an antibody that bound to the IMM20253 epitope. These points all highlight the uniqueness of the IMM20253 antibody [Hastie et al].

[0323] As outlined in Fig 23, binding of IMM20253, but not IMM20190, induces a time-dependent conformational change in the trimeric Spike protein. Dynamic light scattering (DLS) analysis performed at $t = 0$ and $t = 2$ hours, demonstrates that IMM20253 binding results in the complex adopting a conformation with a smaller hydrodynamic radius. In contrast, the IMM20190/Spike trimer complex maintains a similar hydrodynamic radius throughout the two hour incubation.

[0324] The conformational change induced by IMM20253 results in an increased protease sensitivity of the Spike protein (Fig 24). Cleavage of Spike, when incubated in the presence of thrombin protease, is observed at $t = 1$ hour. Similar results are observed when Spike is complexed with either ACE2 or IMM20190. In contrast, proteolytic cleavage of Spike, and release of S2, is observed within 15 minutes when Spike is complexed with the IMM20253. Without being bound by theory, this data suggests that the IMM20253 antibody is particularly effective against variants that have pre-cleaved Spike proteins and/or variants that are more susceptible to cleavage.

Table 9. Neutralization capacity of all single, double, and triple combinations of IMM20184, IMM20190, and IMM20253 in a virus internalization assay.

antibody/ combination	virus batch nr	virus type	WHO label	Pango lineage	IC50 (nM)	IC80 (nM)	IC90 (nM)
IMM20184	VC-210180028	SARS-CoV-2 (UK strain)	Alpha	B.1.1.7	43.32	>393.7	>393.7
IMM20190	VC-210180028	SARS-CoV-2 (UK strain)	Alpha	B.1.1.7	2.66	13.67	>393.7
IMM20253	VC-210180028	SARS-CoV-2 (UK strain)	Alpha	B.1.1.7	1.38	61.11	218.95
Combo 1 (IMM20184/ IMM20190)	VC-210180028	SARS-CoV-2 (UK strain)	Alpha	B.1.1.7	0.98	3.60	6.62
Combo 2 (IMM20184/ IMM20253)	VC-210180028	SARS-CoV-2 (UK strain)	Alpha	B.1.1.7	5.72	21.08	37.28
Combo 3 (IMM20190/ IMM20253)	VC-210180028	SARS-CoV-2 (UK strain)	Alpha	B.1.1.7	0.85	8.49	16.62

Combo 4 (IMM20184/ IMM20253)	VC-210180028	SARS-CoV-2 (UK strain)	Alpha	B.1.1.7	0.44	2.85	5.80
IMM20184	VC-210180051	SARS-CoV-2 (BavPat-1)	n/a	n/a (wild type)	33.81	125.56	235.94
IMM20190	VC-210180051	SARS-CoV-2 (BavPat-1)	n/a	n/a (wild type)	0.35	1.43	3.06
IMM20253	VC-210180051	SARS-CoV-2 (BavPat-1)	n/a	n/a (wild type)	39.38	150.68	289.21
Combo 1 (IMM20184/ IMM20190)	VC-210180051	SARS-CoV-2 (BavPat-1)	n/a	n/a (wild type)	0.37	1.41	3.50
Combo 2 (IMM20184/ IMM20253)	VC-210180051	SARS-CoV-2 (BavPat-1)	n/a	n/a (wild type)	3.89	36.42	78.50
Combo 3 (IMM20190/ IMM20253)	VC-210180051	SARS-CoV-2 (BavPat-1)	n/a	n/a (wild type)	0.35	1.28	3.34
Combo 4 (IMM20184/ IMM20253)	VC-210180051	SARS-CoV-2 (BavPat-1)	n/a	n/a (wild type)	0.24	1.20	2.81

[0325] **Example 13.** *IMM20253, alone or in combination with IMM20184, induces synergy with other ACE2-competitive antibodies.* Binding of either IMM20253, IMM20184, or the combination of the two antibodies (IMM20253/IMM20184), induces combinatorial effects, preferably synergy, when combined with the ACE2-competitive antibody IMM20190. Combinations of IMM20253, IMM20184, or IMM20253/IMM20184, induces synergy with other ACE2-competing enzymes. IMM20253, IMM20184, or IMM20253/IMM20184 combines with one or more of the following antibodies to induce combinatorial, preferably synergistic, viral neutralization in vitro and promote in vivo viral clearance. Examples of antibodies that combine to induce the combinatorial effect with IMM20253, IMM20184 or IMM20253/IMM20184 include, but are not limited to, sotrovimab, casirivimab, imdevimab, bamlanivimab, etesevimab, tixagevimab, cilgavimab, ADG2, ADG10, ADG20, ADG30, and CR3022. As depicted in Fig 25, IMM20253 works in combination with IMM20184, as well as in-house generated versions of REGN987 (imdevimab) and REGN933 (casirivimab) when assayed against B.1.617.2 ay2 pseudovirus. Under the conditions tested all three combinations displayed synergistic neutralization at defined concentrations achievable in vivo (HSA score ≥ 10). Under the conditions tested, the IMM20253/IMM20184 combination achieved an overall HSA score indicative of synergy (12.5). IMM20253/REGN933 achieved an overall HSA score of 9.5, suggestive of additivity (HSA score between -10 and 10). The IMM20253/REGN933 combination demonstrated an overall HSA score of 5.6, consistent with additive activity under the conditions tested. All three antibodies (IMM20184, REGN933 and REGN987) block ACE2 binding. In contrast, IMM20253 in combination with in-house generated S309 (sotrovimab) resulted in strong antagonism across all concentrations tested (Fig. 26). S309 is thought to work through a non-ACE2 dependent neutralization mechanism. This suggests that IMM20253's non-ACE2

dependent neutralization mechanism may enhance neutralization in combination with antibodies that work via an ACE2-dependent neutralization mechanism, but may antagonize other non-ACE2 dependent mechanisms of neutralization.

[0326] **Example 14.** *IMM20253 and IMM20279 and exhibit potent binding to the Spike protein of the Omicron variant.* Individual antibodies were assessed, in the HTRF assay described above, using the full length Spike protein and soluble RBD domains of the Spike protein containing mutations found in the Omicron variant. Figs. 27 (A-D) depict the binding of the individual antibodies to the Spike-RBD of the Omicron variant, expressed as percentage binding, relative to the binding to the reference strain. Binding of the antibodies IMM20190 and IMM20184 (Fig. 27 A and B), are negatively affected by the mutations within the Spike domain of the Omicron variant. In contrast, binding by the IMM20253 (Fig. 27 C) and IMM20279 (Fig. 27 D) antibodies are unaffected by the range of mutations within the Spike protein of the Omicron variant. The binding affinity of the IMM20279 antibody to the RBD as well as the full-length Spike protein is comparable to that of the reference strain (Fig. 27 D).

[0327] **Example 15.** *IMM20253 antibody neutralizes SARS-CoV-2 pseudovirus expressing the Omicron variant.* The functional consequence of the IMM20253 antibody binding to Spike was assessed. Pseudovirus infection and neutralization assays were performed by using standard methods described above. The IMM20253 antibody exhibited potent neutralization against pseudovirus expressing the Spike protein from the B.1.1.529 (Omicron) variant (Fig. 28). The neutralization activity was comparable to the activity against pseudovirus expressing the Spike protein from the reference strain (SARS-CoV-2/human/USA/WA_CDC-WA1/2020), D614G (SARS-CoV-2/human/Germany/BavPat 1/2020), B.1.351 (beta/S. African), B.1.617.2 Ay.2 (Delta Plus) variants of SARS-CoV-2 (Fig. 28).

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CLAIMS

What is claimed:

1. A composition comprising at least first and second recombinant antibodies that specifically bind to distinct epitopes of a Spike protein of SARS-CoV-2, wherein the first antibody binds to an epitope in an ACE2 receptor binding site of the Spike protein and the second antibody binds to an epitope outside of the ACE2 receptor binding site of the Spike protein.
2. A composition comprising at least first and second antibodies that specifically bind to distinct epitopes of a Spike protein of SARS-CoV-2, wherein the first antibody neutralizes SARS-CoV-2 via an ACE2 independent mechanism and the second antibody neutralizes SARS-CoV-2 via an ACE2 dependent mechanism, wherein the first and second antibodies are recombinant antibodies.
3. The composition of claim 1 or claim 2, further comprising a third antibody that specifically binds to the Spike protein of SARS-CoV-2 at an epitope distinct from the first and second antibodies.
4. The composition of claim 3, wherein the third antibody binds to an epitope outside of the ACE2 receptor binding site of the Spike protein.
5. The composition of any one of claims 3-4, wherein the third recombinant antibody neutralizes SARS-CoV-2 via an ACE2 dependent mechanism.
6. An antibody or antigen-binding fragment thereof that binds a SARS-CoV-2 Spike protein comprising

a HCDR1, HCDR2, and HCDR3 of a heavy chain variable region (HCVR) comprising the amino acid sequence set forth in SEQ ID NO: 1, and a LCDR1, LCDR2, and LCDR3 of a light chain variable region (LCVR) comprising the amino acid sequence is set forth in SEQ ID NO: 2;

a HCDR1, HCDR2, and HCDR3 of a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 3, and a LCDR1, LCDR2, and LCDR3 of a LCVR comprising the amino acid sequence is set forth in SEQ ID NO: 4;

a HCDR1, HCDR2, and HCDR3 of a HCVR comprising the amino acid sequence set forth in SEQ ID NO: 5, and a LCDR1, LCDR2, and LCDR3 of a LCVR comprising the amino acid sequence is set forth in SEQ ID NO: 6;

a HCDR1, HCDR2, and HCDR3 of a HCVR comprising the amino acid sequence set forth in SEQ ID NO: 7, and a LCDR1, LCDR2, and LCDR3 of a LCVR comprising the amino acid sequence is set forth in SEQ ID NO: 8;

a HCDR1, HCDR2, and HCDR3 of a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 9, and a LCDR1, LCDR2, and LCDR3 of a light chain variable region (LCVR) comprising the amino acid sequence is set forth in SEQ ID NO: 10;

a HCDR1, HCDR2, and HCDR3 of a HCVR comprising the amino acid sequence set forth in SEQ ID NO: 11, and a LCDR1, LCDR2, and LCDR3 of a LCVR comprising the amino acid sequence is set forth in SEQ ID NO: 12;

a HCDR1, HCDR2, and HCDR3 of a HCVR comprising the amino acid sequence set forth in SEQ ID NO: 13, a LCDR1, LCDR2, and LCDR3 of a LCVR comprising the amino acid sequence is set forth in SEQ ID NO: 14

a HCDR1, HCDR2, and HCDR3 of a HCVR comprising the amino acid sequence set forth in SEQ ID NO: 15, and a LCDR1, LCDR2, and LCDR3 of a LCVR comprising the amino acid sequence is set forth in SEQ ID NO: 16

a HCDR1, HCDR2, and HCDR3 of a HCVR comprising the amino acid sequence set forth in SEQ ID NO: 17, and a LCDR1, LCDR2, and LCDR3 of a LCVR comprising the amino acid sequence is set forth in SEQ ID NO: 18

a HCDR1, HCDR2, and HCDR3 of a HCVR comprising the amino acid sequence set forth in SEQ ID NO: 19, and a LCDR1, LCDR2, and LCDR3 of a LCVR comprising the amino acid sequence is set forth in SEQ ID NO: 20;

a HCDR1, HCDR2, and HCDR3 of a HCVR comprising the amino acid sequence set forth in SEQ ID NO: 21, and a LCDR1, LCDR2, and LCDR3 of a LCVR comprising the amino acid sequence is set forth in SEQ ID NO: 22;

a HCDR1, HCDR2, and HCDR3 of a HCVR comprising the amino acid sequence set forth in SEQ ID NO: 23, and a LCDR1, LCDR2, and LCDR3 of a LCVR comprising the amino acid sequence is set forth in SEQ ID NO: 24; or

a HCDR1, HCDR2, and HCDR3 of a HCVR comprising the amino acid sequence set forth in SEQ ID NO: 25 and a LCDR1, LCDR2, and LCDR3 of a LCVR comprising the amino acid sequence is set forth in SEQ ID NO: 26.

7. The antibody or antigen binding fragment thereof of claim 6, wherein the antibody comprises

a HCVR comprising the amino acid sequence set forth in SEQ ID NO: 1, and a LCVR comprising the amino acid sequence is set forth in SEQ ID NO: 2;

a HCVR comprising the amino acid sequence set forth in SEQ ID NO: 3, and a LCVR comprising the amino acid sequence is set forth in SEQ ID NO: 4;

a HCVR comprising the amino acid sequence set forth in SEQ ID NO: 5, and a LCVR comprising the amino acid sequence is set forth in SEQ ID NO: 6;

a HCVR comprising the amino acid sequence set forth in SEQ ID NO: 7, and a LCVR comprising the amino acid sequence is set forth in SEQ ID NO: 8;

a HCVR comprising the amino acid sequence set forth in SEQ ID NO: 9, and a LCVR comprising the amino acid sequence is set forth in SEQ ID NO: 10;

a HCVR comprising the amino acid sequence set forth in SEQ ID NO: 11, and a LCVR comprising the amino acid sequence is set forth in SEQ ID NO: 12;

a HCVR comprising the amino acid sequence set forth in SEQ ID NO: 13, a LCVR comprising the amino acid sequence is set forth in SEQ ID NO: 14;

a HCVR comprising the amino acid sequence set forth in SEQ ID NO: 15, and a LCVR comprising the amino acid sequence is set forth in SEQ ID NO: 16;

a HCVR comprising the amino acid sequence set forth in SEQ ID NO: SEQ ID NO: 17, and a LCVR comprising the amino acid sequence is set forth in SEQ ID NO: 18;

a HCVR comprising the amino acid sequence set forth in SEQ ID NO: 19, and a LCVR comprising the amino acid sequence is set forth in SEQ ID NO: 20;

a HCVR comprising the amino acid sequence set forth in SEQ ID NO: 21, and a LCVR comprising the amino acid sequence is set forth in SEQ ID NO: 22;

a HCVR comprising the amino acid sequence set forth in SEQ ID NO: 23, and a LCVR comprising the amino acid sequence is set forth in SEQ ID NO: 24; or

a HCVR comprising the amino acid sequence set forth in SEQ ID NO: 25 and a LCVR comprising the amino acid sequence is set forth in SEQ ID NO: 26.

8. An antibody or antigen-binding fragment thereof that binds a SARS-CoV-2 Spike protein comprising

a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:55, a HCDR2 comprising the amino acid sequence of SEQ ID NO:56, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:57; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:58, a LCDR2 comprising the amino acid sequence of SEQ ID NO:59, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:60;

a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:61, a HCDR2 comprising the amino acid sequence of SEQ ID NO:62, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:63; and a VL comprising a LCDR1 comprising the

amino acid sequence of SEQ ID NO:64 a LCDR2 comprising the amino acid sequence of SEQ ID NO:65, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:66; a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:67, a HCDR2 comprising the amino acid sequence of SEQ ID NO:68, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:69; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:70, a LCDR2 comprising the amino acid sequence of SEQ ID NO:71, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:72; or a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:109, a HCDR2 comprising the amino acid sequence of SEQ ID NO:110, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:111; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:112, a LCDR2 comprising the amino acid sequence of SEQ ID NO:113, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:114.

9. The antibody or antigen-binding fragment thereof of any one of claims 6-8, wherein the antibody is an an Fc IgG1, IgG2, IgG3, IgG4, IgM, IgD, IgA1, IgA2 or IgE isotype.

10. The antibody or antigen-binding fragment thereof of claim 9, wherein the antibody is an IgG1.

11. The antibody or antigen-binding fragment thereof of claim 9, wherein the IgG1 is a G1m1 or nG1m1 allotype.

12. The antibody or antigen-binding fragment thereof of any one of claims 6-11, comprising an immunoglobulin Fc region or fragment thereof of a human IgM.

13. The antibody of any one of claims 6-12, wherein the antibody is a fully human antibody.

14. The antibody of any one of claims 6-13, wherein the antibody is a full length antibody.

15. The antibody or antigen-binding fragment thereof of any one of claims 6-14, wherein binding of the antibody or antigen-binding fragment thereof:

inhibits binding of a SARS-CoV-2 virus to a host ACE2 receptor;

fixes complement to a SARS-CoV-2 virus;

induces phagocytosis of a SARS-CoV-2 virus; or

any combination thereof.

16. The antibody or antigen-binding fragment of any one of claims 6-15, wherein the binding of the antibody or antigen-binding fragment thereof neutralizes a SARS-CoV-2 virus by blocking binding of the receptor binding domain (RBD) of the virus with an ACE2 receptor.

17. The isolated antibody or antigen-binding fragment thereof of any one of claims 6-16, wherein the SARS-CoV-2 virus is a SARS-CoV-2 variant.

18. The isolated antibody or antigen-binding fragment thereof of claim 16, wherein the SARS-CoV-2 variant is the U.K. (B.1.1.7) variant of SARS-CoV-2, the South African (B.1.351) variant of SARS-CoV-2, the California (B.1.429) variant of SARS-CoV-2, the California (B.1.427) variant of SARS-CoV-2, the Brazilian (P.1) variant of SARS-CoV-2, the New York (B.1.526) variant of SARS-CoV-2, the New York (B.1.526.1) variant of SARS-CoV-2, the UK/Nigeria (B.1.525) variant of SARS-CoV-2, the Brazilian (P.2) variant of SARS-CoV-2 or the Omicron (B.1.1.529) variant.

19. The antibody of any one of claims 6-18, wherein the antibody is isolated.

20. A composition comprising the antibody of any one of claims 6-19.

21. A composition comprising two, three, or four of the antibodies of any one of claims 6-19.

22. A composition comprising

a) a first antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:55, a HCDR2 comprising the amino acid sequence of SEQ ID NO:56, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:57; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:58, a LCDR2 comprising the amino acid sequence of SEQ ID NO:59, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:60, and

a second antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:61, a HCDR2 comprising the amino acid sequence of SEQ ID NO:62, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:63; and a

VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:64 a LCDR2 comprising the amino acid sequence of SEQ ID NO:65, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:66;

b) a first antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:55, a HCDR2 comprising the amino acid sequence of SEQ ID NO:56, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:57; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:58, a LCDR2 comprising the amino acid sequence of SEQ ID NO:59, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:60, and

a second antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:67, a HCDR2 comprising the amino acid sequence of SEQ ID NO:68, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:69; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:70, a LCDR2 comprising the amino acid sequence of SEQ ID NO:71, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:72;

c) a first antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:55, a HCDR2 comprising the amino acid sequence of SEQ ID NO:56, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:57; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:58, a LCDR2 comprising the amino acid sequence of SEQ ID NO:59, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:60, and

a second antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:109, a HCDR2 comprising the amino acid sequence of SEQ ID NO:110, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:111; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:112, a LCDR2 comprising the amino acid sequence of SEQ ID NO:113, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:114;

d) a first antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:61, a HCDR2 comprising the amino acid sequence of SEQ ID NO:62, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:63; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:64 a LCDR2

comprising the amino acid sequence of SEQ ID NO:65, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:66, and

a second antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:67, a HCDR2 comprising the amino acid sequence of SEQ ID NO:68, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:69; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:70, a LCDR2 comprising the amino acid sequence of SEQ ID NO:71, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:72;

e) a first antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:61, a HCDR2 comprising the amino acid sequence of SEQ ID NO:62, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:63; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:64 a LCDR2 comprising the amino acid sequence of SEQ ID NO:65, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:66, and

a second antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:109, a HCDR2 comprising the amino acid sequence of SEQ ID NO:110, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:111; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:112, a LCDR2 comprising the amino acid sequence of SEQ ID NO:113, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:114; or

f) a first antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:67, a HCDR2 comprising the amino acid sequence of SEQ ID NO:68, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:69; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:70, a LCDR2 comprising the amino acid sequence of SEQ ID NO:71, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:72, and

a second antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:109, a HCDR2 comprising the amino acid sequence of SEQ ID NO:110, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:111; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:112, a LCDR2 comprising the amino acid sequence of SEQ ID NO:113, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:114.

23. A composition comprising

a) a first antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:55, a HCDR2 comprising the amino acid sequence of SEQ ID NO:56, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:57; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:58, a LCDR2 comprising the amino acid sequence of SEQ ID NO:59, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:60,

a second antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:61, a HCDR2 comprising the amino acid sequence of SEQ ID NO:62, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:63; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:64 a LCDR2 comprising the amino acid sequence of SEQ ID NO:65, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:66, and

a third antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:67, a HCDR2 comprising the amino acid sequence of SEQ ID NO:68, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:69; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:70, a LCDR2 comprising the amino acid sequence of SEQ ID NO:71, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:72;

b) a first antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:55, a HCDR2 comprising the amino acid sequence of SEQ ID NO:56, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:57; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:58, a LCDR2 comprising the amino acid sequence of SEQ ID NO:59, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:60,

a second antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:61, a HCDR2 comprising the amino acid sequence of SEQ ID NO:62, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:63; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:64 a LCDR2 comprising the amino acid sequence of SEQ ID NO:65, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:66, and

a third antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:109, a HCDR2 comprising the amino acid sequence of SEQ ID NO:110, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:111; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:112, a LCDR2 comprising the amino acid sequence of SEQ ID NO:113, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:114; or

c) a first antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:61, a HCDR2 comprising the amino acid sequence of SEQ ID NO:62, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:63; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:64 a LCDR2 comprising the amino acid sequence of SEQ ID NO:65, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:66, and

a second antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:67, a HCDR2 comprising the amino acid sequence of SEQ ID NO:68, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:69; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:70, a LCDR2 comprising the amino acid sequence of SEQ ID NO:71, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:72, and

a third antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:109, a HCDR2 comprising the amino acid sequence of SEQ ID NO:110, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:111; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:112, a LCDR2 comprising the amino acid sequence of SEQ ID NO:113, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:114.

24. A composition comprising

a first antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:55, a HCDR2 comprising the amino acid sequence of SEQ ID NO:56, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:57; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:58, a LCDR2 comprising the amino acid sequence of SEQ ID NO:59, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:60,

a second antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:61, a HCDR2 comprising the amino acid sequence of SEQ ID NO:62, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:63; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:64 a LCDR2 comprising the amino acid sequence of SEQ ID NO:65, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:66,

a third antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:67, a HCDR2 comprising the amino acid sequence of SEQ ID NO:68, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:69; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:70, a LCDR2 comprising the amino acid sequence of SEQ ID NO:71, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:72, and

a fourth antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:109, a HCDR2 comprising the amino acid sequence of SEQ ID NO:110, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:111; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:112, a LCDR2 comprising the amino acid sequence of SEQ ID NO:113, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:114.

25. The composition of any one of claims 1-5 and 21-24, wherein the ratio between the first and the second recombinant antibodies is about 1 : 1.

26. The composition of any one of claims 3-5 and 23-24, wherein the ratios between the first, second, and third antibodies are about 1 : 1 : 1.

27. The composition of claim 21 or 24, wherein the ratio between the first, second, third, and fourth antibodies is about 1 : 1 : 1: 1.

28. The composition of any one of claims 1-5 or 20-27, wherein the composition neutralizes at least 50% of one or more of the following variants of SARS-CoV-2: U.K. B.1.1.7; South African B.1.351; Brazil P.1; Omicron B.1.1.529 variant; and California B.1.429/427 relative to the neutralization of the USA/WA_CDC-WA1/2020 SARS-CoV-2 by the composition.

29. The composition of any one of claims 1-5 or 20-27, wherein the composition neutralizes about 100% of one or more of the following variants of SARS-CoV-2: U.K. B.1.1.7; South African B.1.351; Brazil P.1; Omicron B.1.1.529 variant; and California B.1.429/427 relative to the neutralization of the USA/WA_CDC-WA1/2020 SARS-CoV-2 by the composition.
30. The composition of any one of claims 1-5 or 20-29, further comprising a pharmaceutically acceptable carrier or diluent.
31. A method of treating or preventing a SARS-CoV-2 infection in a subject, comprising administering a first antibody that neutralizes SARS-CoV-2 via an ACE2 independent mechanism and a second antibody that neutralizes SARS-CoV-2 via an ACE2 dependent mechanism.
32. A method of treating or preventing a SARS-CoV-2 infection in a subject, comprising administering the composition of any one of claims 1-5 or 20-31 or the antibody of any one of claims 6-19 to the subject.
33. A method of treating or preventing a SARS-CoV-2 infection in a subject, comprising administering two, three, or four of the antibodies of any of claims 6-19 to the subject.
34. A method of treating or preventing a SARS-CoV-2 infection in a subject, comprising administering
- a) a first antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:55, a HCDR2 comprising the amino acid sequence of SEQ ID NO:56, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:57; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:58, a LCDR2 comprising the amino acid sequence of SEQ ID NO:59, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:60, and
- a second antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:61, a HCDR2 comprising the amino acid sequence of SEQ ID NO:62, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:63; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:64 a LCDR2

comprising the amino acid sequence of SEQ ID NO:65, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:66;

b) a first antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:55, a HCDR2 comprising the amino acid sequence of SEQ ID NO:56, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:57; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:58, a LCDR2 comprising the amino acid sequence of SEQ ID NO:59, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:60, and

a second antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:67, a HCDR2 comprising the amino acid sequence of SEQ ID NO:68, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:69; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:70, a LCDR2 comprising the amino acid sequence of SEQ ID NO:71, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:72;

c) a first antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:55, a HCDR2 comprising the amino acid sequence of SEQ ID NO:56, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:57; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:58, a LCDR2 comprising the amino acid sequence of SEQ ID NO:59, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:60, and

a second antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:109, a HCDR2 comprising the amino acid sequence of SEQ ID NO:110, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:111; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:112, a LCDR2 comprising the amino acid sequence of SEQ ID NO:113, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:114;

d) a first antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:61, a HCDR2 comprising the amino acid sequence of SEQ ID NO:62, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:63; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:64 a LCDR2

comprising the amino acid sequence of SEQ ID NO:65, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:66, and

a second antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:67, a HCDR2 comprising the amino acid sequence of SEQ ID NO:68, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:69; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:70, a LCDR2 comprising the amino acid sequence of SEQ ID NO:71, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:72;

e) a first antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:61, a HCDR2 comprising the amino acid sequence of SEQ ID NO:62, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:63; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:64 a LCDR2 comprising the amino acid sequence of SEQ ID NO:65, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:66, and

a second antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:109, a HCDR2 comprising the amino acid sequence of SEQ ID NO:110, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:111; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:112, a LCDR2 comprising the amino acid sequence of SEQ ID NO:113, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:114; or

f) a first antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:67, a HCDR2 comprising the amino acid sequence of SEQ ID NO:68, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:69; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:70, a LCDR2 comprising the amino acid sequence of SEQ ID NO:71, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:72, and

a second antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:109, a HCDR2 comprising the amino acid sequence of SEQ ID NO:110, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:111; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:112, a LCDR2 comprising the amino acid sequence of SEQ ID NO:113, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:114.

35. A method of treating or preventing a SARS-CoV-2 infection in a subject, comprising administering

a) a first antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:55, a HCDR2 comprising the amino acid sequence of SEQ ID NO:56, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:57; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:58, a LCDR2 comprising the amino acid sequence of SEQ ID NO:59, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:60,

a second antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:61, a HCDR2 comprising the amino acid sequence of SEQ ID NO:62, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:63; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:64 a LCDR2 comprising the amino acid sequence of SEQ ID NO:65, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:66, and

a third antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:67, a HCDR2 comprising the amino acid sequence of SEQ ID NO:68, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:69; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:70, a LCDR2 comprising the amino acid sequence of SEQ ID NO:71, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:72;

b) a first antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:55, a HCDR2 comprising the amino acid sequence of SEQ ID NO:56, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:57; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:58, a LCDR2 comprising the amino acid sequence of SEQ ID NO:59, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:60,

a second antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:61, a HCDR2 comprising the amino acid sequence of SEQ ID NO:62, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:63; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:64 a LCDR2

comprising the amino acid sequence of SEQ ID NO:65, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:66, and

a third antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:109, a HCDR2 comprising the amino acid sequence of SEQ ID NO:110, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:111; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:112, a LCDR2 comprising the amino acid sequence of SEQ ID NO:113, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:114; or

c) a first antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:61, a HCDR2 comprising the amino acid sequence of SEQ ID NO:62, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:63; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:64 a LCDR2 comprising the amino acid sequence of SEQ ID NO:65, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:66, and

a second antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:67, a HCDR2 comprising the amino acid sequence of SEQ ID NO:68, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:69; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:70, a LCDR2 comprising the amino acid sequence of SEQ ID NO:71, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:72, and

a third antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:109, a HCDR2 comprising the amino acid sequence of SEQ ID NO:110, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:111; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:112, a LCDR2 comprising the amino acid sequence of SEQ ID NO:113, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:114.

36. A method of treating or preventing a SARS-CoV-2 infection in a subject, comprising administering a first antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:55, a HCDR2 comprising the amino acid sequence of SEQ ID NO:56, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:57; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:58, a LCDR2

comprising the amino acid sequence of SEQ ID NO:59, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:60,

a second antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:61, a HCDR2 comprising the amino acid sequence of SEQ ID NO:62, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:63; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:64 a LCDR2 comprising the amino acid sequence of SEQ ID NO:65, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:66,

a third antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:67, a HCDR2 comprising the amino acid sequence of SEQ ID NO:68, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:69; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:70, a LCDR2 comprising the amino acid sequence of SEQ ID NO:71, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:72, and

a fourth antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:109, a HCDR2 comprising the amino acid sequence of SEQ ID NO:110, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:111; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:112, a LCDR2 comprising the amino acid sequence of SEQ ID NO:113, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:114.

37. The method of any one of claims 31-36, wherein antibodies or antigen-binding fragments thereof in the composition

inhibit binding of SARS-CoV-2 viruses to host ACE2 receptors;

induce clearance of SARS-CoV-2 viruses by fixing complement to the viruses;

and/or

induce phagocytosis of the of SARS-CoV-2 viruses virus.

38. The method of any one of claims 31-37, wherein the SARS-CoV-2 virus is a SARS-CoV-2 variant.

39. The method of claim 38, wherein the SARS-CoV-2 variant is the U.K. (B.1.1.7) variant of SARS-CoV-2, the South African (B.1.351) variant of SARS-CoV-2, the California (B.1.429) variant of SARS-CoV-2, the California (B.1.427) variant of SARS-CoV-2, the

Brazilian (P.1) variant of SARS-CoV-2, the New York (B.1.526) variant of SARS-CoV-2, the New York (B.1.526.1) variant of SARS-CoV-2, the UK/Nigeria (B.1.525) variant of SARS-CoV-2, the Brazilian (P.2) variant of SARS-CoV-2, or the Omicron (B.1.1.529) variant.

40. The method of any one of claims 31-39, wherein the antibody or composition treats or prevents SARS-CoV-2 variant and nonvariant infections with about equivalent efficacies.

41. The method of any one of claims 31-40, wherein the administering of the antibody or composition to the subject in need thereof comprises administering the composition into the body of the subject subcutaneously, intravenously, intranasally or intramuscularly.

42. The method of any one of claims 31-41, for treating a SARS-CoV-2 infection.

43. A kit for treating or preventing a SARS-CoV-2 infection in a subject comprising a first antibody that specifically binds to a Spike protein of SARS-CoV-2 and neutralizes SARS-CoV-2 via an ACE2 independent mechanism and a second antibody that specifically binds to a Spike protein of SARS-CoV-2 and neutralizes SARS-CoV-2 via an ACE2 dependent mechanism.

44. A kit for treating or preventing a SARS-CoV-2 infection in a subject comprising the composition of any one of claims 1-5 or 20-30 or the antibody of any one of claims 6-19

45. A kit for treating or preventing a SARS-CoV-2 infection in a subject comprising two, three, or four of the antibodies of any one of claims 6-19.

46. A kit for treating or preventing a SARS-CoV-2 infection in a subject comprising

a) a first antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:55, a HCDR2 comprising the amino acid sequence of SEQ ID NO:56, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:57; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:58, a LCDR2 comprising the amino acid sequence of SEQ ID NO:59, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:60, and

a second antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:61, a HCDR2 comprising the amino acid sequence of SEQ ID NO:62, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:63; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:64 a LCDR2 comprising the amino acid sequence of SEQ ID NO:65, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:66;

b) a first antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:55, a HCDR2 comprising the amino acid sequence of SEQ ID NO:56, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:57; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:58, a LCDR2 comprising the amino acid sequence of SEQ ID NO:59, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:60, and

a second antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:67, a HCDR2 comprising the amino acid sequence of SEQ ID NO:68, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:69; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:70, a LCDR2 comprising the amino acid sequence of SEQ ID NO:71, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:72;

c) a first antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:55, a HCDR2 comprising the amino acid sequence of SEQ ID NO:56, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:57; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:58, a LCDR2 comprising the amino acid sequence of SEQ ID NO:59, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:60, and

a second antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:109, a HCDR2 comprising the amino acid sequence of SEQ ID NO:110, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:111; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:112, a LCDR2 comprising the amino acid sequence of SEQ ID NO:113, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:114;

d) a first antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:61, a HCDR2 comprising the amino acid sequence of SEQ ID NO:62, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:63; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:64 a LCDR2 comprising the amino acid sequence of SEQ ID NO:65, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:66, and

a second antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:67, a HCDR2 comprising the amino acid sequence of SEQ ID NO:68, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:69; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:70, a LCDR2 comprising the amino acid sequence of SEQ ID NO:71, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:72;

e) a first antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:61, a HCDR2 comprising the amino acid sequence of SEQ ID NO:62, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:63; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:64 a LCDR2 comprising the amino acid sequence of SEQ ID NO:65, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:66, and

a second antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:109, a HCDR2 comprising the amino acid sequence of SEQ ID NO:110, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:111; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:112, a LCDR2 comprising the amino acid sequence of SEQ ID NO:113, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:114; or

f) a first antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:67, a HCDR2 comprising the amino acid sequence of SEQ ID NO:68, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:69; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:70, a LCDR2 comprising the amino acid sequence of SEQ ID NO:71, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:72, and

a second antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:109, a HCDR2 comprising the amino acid sequence of

SEQ ID NO:110, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:111; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:112, a LCDR2 comprising the amino acid sequence of SEQ ID NO:113, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:114.

47. A kit for treating or preventing a SARS-CoV-2 infection in a subject comprising

a) a first antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:55, a HCDR2 comprising the amino acid sequence of SEQ ID NO:56, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:57; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:58, a LCDR2 comprising the amino acid sequence of SEQ ID NO:59, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:60,

a second antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:61, a HCDR2 comprising the amino acid sequence of SEQ ID NO:62, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:63; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:64 a LCDR2 comprising the amino acid sequence of SEQ ID NO:65, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:66, and

a third antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:67, a HCDR2 comprising the amino acid sequence of SEQ ID NO:68, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:69; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:70, a LCDR2 comprising the amino acid sequence of SEQ ID NO:71, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:72;

b) a first antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:55, a HCDR2 comprising the amino acid sequence of SEQ ID NO:56, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:57; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:58, a LCDR2 comprising the amino acid sequence of SEQ ID NO:59, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:60,

a second antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:61, a HCDR2 comprising the amino acid sequence of

SEQ ID NO:62, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:63; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:64 a LCDR2 comprising the amino acid sequence of SEQ ID NO:65, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:66, and

a third antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:109, a HCDR2 comprising the amino acid sequence of SEQ ID NO:110, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:111; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:112, a LCDR2 comprising the amino acid sequence of SEQ ID NO:113, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:114; or

c) a first antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:61, a HCDR2 comprising the amino acid sequence of SEQ ID NO:62, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:63; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:64 a LCDR2 comprising the amino acid sequence of SEQ ID NO:65, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:66, and

a second antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:67, a HCDR2 comprising the amino acid sequence of SEQ ID NO:68, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:69; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:70, a LCDR2 comprising the amino acid sequence of SEQ ID NO:71, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:72, and

a third antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:109, a HCDR2 comprising the amino acid sequence of SEQ ID NO:110, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:111; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:112, a LCDR2 comprising the amino acid sequence of SEQ ID NO:113, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:114.

48. A kit for treating or preventing a SARS-CoV-2 infection in a subject comprising

a first antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:55, a HCDR2 comprising the amino acid sequence of SEQ ID NO:56, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:57; and a VL

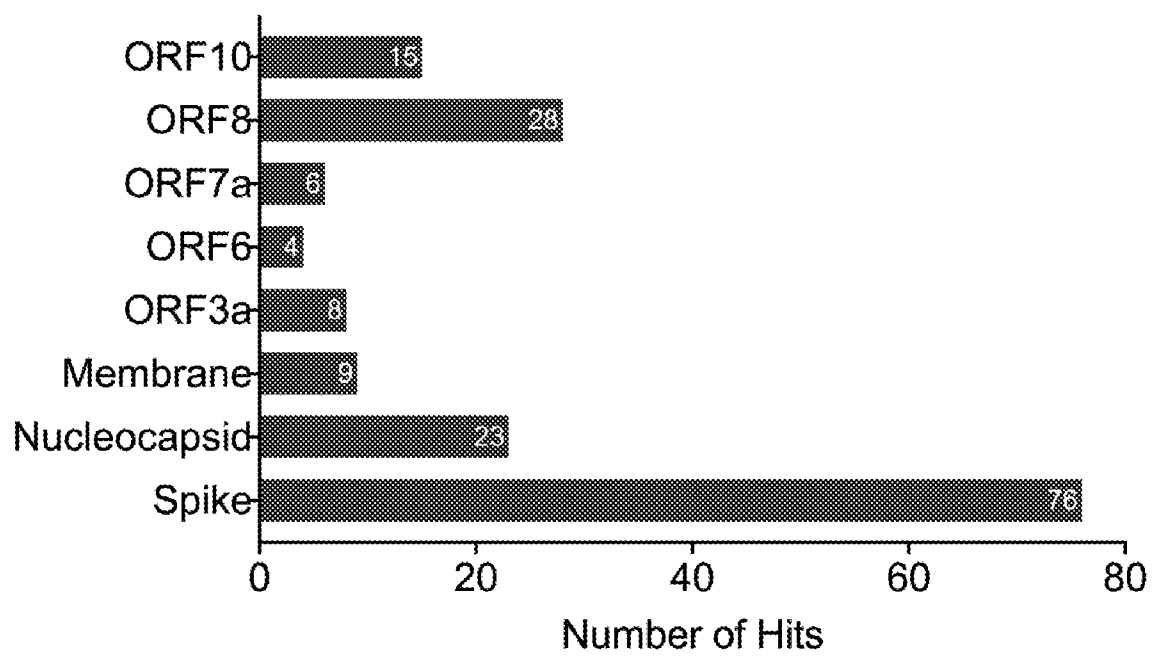
comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:58, a LCDR2 comprising the amino acid sequence of SEQ ID NO:59, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:60,

a second antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:61, a HCDR2 comprising the amino acid sequence of SEQ ID NO:62, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:63; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:64 a LCDR2 comprising the amino acid sequence of SEQ ID NO:65, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:66,

a third antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:67, a HCDR2 comprising the amino acid sequence of SEQ ID NO:68, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:69; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:70, a LCDR2 comprising the amino acid sequence of SEQ ID NO:71, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:72, and

a fourth antibody comprising a VH comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO:109, a HCDR2 comprising the amino acid sequence of SEQ ID NO:110, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:111; and a VL comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO:112, a LCDR2 comprising the amino acid sequence of SEQ ID NO:113, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:114.

49. The kit of any one of claims 43-48 further comprising instructions for use according to the method of any one of claims 31-41.

*FIG. 1*

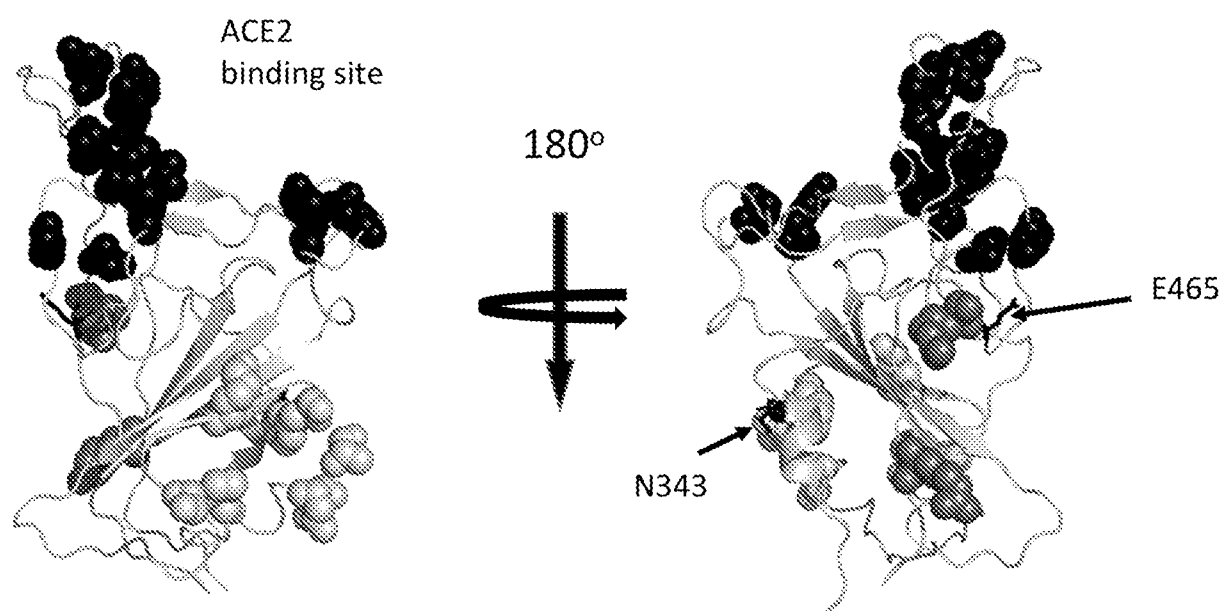


Fig 2.

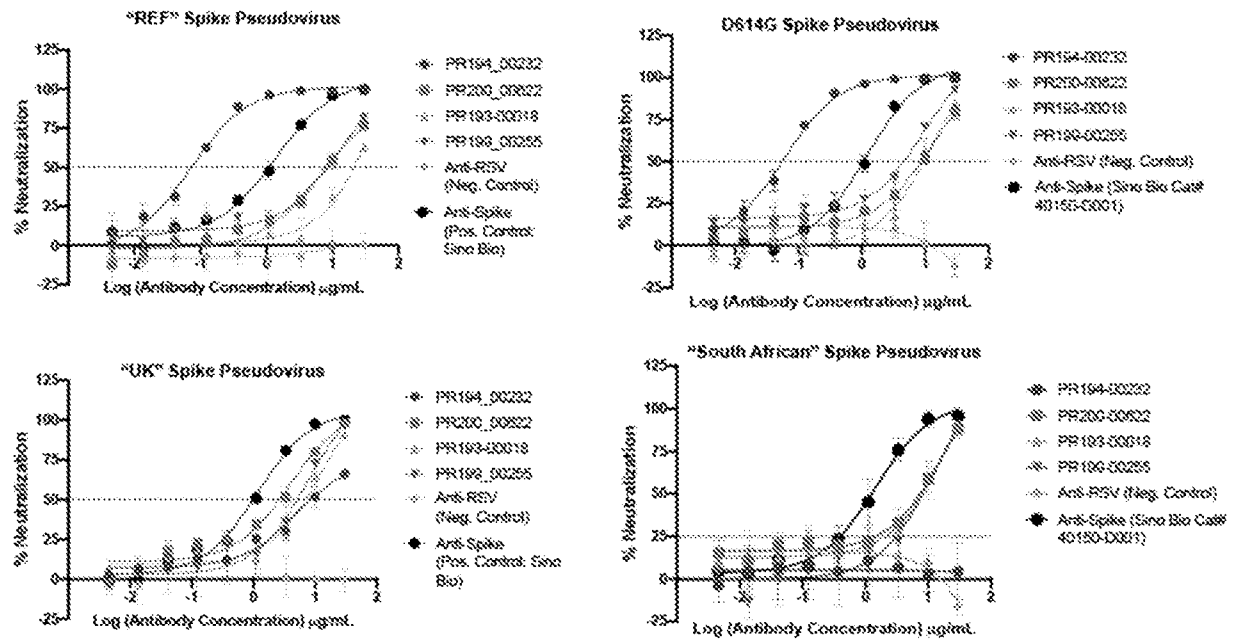
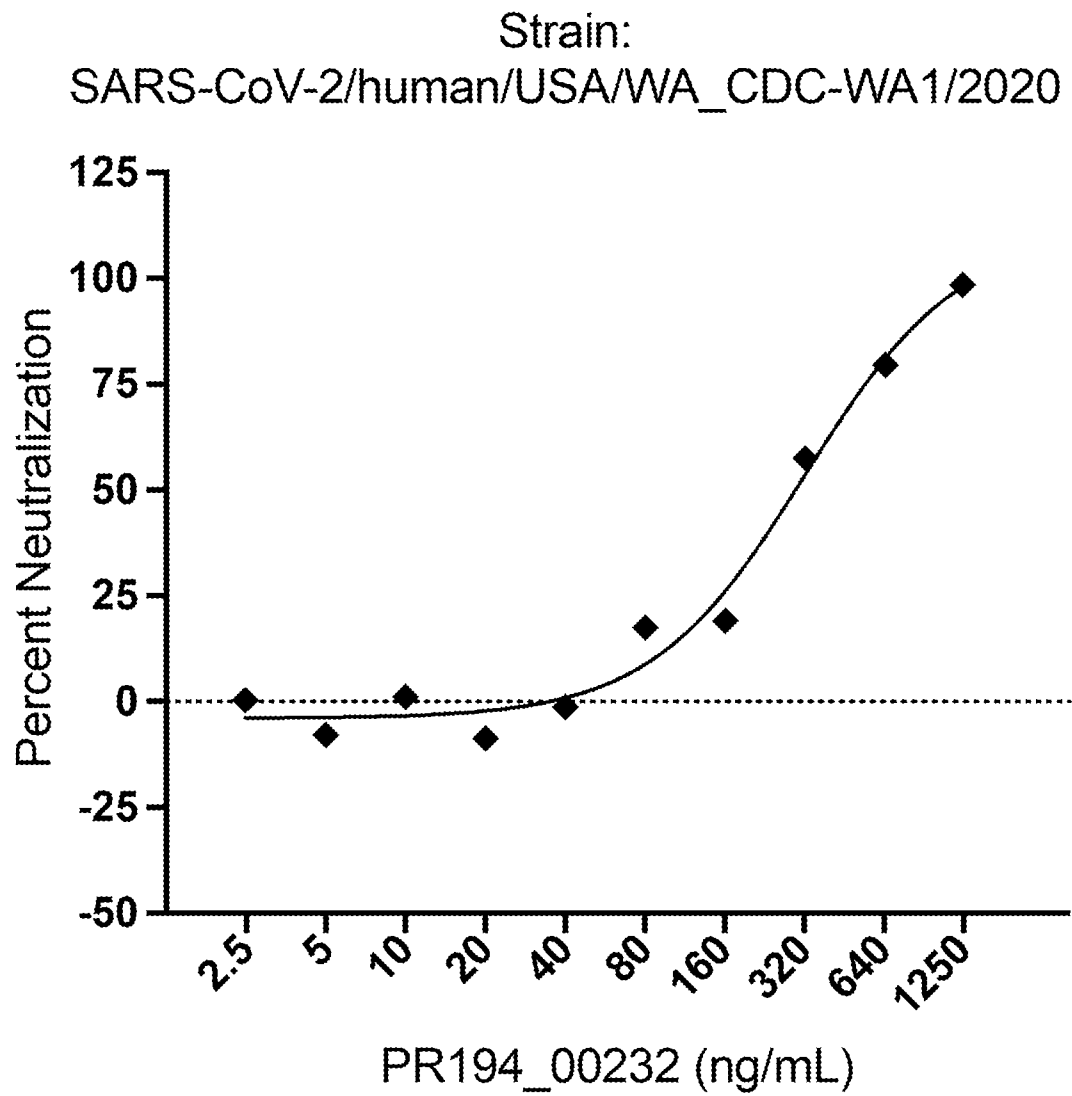
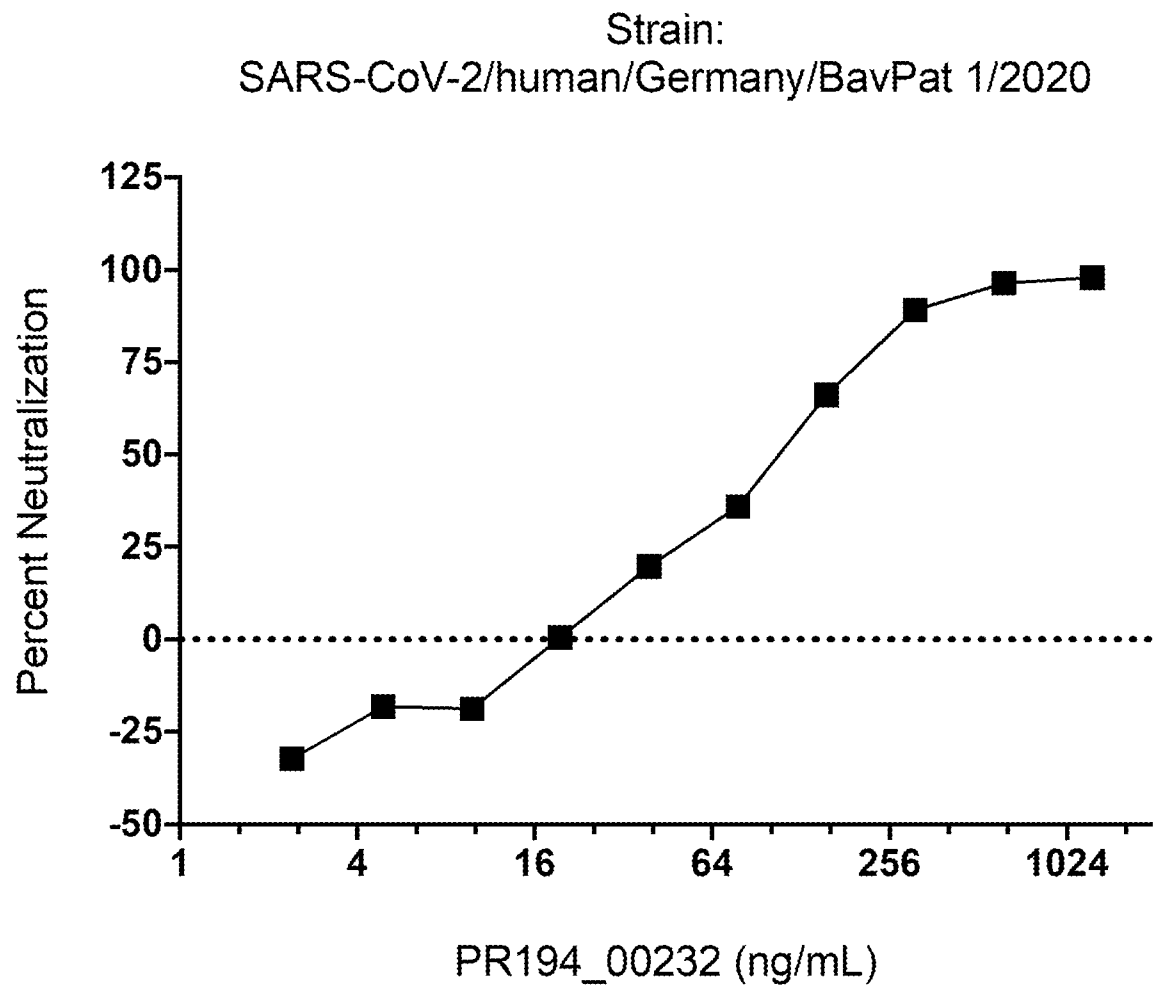


Fig. 3

*FIG. 4A*

*FIG. 4B*

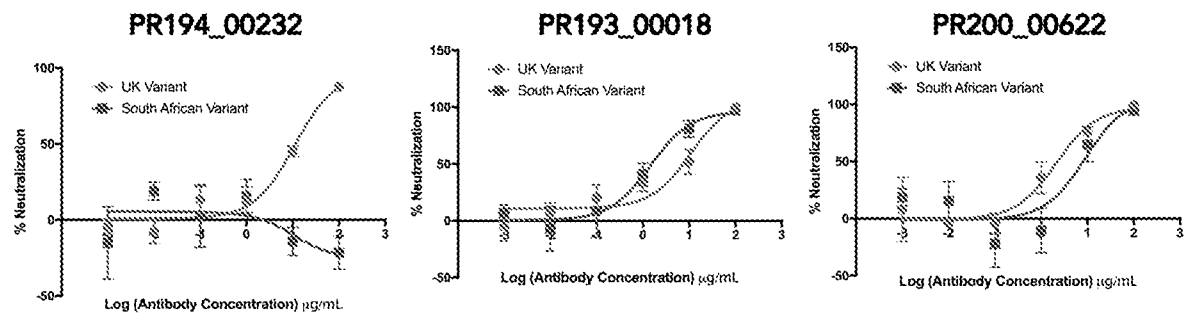
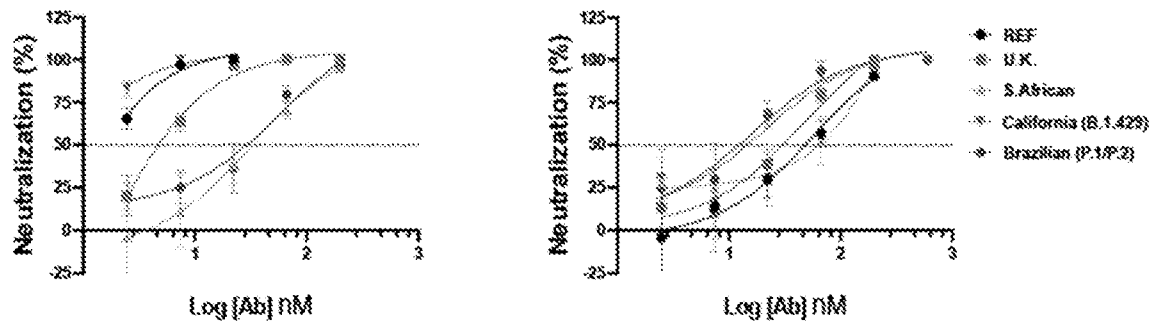


Fig. 5



	EC50 (nM)				
	REF	U.K.	S. African	California	Brazilian
IMM20184/IMM20190/IMM20253	ND	0.7	23	ND	31
IMM20184/IMM20253	37	25	66	15	12

Fig. 6.

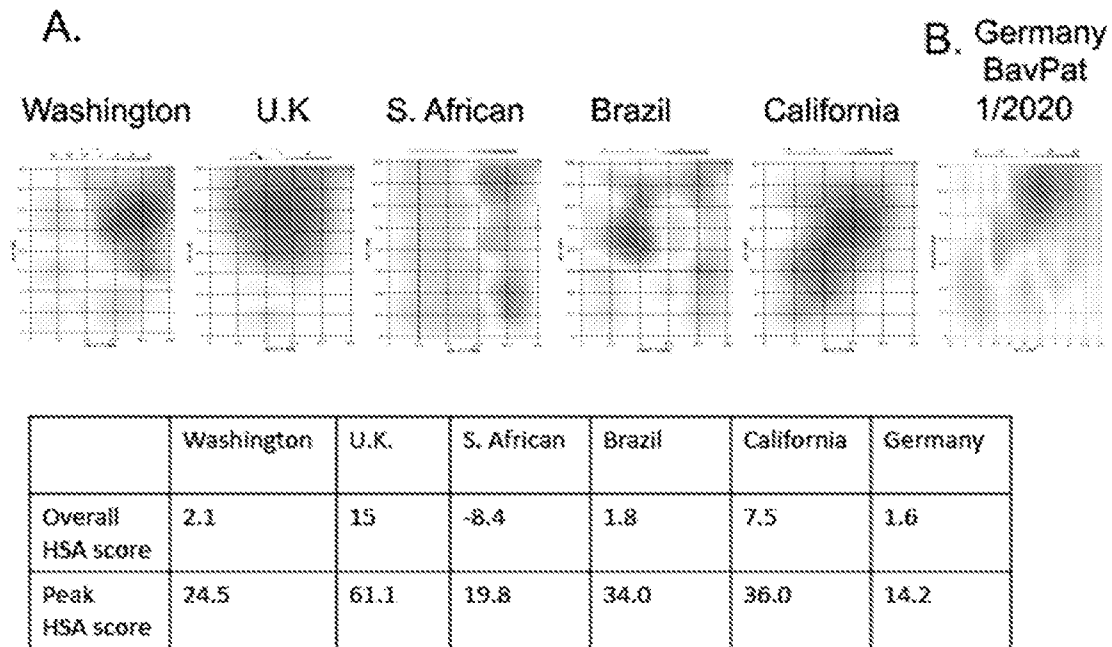
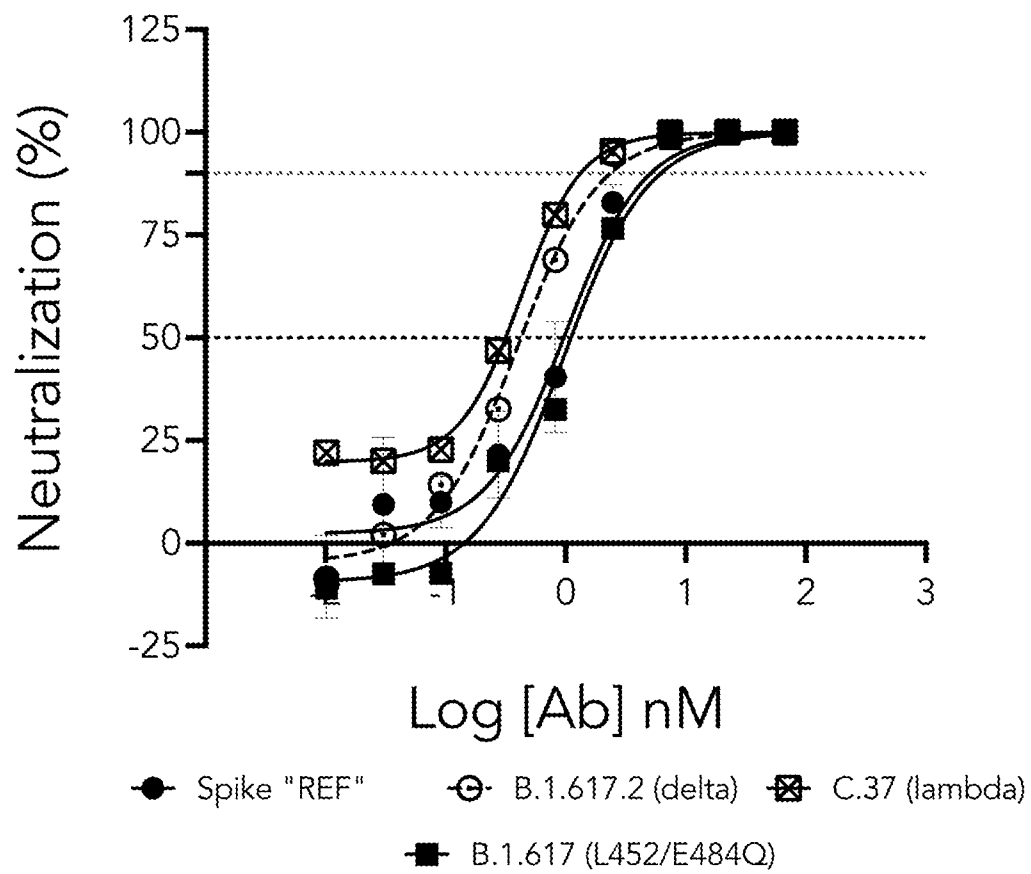
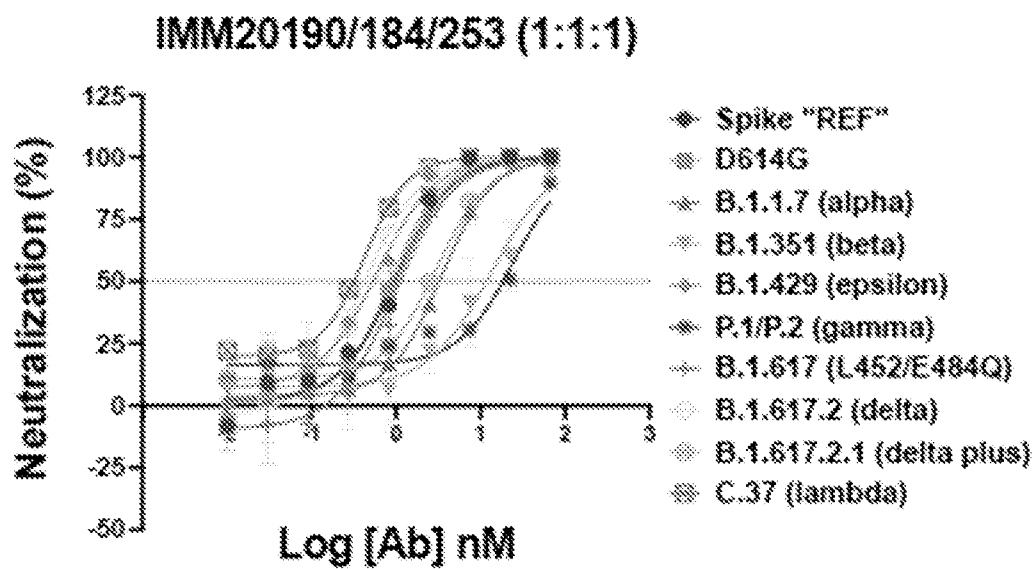


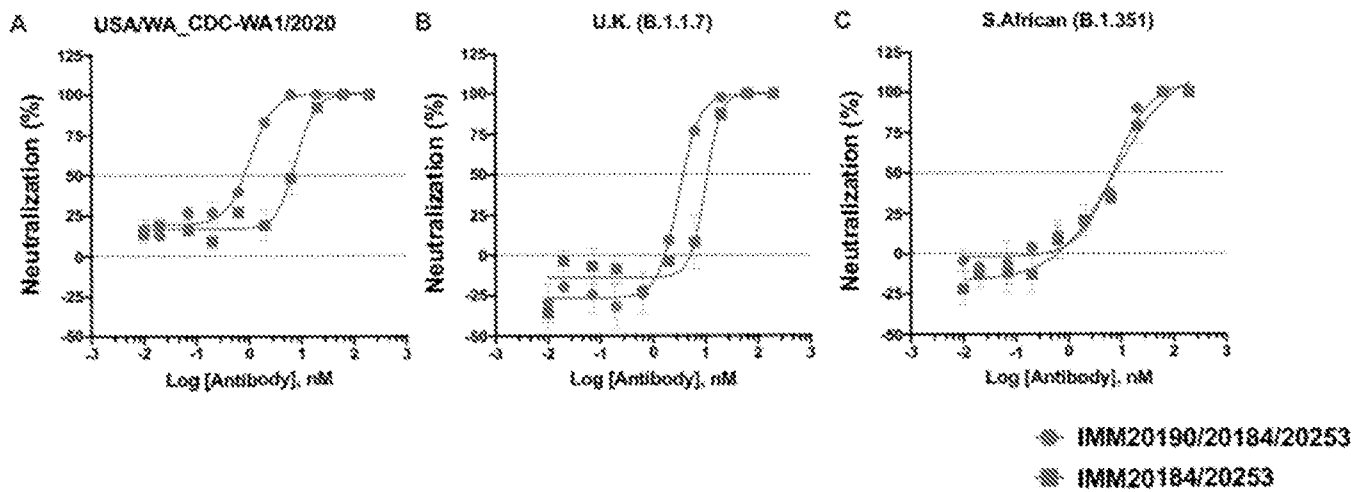
Fig. 7



Fig. 8

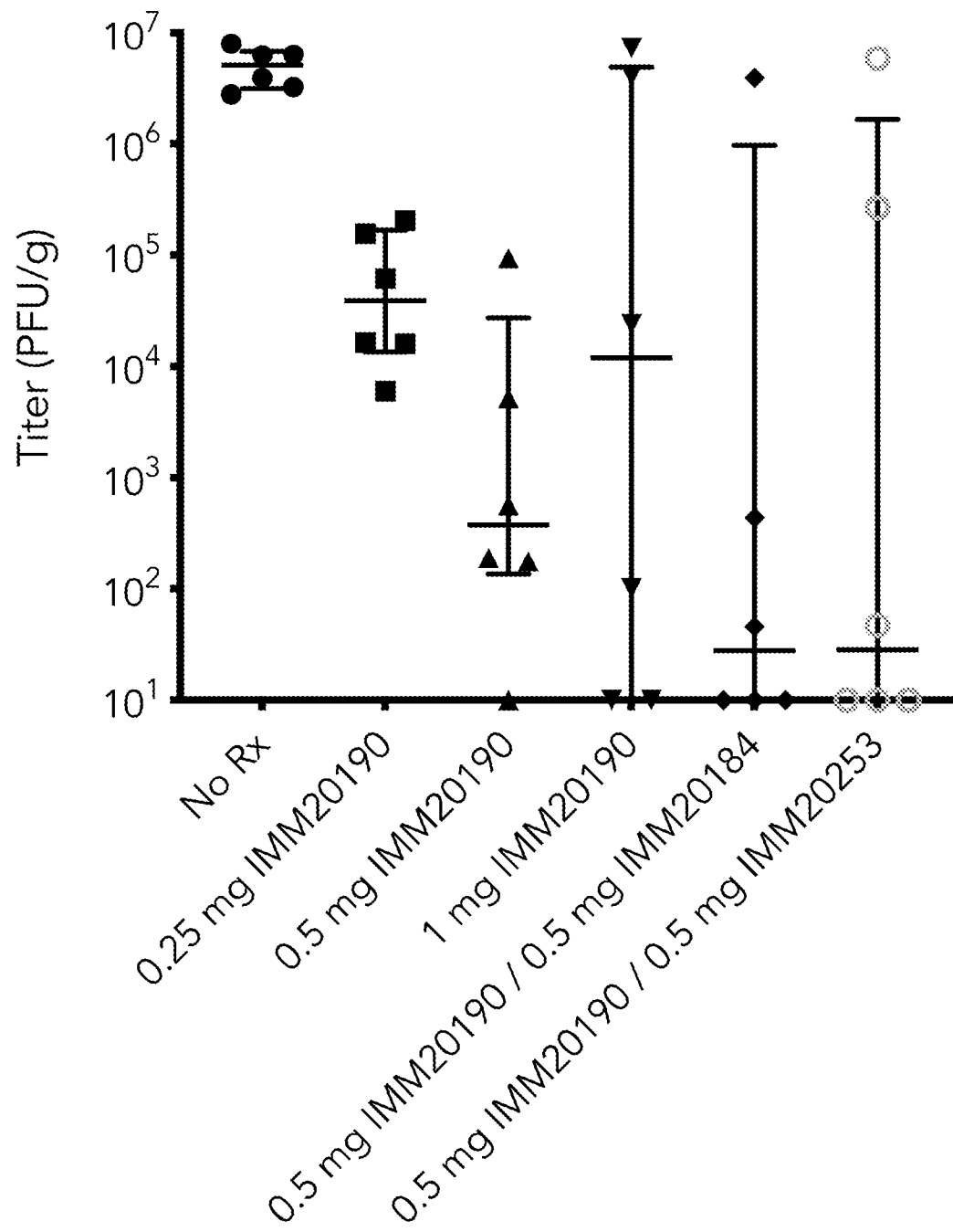
*Fig. 9*

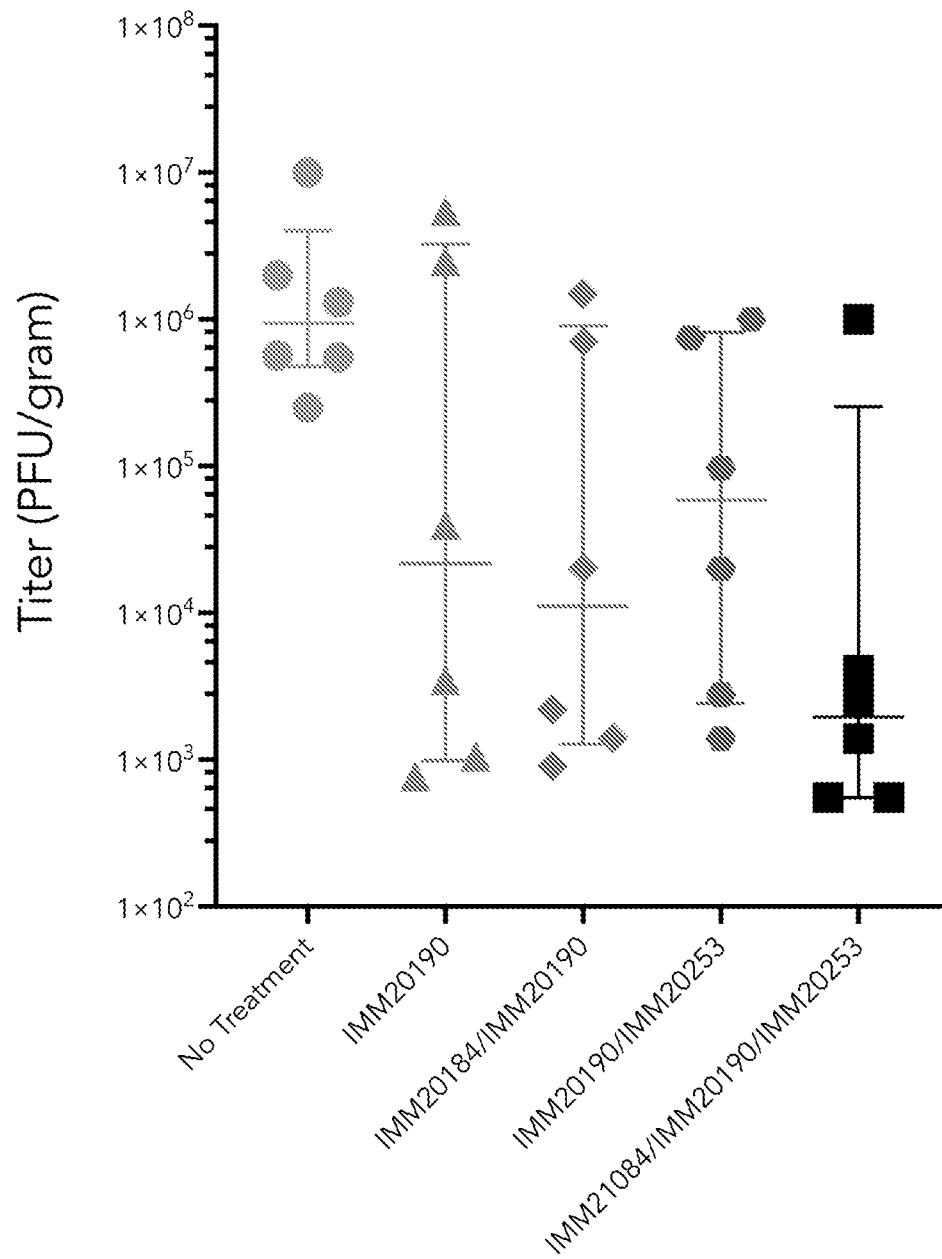
*Fig. 10*

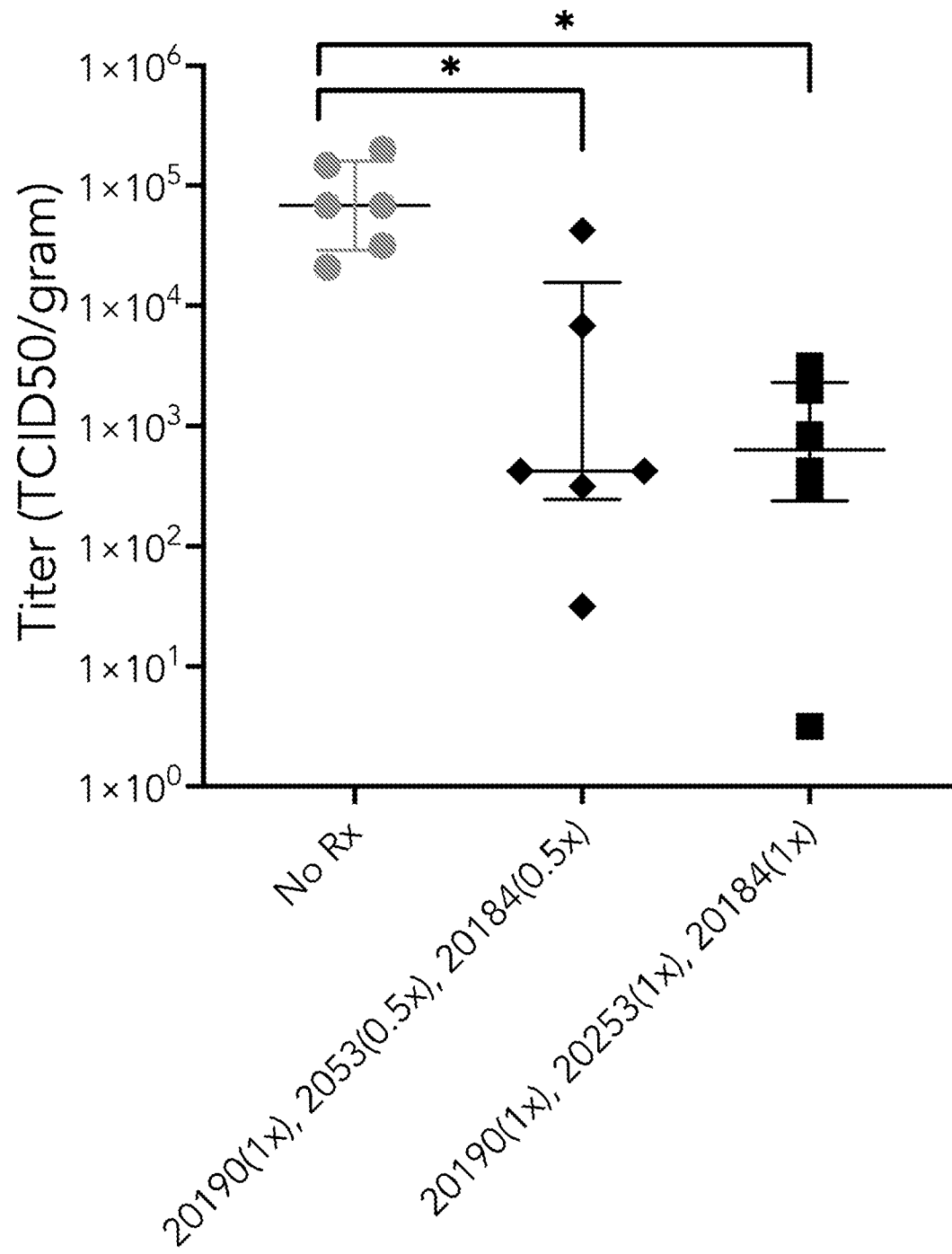


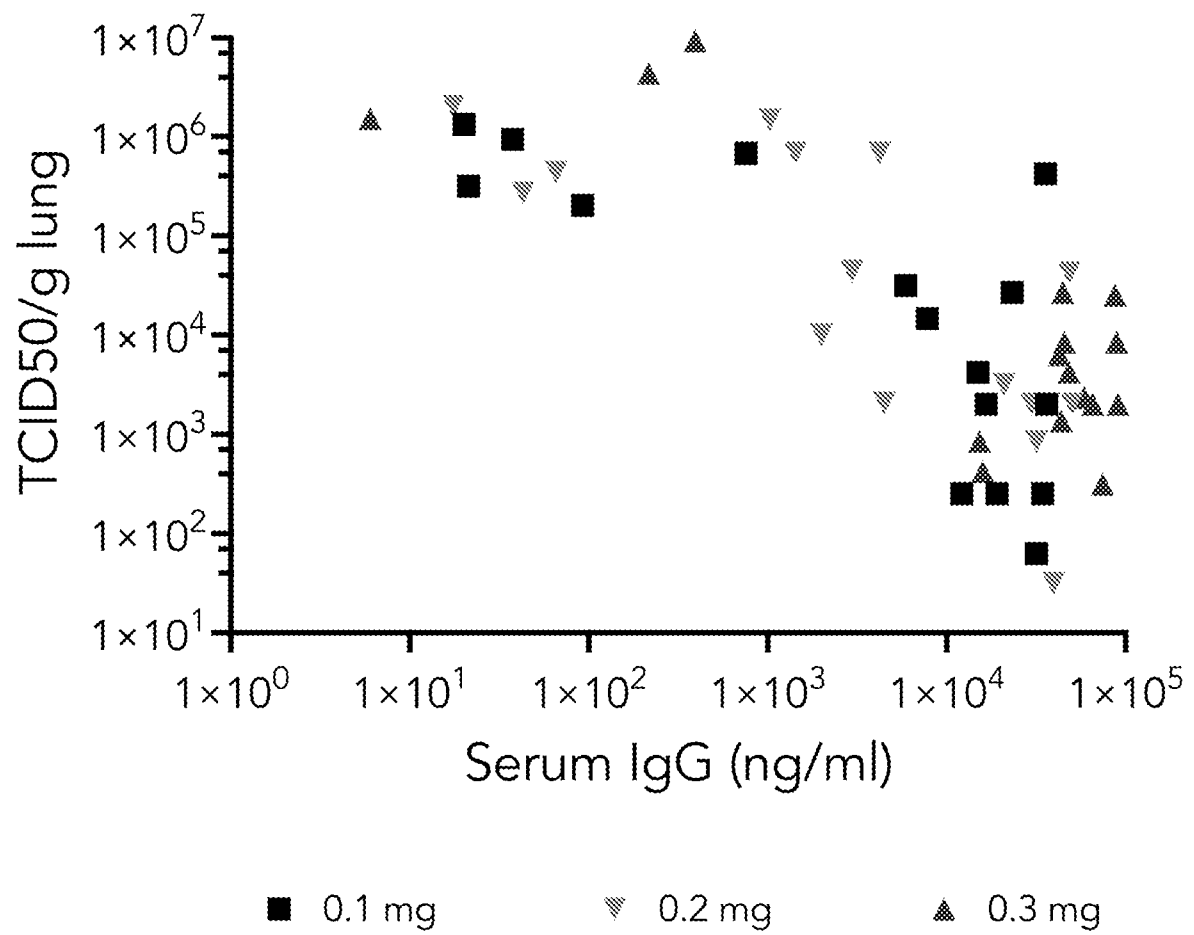
	EC50 (nM)		
	REF	UK	S. African
IMM20184/IMM20190/IMM20253	1.1	3.1	7.4
IMM20184/IMM20253	7.9	10.2	7.4

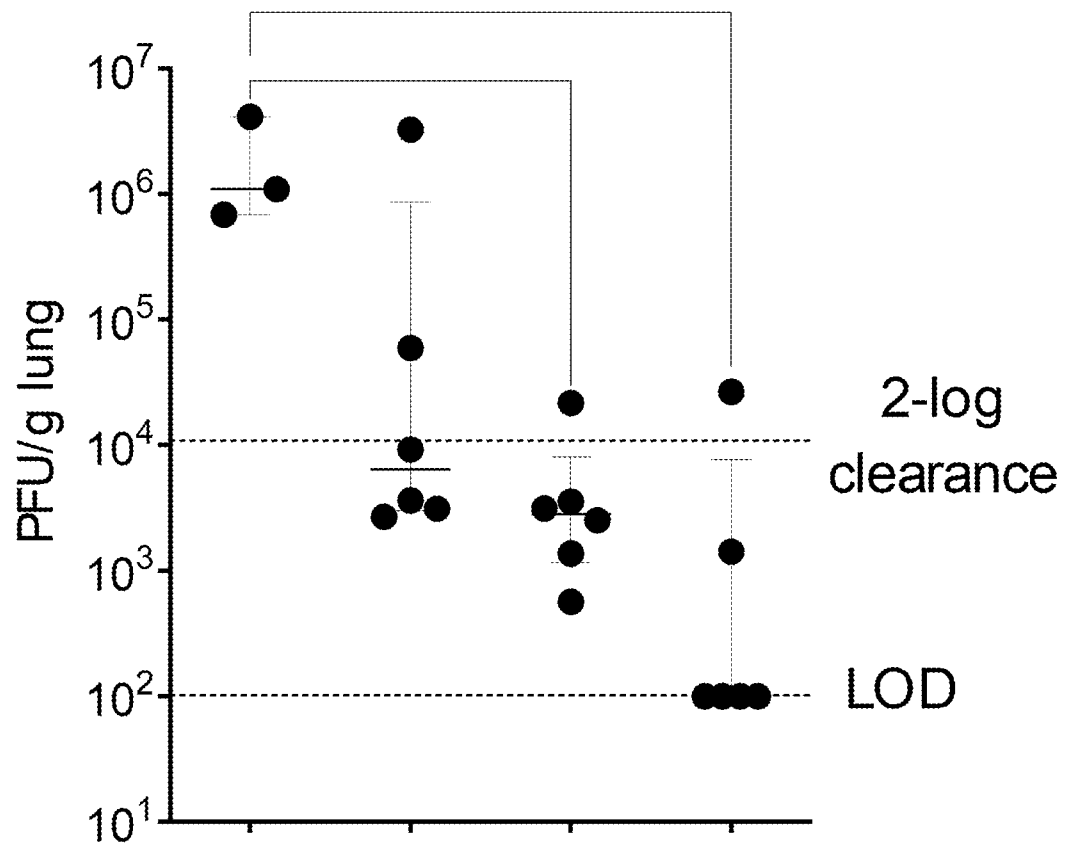
Fig. 11

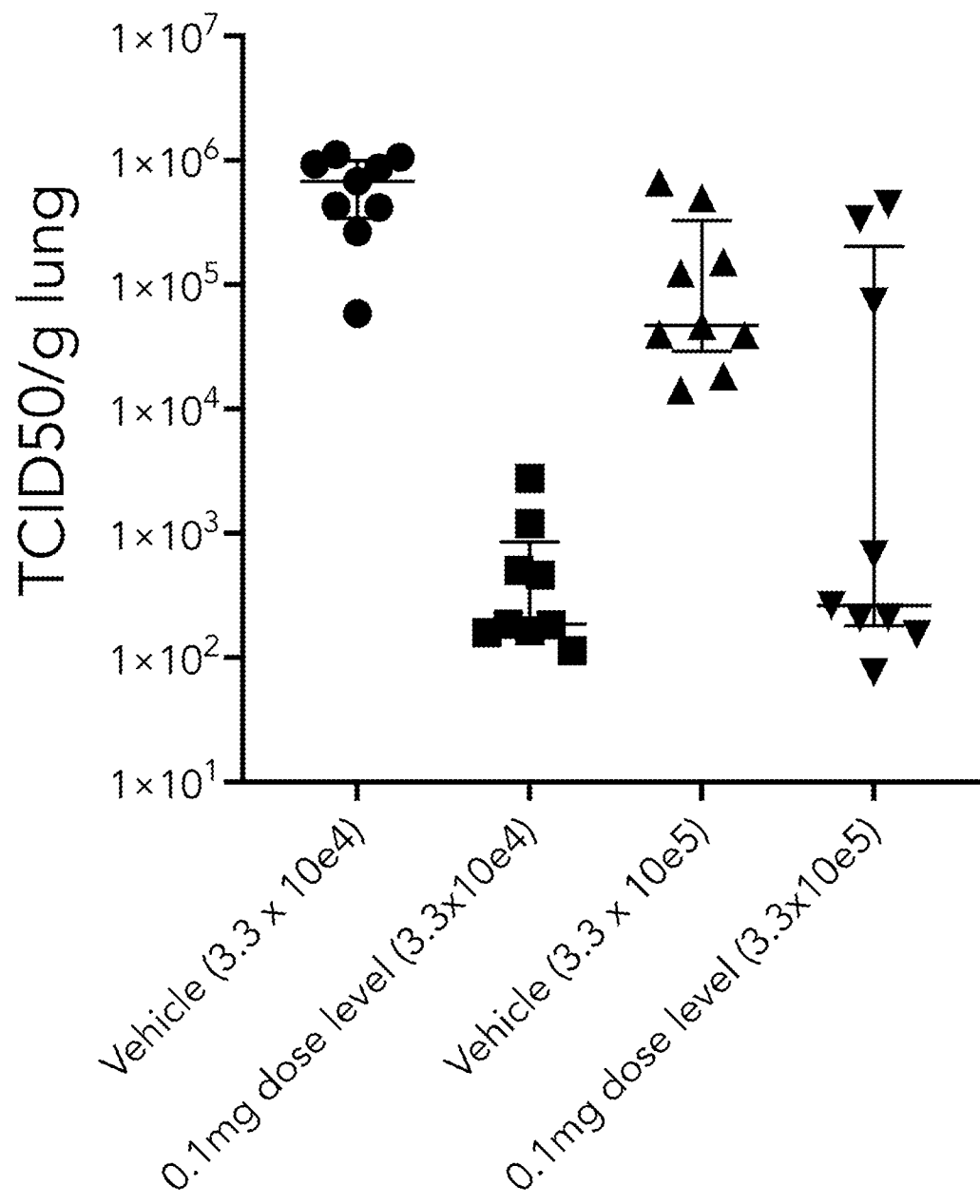
*Fig. 12*

*Fig. 13*

*Fig. 14*

*Fig. 15*

*Fig. 16A*

*Fig. 17*

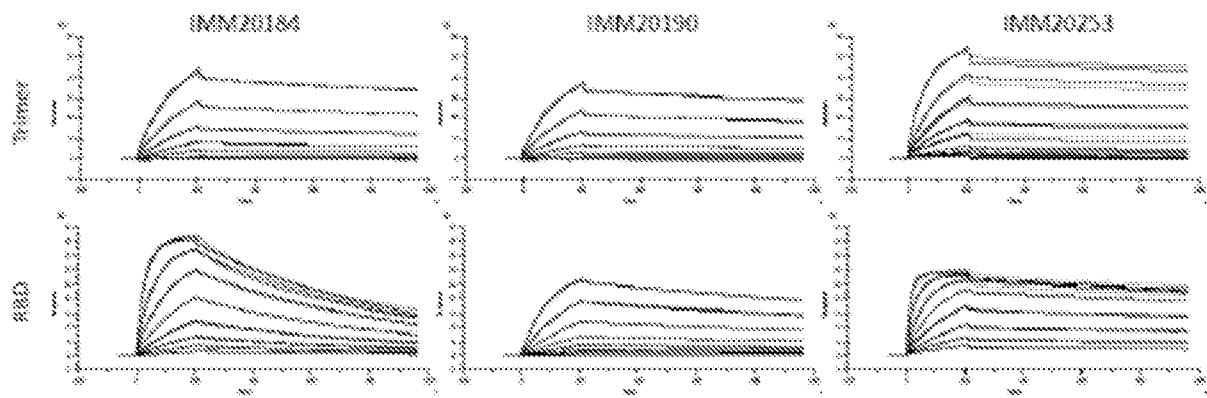


Fig. 18

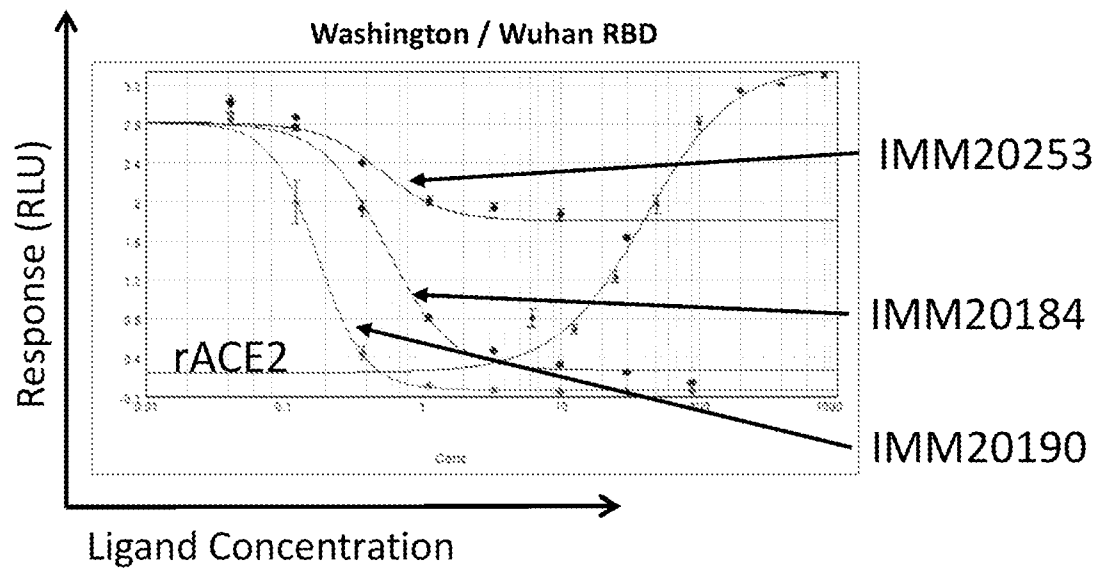


Fig. 19A

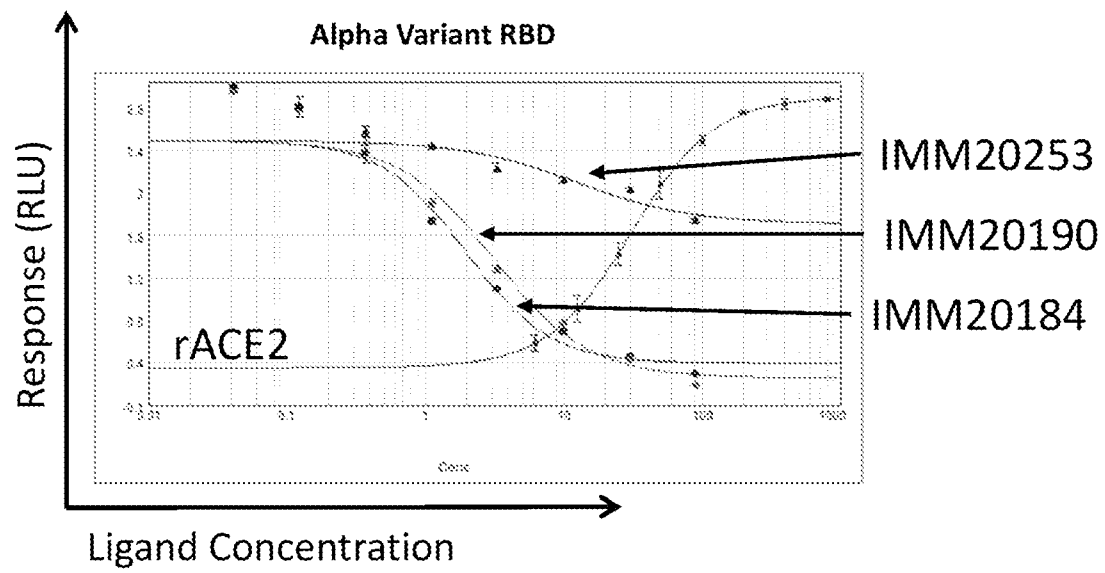


Fig. 19B

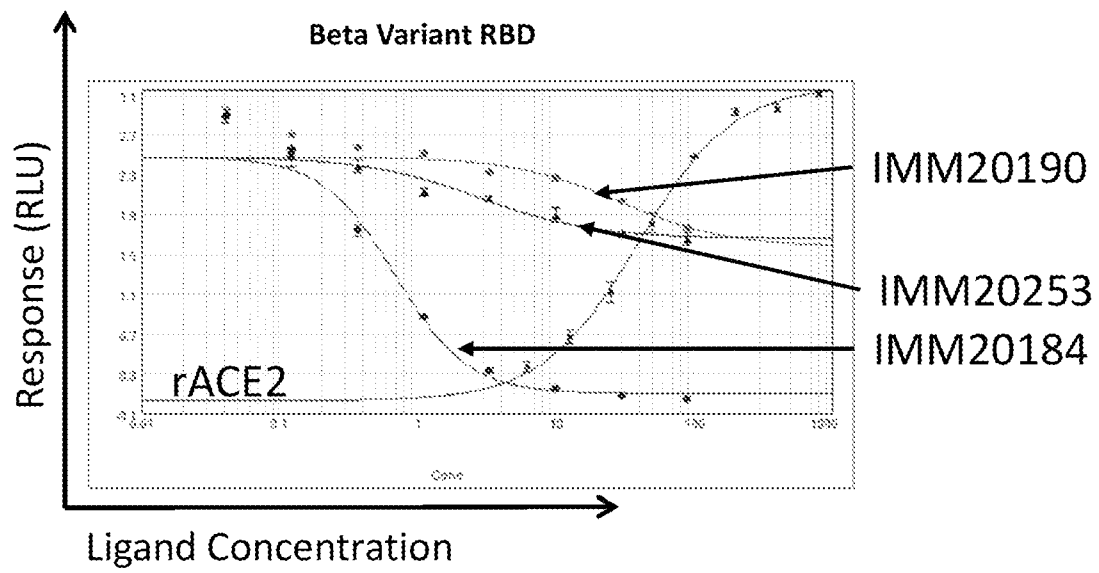
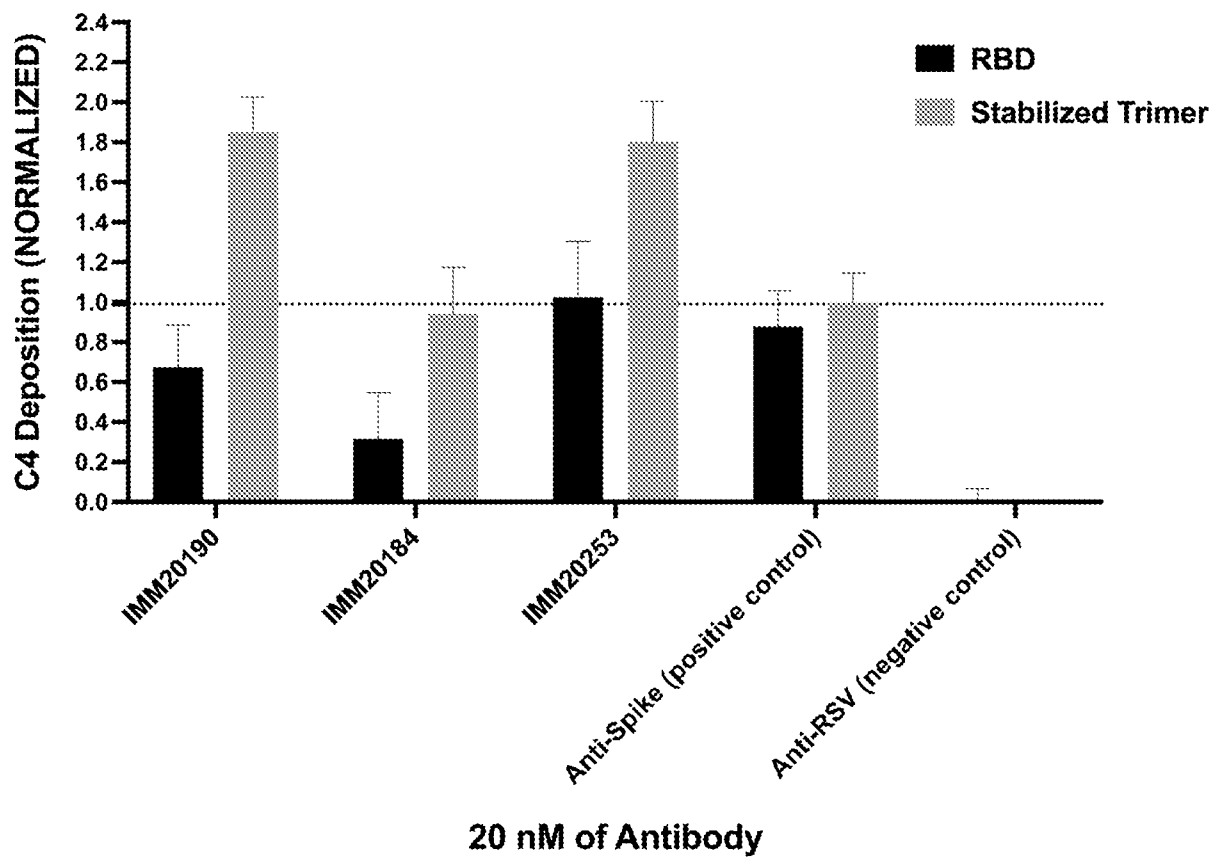
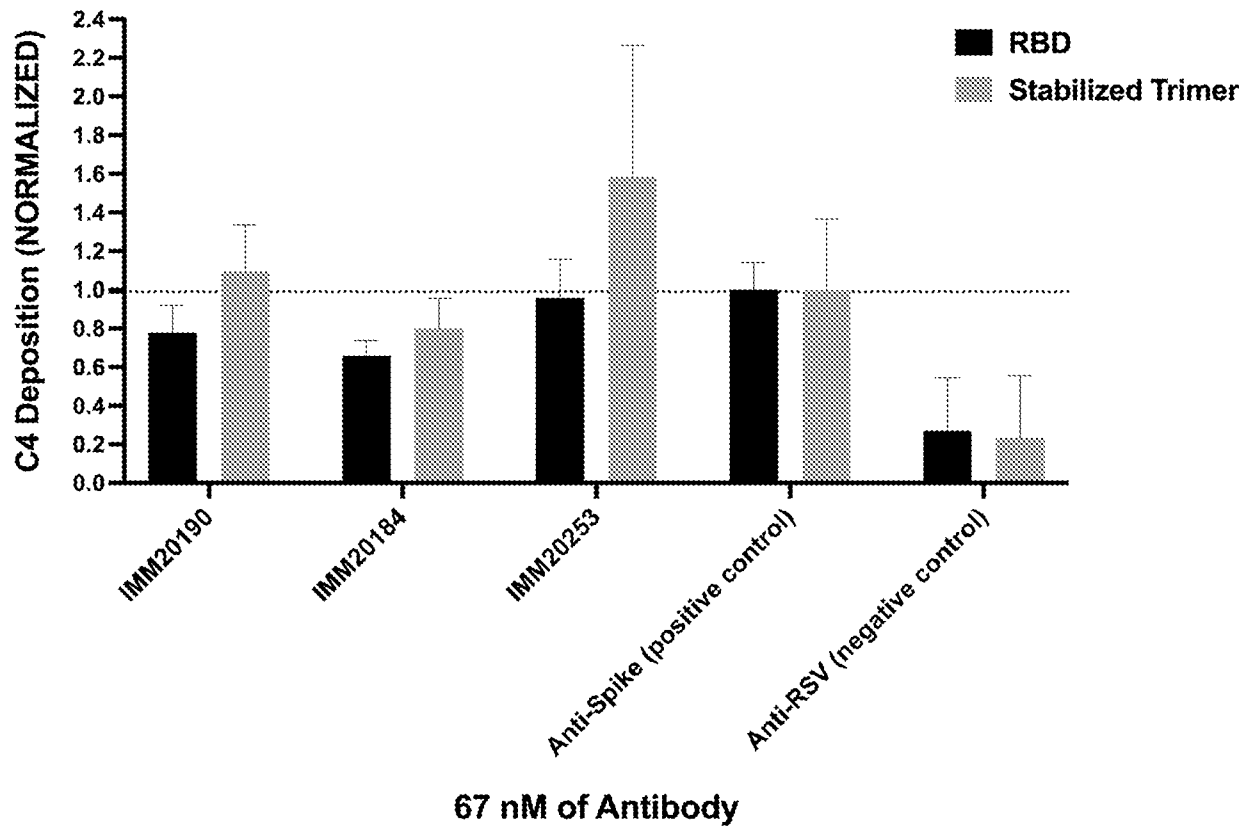
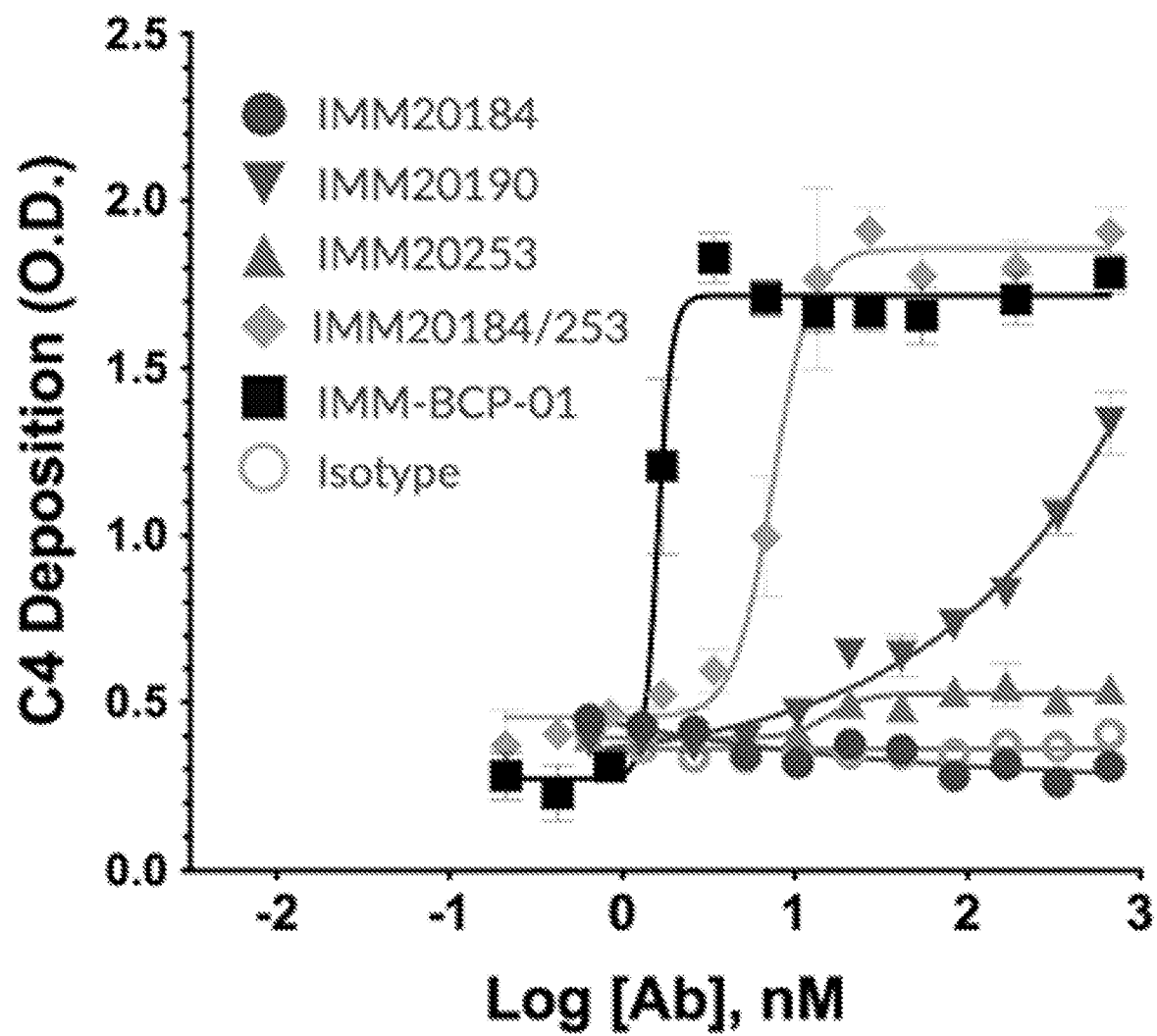
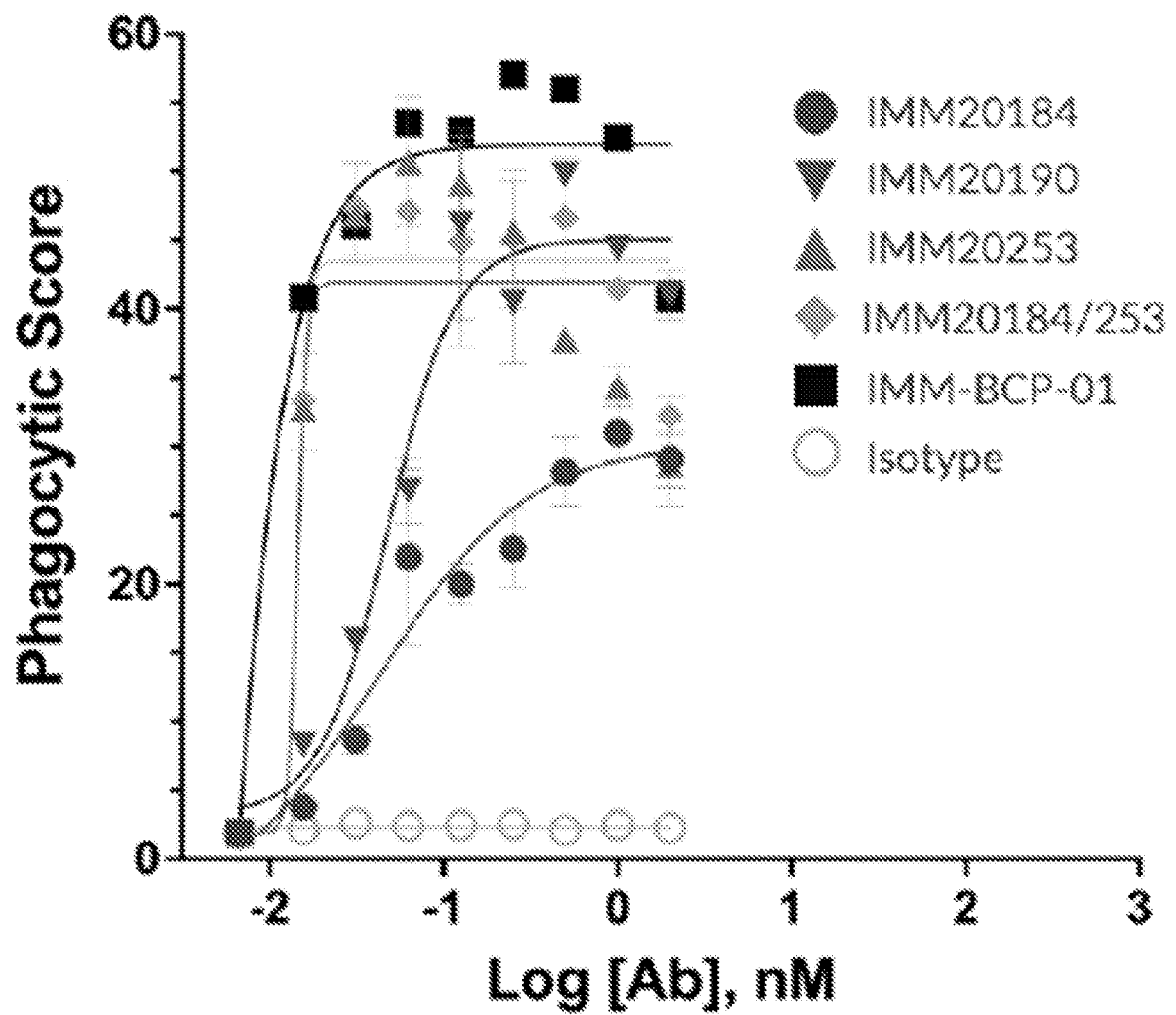


Fig. 19C

*Fig 20A*

*Fig 20B*

*Fig. 20C*

*Fig. 21*

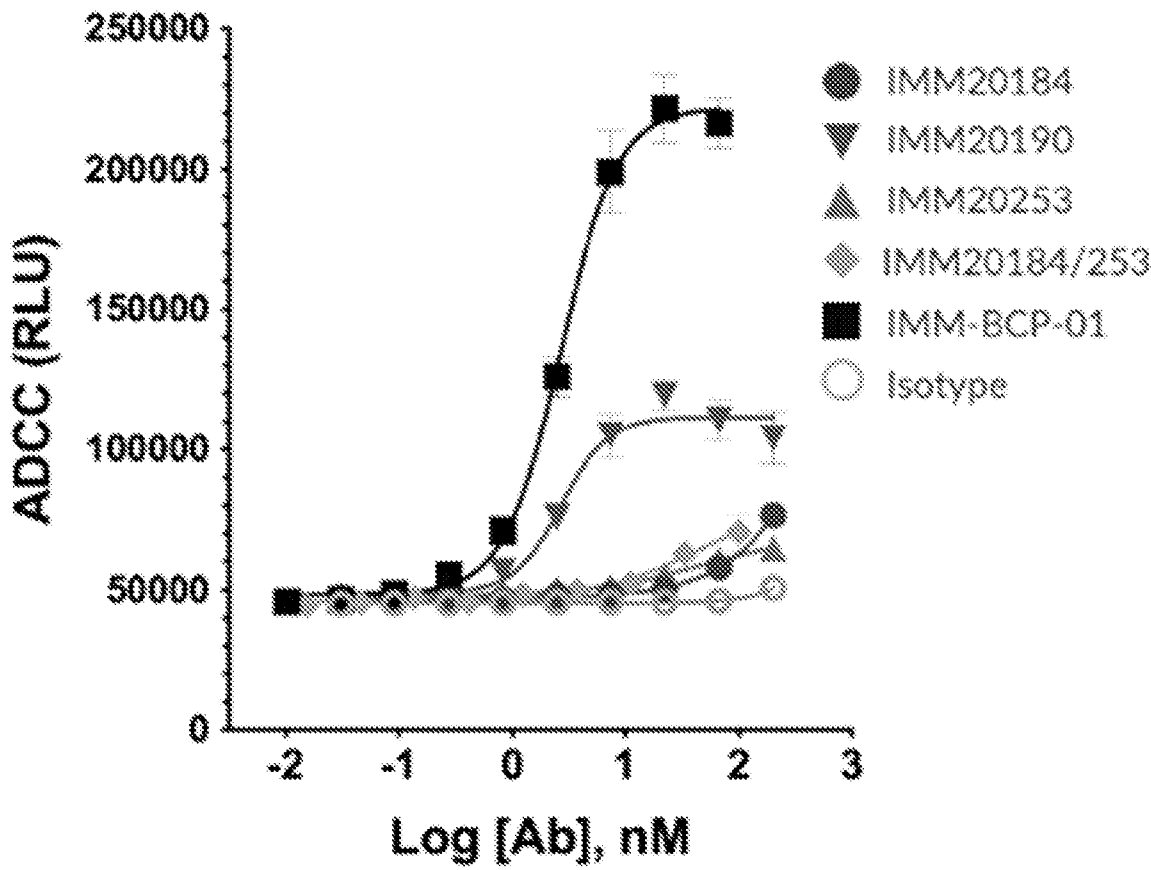
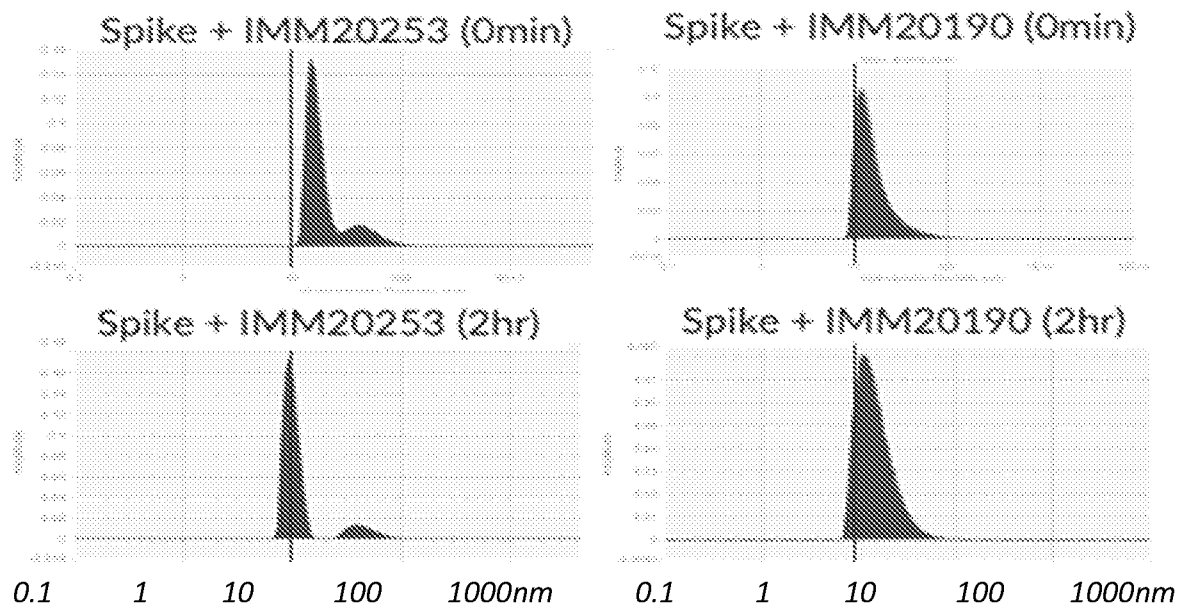


Fig. 22

*Fig. 23*

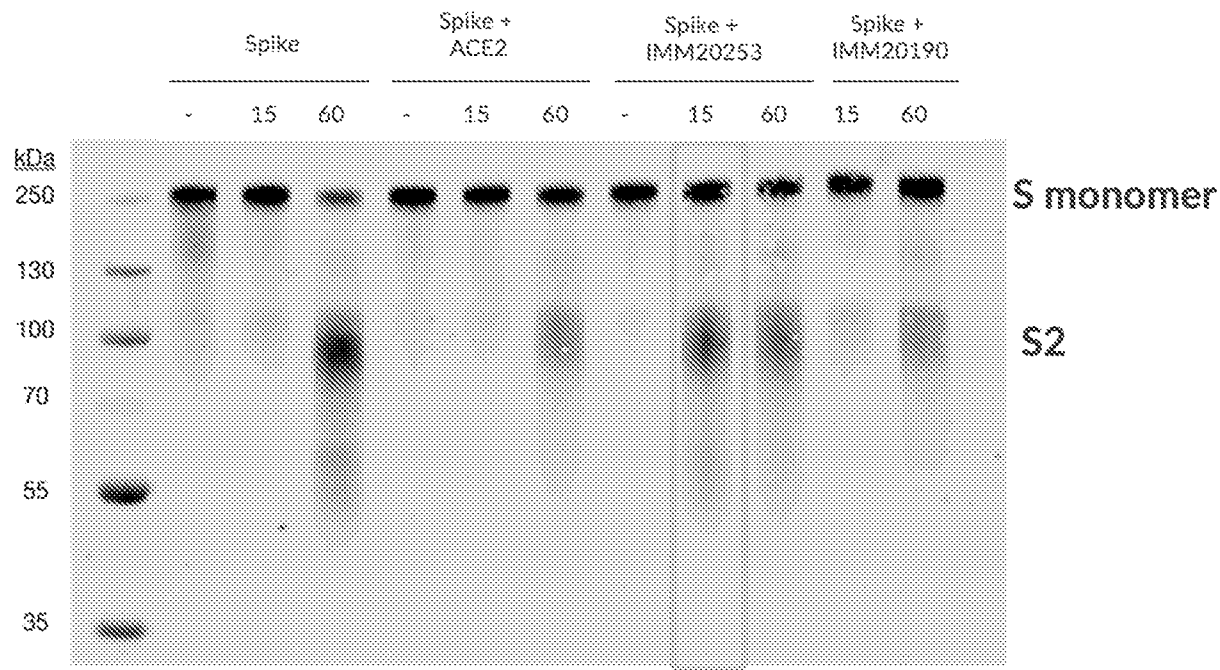


Fig. 24

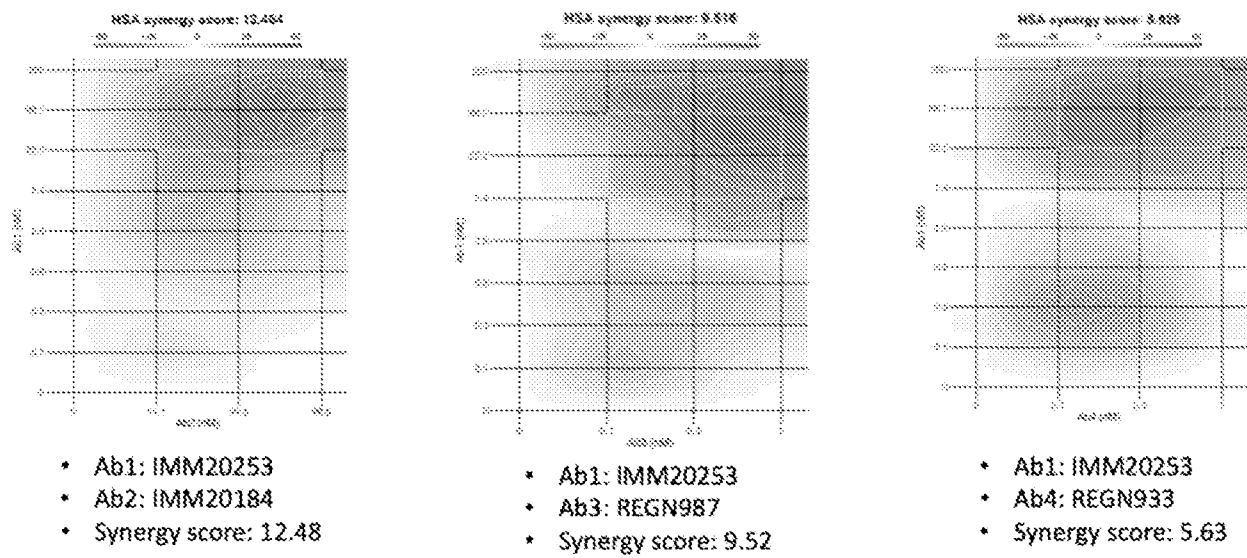
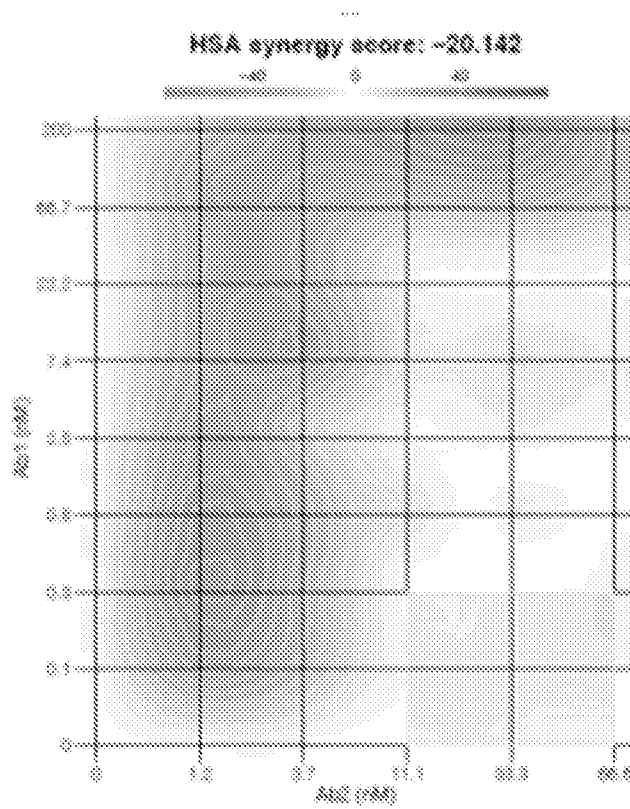


Fig. 25



- Ab1: IMM20253
- Ab2: S309
- Synergy score: -20.1

Fig. 26

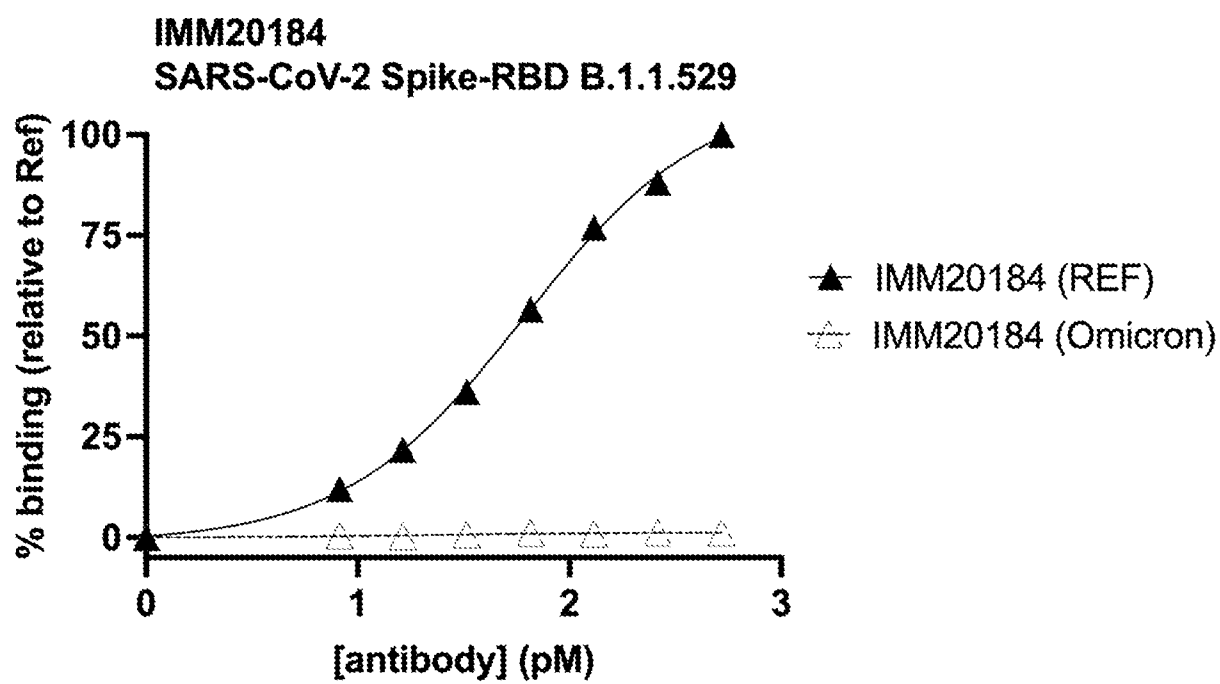
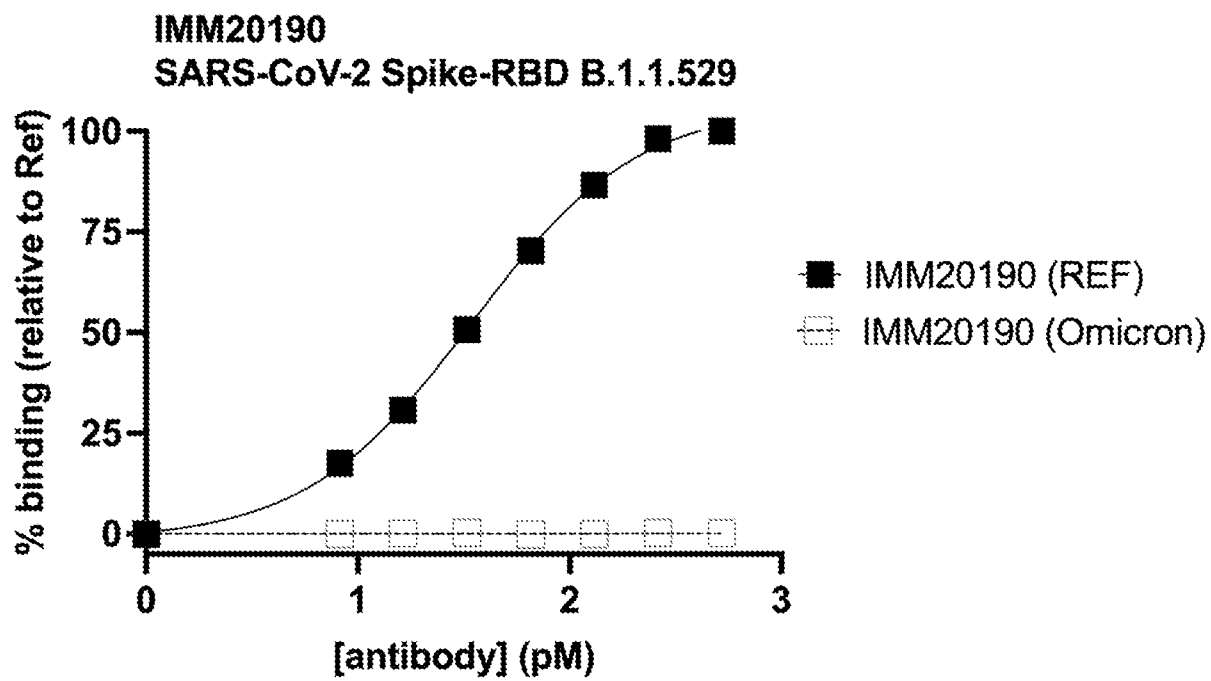


Fig. 27A

*Fig. 27B*

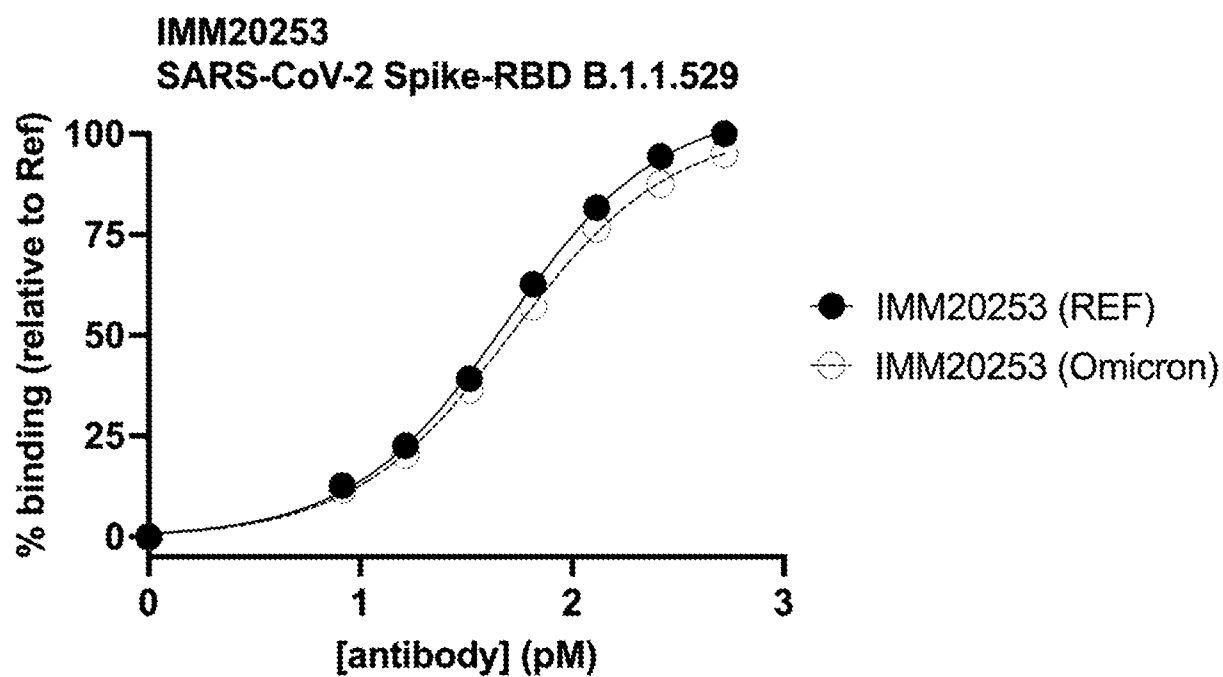


Fig. 27C

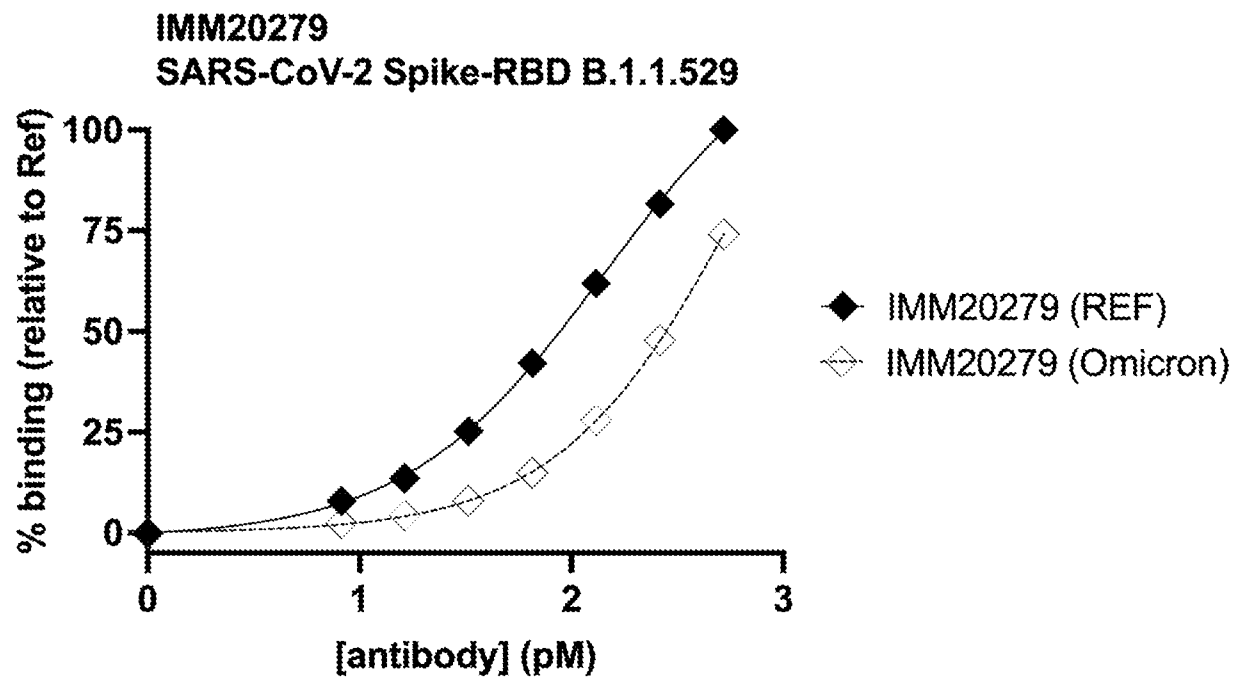


Fig. 27D

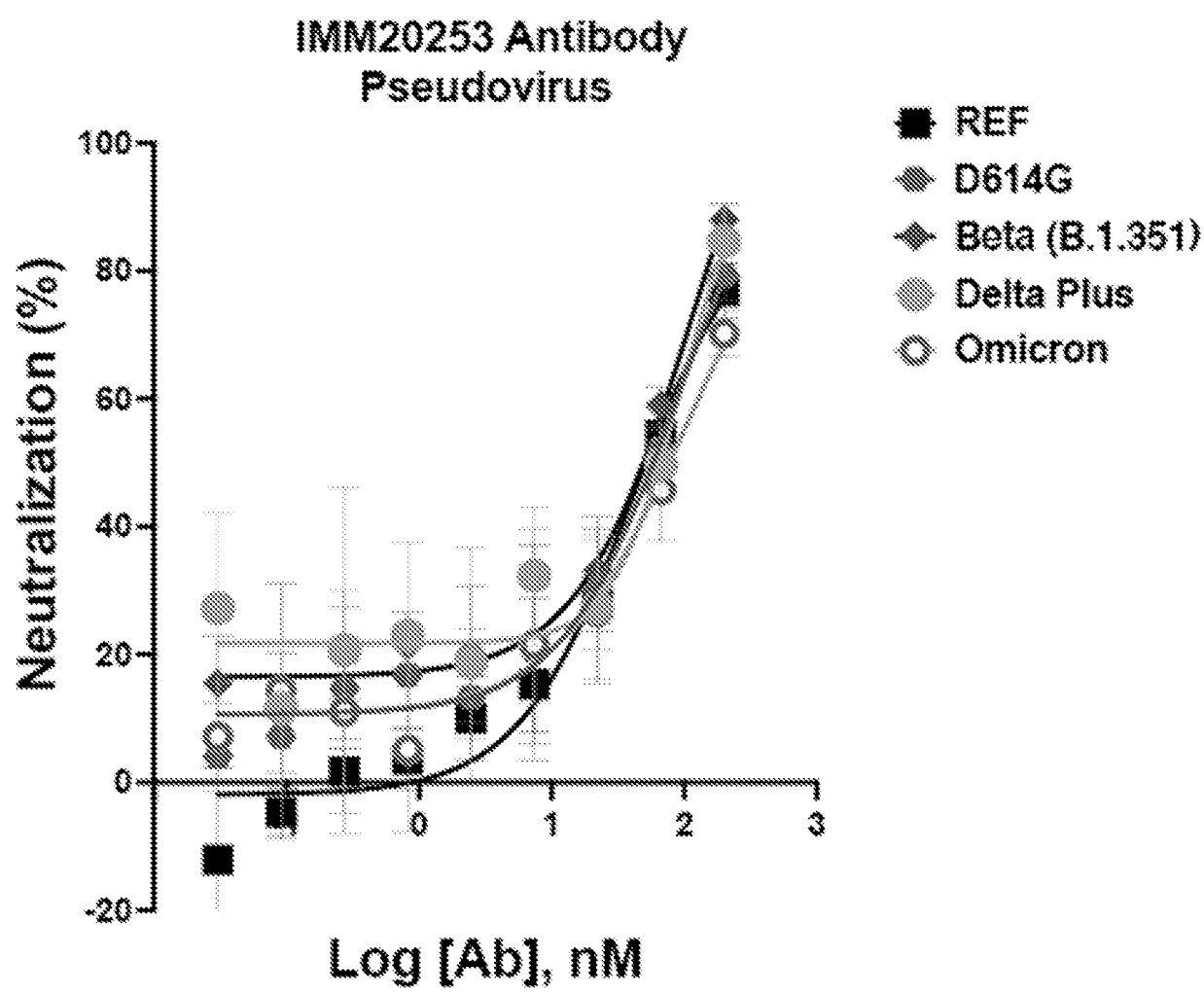


Fig. 28

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2022/070026

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 39/215; A61K 39/395; A61K 45/06 (2022.01)

CPC - A61K 39/00; A61K 39/15; A61K 39/395; A61K 2039/505; A61K 2039/507 (2022.05)

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)

see Search History document

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

see Search History document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

see Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 10,787,501 B1 (BABB et al) 29 September 2020 (29.09.2020) entire document	1-4, 6, 9-11, 31, 43
A	CN 111925444 A (CHONGQING UNIVERSITY) 13 November 2020 (13.11.2020) entire document	1-4, 6, 9-11, 31, 43
A	US 2018/0371085 A1 (MEMORIAL SLOAN-KETTERING CANCER CENTER et al) 27 December 2018 (27.12.2018) entire document	1-4, 6, 9-11, 31, 43
A	US 8,980,268 B2 (LOWY et al) 17 March 2015 (17.03.2015) entire document	1-4, 6, 9-11, 31, 43
A	US 7,566,772 B2 (GREEN et al) 28 July 2009 (28.07.2009) entire document	1-4, 6, 9-11, 31, 43
A	US 2019/0351049 A1 (REGENERON PHARMACEUTICALS INC.) 21 November 2019 (21.11.2019) entire document	1-4, 6, 9-11, 31, 43

☐ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

* Special categories of cited documents:

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

"D" document cited by the applicant in the international application

"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

23 May 2022

Date of mailing of the international search report

JUN 15 2022

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents

P.O. Box 1450, Alexandria, VA 22313-1450

Facsimile No. 571-273-8300

Authorized officer

Harry Kim

Telephone No. PCT Helpdesk: 571-272-4300

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2022/070026

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item I.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:

☒ in the form of an Annex C/ST.25 text file.

☐ on paper or in the form of an image file.

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

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

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

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

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

3. Additional comments:

SEQ ID NOs: 1, 2, 9 and 10 were searched.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2022/070026

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.:
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:

3. ☒ Claims Nos.: 5, 12-21, 25-30, 32, 33, 37-42, 44, 45, 49
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 extra sheet(s).

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 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.:
1-4, 6, 9-11, 31, 43

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.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2022/070026

Continued from Box No. III Observations where unity of invention is lacking

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees need to be paid.

Group I+: claims 1-4, 6-11, 22-24, 31, 34-36, 43, and 46-48 are drawn to antibodies which bind distinct Spike protein epitopes of SARS-CoV-2, and compositions, methods, and kits comprising the same.

The first invention of Group I+ is restricted to a first recombinant antibody and a second recombinant antibody, where the first recombinant antibody comprises a heavy chain variable region (HCVR), and a light chain variable region (LCVR), and where the second recombinant antibody comprises a heavy chain variable region (HCVR), and a light chain variable region (LCVR), where the first HCVR is selected to be SEQ ID NO:1, which further contains HCDR1 (SEQ ID NO:55), HCDR2 (SEQ ID NO:56), HCDR3 (SEQ ID NO:57); the first LCVR is selected to be SEQ ID NO:2, which further contains LCDR1 (SEQ ID NO:58), LCDR2 (SEQ ID NO:59), LCDR3 (SEQ ID NO:60); the second HCVR is selected to be SEQ ID NO:9, which further contains HCDR1 (SEQ ID NO:79), HCDR2 (SEQ ID NO:80), HCDR3 (SEQ ID NO:81); the second LCVR is selected to be SEQ ID NO:10, which further contains LCDR1 (SEQ ID NO:82), LCDR2 (SEQ ID NO:83), LCDR3 (SEQ ID NO:84), and compositions, methods, and kits comprising the same. It is believed that claims 1-4, 6-11, 22-24, 31, 34-36, 43, and 46-48 read on this first named invention and thus these claims will be searched without fee to the extent that they read on SEQ ID NOs: 1, 2, 9, and 10.

Applicant is invited to elect additional HCVR and LCVR for each antibody, and their respective, corresponding, SEQ ID NOs to be searched in a specific combination by paying additional fee for each set of election. An exemplary election would be a first recombinant antibody and a second recombinant antibody, where the first recombinant antibody comprises a heavy chain variable region (HCVR), and a light chain variable region (LCVR), and where the second recombinant antibody comprises a heavy chain variable region (HCVR), and a light chain variable region (LCVR), where the first HCVR is selected to be SEQ ID NO:3, which further contains HCDR1 (SEQ ID NO:61), HCDR2 (SEQ ID NO:62), HCDR3 (SEQ ID NO:63); the first LCVR is selected to be SEQ ID NO:4, which further contains LCDR1 (SEQ ID NO:64), LCDR2 (SEQ ID NO:65), LCDR3 (SEQ ID NO:66); the second HCVR is selected to be SEQ ID NO:11, which further contains HCDR1 (SEQ ID NO:85), HCDR2 (SEQ ID NO:86), HCDR3 (SEQ ID NO:87); the second LCVR is selected to be SEQ ID NO:12, which further contains LCDR1 (SEQ ID NO:88), LCDR2 (SEQ ID NO:89), LCDR3 (SEQ ID NO:90), and compositions, methods, and kits comprising the same. Additional HCVR and LCVR for each antibody, and their respective, corresponding, SEQ ID NOs will be searched upon the payment of additional fees. Applicants must specify the claims that read on any additional elected inventions. Applicants must further indicate, if applicable, the claims which read on the first named invention if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined.

The inventions listed in Groups I+ do not relate to a single general inventive concept under PCT Rule 13.1, because under PCT Rule 13.2 they lack the same or corresponding special technical features for the following reasons:

The Groups I+ formulas do not share a significant structural element responsible for binding to Sars-CoV-2 Spike proteins, requiring the selection of alternative HCVR and LCVR where "An antibody or antigen-binding fragment thereof that binds a SARS-CoV-2 Spike protein comprising a HCDR1, HCDR2, and HCDR3 of a heavy chain variable region (HCVR) comprising the amino acid sequence set forth in SEQ ID NO: 1, and a LCDR1, LCDR2, and LCDR3 of a light chain variable region (LCVR) comprising the amino acid sequence is set forth in SEQ ID NO: 2; a HCDR1, HCDR2, and HCDR3 of a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 3, and a LCDR1, LCDR2, and LCDR3 of a LCVR comprising the amino acid sequence is set forth in SEQ ID NO: 4; a HCDR1, HCDR2, and HCDR3 of a HCVR comprising the amino acid sequence set forth in SEQ ID NO: 5, and a LCDR1, LCDR2, and LCDR3 of a LCVR comprising the amino acid sequence is set forth in SEQ ID NO: 6; a HCDR1, HCDR2, and HCDR3 of a HCVR comprising the amino acid sequence set forth in SEQ ID NO: 7, and a LCDR1, LCDR2, and LCDR3 of a LCVR comprising the amino acid sequence is set forth in SEQ ID NO: 8; a HCDR1, HCDR2, and HCDR3 of a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 9, and a LCDR1, LCDR2, and LCDR3 of a light chain variable region (LCVR) comprising the amino acid sequence is set forth in SEQ ID NO: 10; a HCDR1, HCDR2, and HCDR3 of a HCVR comprising the amino acid sequence set forth in SEQ ID NO: 11, and a LCDR1, LCDR2, and LCDR3 of a LCVR comprising the amino acid sequence is set forth in SEQ ID NO: 12; a HCDR2, and HCDR3 of a HCVR comprising the amino acid sequence set forth in SEQ ID NO: 13, a LCDR1, LCDR2, and LCDR3 of a LCVR comprising the amino acid sequence is set forth in SEQ ID NO: 14; a HCDR1, HCDR2, and HCDR3 of a HCVR comprising the amino acid sequence set forth in SEQ ID NO: 15, and a LCDR1, LCDR2, and LCDR3 of a LCVR comprising the amino acid sequence is set forth in SEQ ID NO: 16; a HCDR1, HCDR2, and HCDR3 of a HCVR comprising the amino acid sequence set forth in SEQ ID NO: 17, and a LCDR1, LCDR2, and LCDR3 of a LCVR comprising the amino acid sequence is set forth in SEQ ID NO: 18; a HCDR1, HCDR2, and HCDR3 of a HCVR comprising the amino acid sequence set forth in SEQ ID NO: 19, and a LCDR1, LCDR2, and LCDR3 of a LCVR comprising the amino acid sequence is set forth in SEQ ID NO: 20; a HCDR1, HCDR2, and HCDR3 of a HCVR comprising the amino acid sequence set forth in SEQ ID NO: 21 and a LCDR1, LCDR2, and LCDR3 of a LCVR comprising the amino acid sequence is set forth in SEQ ID NO: 22; a HCDR1, HCDR2, and HCDR3 of a HCVR comprising the amino acid sequence set forth in SEQ ID NO: 23, and a LCDR1, LCDR2, and LCDR3 of a LCVR comprising the amino acid sequence is set forth in SEQ ID NO: 24; or a HCDR1, HCDR2, and HCDR3 of a HCVR comprising the amino acid sequence set forth in SEQ ID NO: 25 and a LCDR1, LCDR2, and LCDR3 of a LCVR comprising the amino acid sequence is set forth in SEQ ID NO: 26."

Additionally, even if Groups I+ were considered to share the technical features of a composition comprising at least first and second recombinant antibodies that specifically bind to distinct epitopes of a Spike protein of SARS-CoV-2, wherein the first antibody binds to an epitope in an ACE2 receptor binding site of the Spike protein and the second antibody binds to an epitope outside of the ACE2 receptor binding site of the Spike protein; a composition comprising at least first and second antibodies that specifically bind to distinct epitopes of a Spike protein of SARS-CoV-2, wherein the first antibody neutralizes SARS-CoV-2 via an ACE2 independent mechanism and the second antibody neutralizes SARS-CoV-2 via an ACE2 dependent mechanism, wherein the first and second antibodies are recombinant antibodies; an antibody or antigen-binding fragment thereof that binds a SARS-CoV-2 Spike protein comprising a HCDR1, HCDR2, and HCDR3 of a heavy chain variable region (HCVR); an antibody or antigen binding fragment thereof that binds a SARS-CoV-2 Spike protein comprising a VH comprising a HCDR1, HCDR2, HCDR3, and a VL comprising LCDR1, LCDR2, and LCDR3, a composition comprising a first antibody and a second antibody; a method of treating or preventing a SARS-CoV-2 infection in a subject, comprising administering a first antibody that neutralizes SARS-CoV-2 via an ACE2 independent mechanism and a second antibody that neutralizes SARS-CoV-2 via an ACE2 dependent mechanism; a kit for treating or preventing a SARS-CoV-2 infection in a subject comprising a first

antibody that specifically binds to a Spike protein of SARS-CoV-2 and neutralizes SARS-CoV-2 via an ACE2 independent mechanism and a second antibody that specifically binds to a Spike protein of SARS-CoV-2 and neutralizes SARS-CoV-2 via an ACE2 dependent mechanism. However, these shared technical features do not represent a contribution over the prior art.

Specifically, US 10,787,501 B1 to Babb et al. discloses a composition (composition, Col. 3, Lns. 37-38) comprising at least first and second recombinant antibodies that specifically bind to distinct epitopes of a Spike protein of SARS-CoV-2 (the present disclosure provides a pharmaceutical composition comprising the antigen-binding protein, antibody ...discussed above ...the further therapeutic agent is ...and antibody, Col. 3, Lns. 42-55; recombinant antibody, Col. 5, Ln. 38; anti-SARS CoV-2 Spike protein ...antibodies, Col. 2, Lns. 58-60), wherein the first antibody binds to an epitope in an ACE2 receptor binding site of the Spike protein and the second antibody binds to an epitope outside of the ACE2 receptor binding site of the Spike protein (the first and second antigen-binding proteins (e.g., antibodies) may bind to different, but, for example, overlapping epitopes, Col. 2, Lns. 57-60; ability of anti-SARS-CoV-2-S antibodies to block SARS-CoV-2-S RBD from binding to human ACE2, Col. 89, Lns. 11-13); a composition (composition, Col. 3, Lns. 37-38) comprising at least first and second antibodies that specifically bind to distinct epitopes of a Spike protein of SARS-CoV-2 (the present disclosure provides a pharmaceutical composition comprising the antigen-binding protein, antibody ...discussed above ...the further therapeutic agent is ...and antibody, Col. 3, Lns. 42-55; recombinant antibody, Col. 5, Ln. 38; anti-SARS CoV-2 Spike protein ...antibodies, Col. 2, Lns. 58-60), wherein the first antibody neutralizes SARS-CoV-2 via an ACE2 independent mechanism and the second antibody neutralizes SARS-CoV-2 via an ACE2 dependent mechanism, wherein the first and second antibodies are recombinant antibodies (the present disclosure provides a pharmaceutical composition comprising the antigen-binding protein, antibody ...discussed above ...the further therapeutic agent is ...and antibody, Col. 3, Lns. 42-55; recombinant antibody, Col. 5, Ln. 38; anti-SARS CoV-2 Spike protein ...antibodies, Col. 2, Lns. 58-60; the majority of the neutralizing antibodies tested contact the RBD in a manner that overlaps the RBD residues that comprise the ACE2 interface, Col. 94, Lns. 9-11); an antibody or antigen-binding fragment thereof that binds a SARS-CoV-2 Spike protein comprising a HCDR1, HCDR2, and HCDR3 of a heavy chain variable region (HCVR (anti-SARS CoV-2 Spike protein ...antibodies, Col. 2, Lns. 58-60; heavy and/or light chain amino acid sequences set forth herein (e.g., CDR-H1, CDR-H2, CDR- H3, CDR-L1, CDR-L2 and/or CDR-L3), Col. 22, Lns. 44-43); an antibody or antigen binding fragment thereof that binds a SARS-CoV-2 Spike protein comprising a VH comprising a HCDR1, HCDR2, HCDR3, and a VL comprising LCDR1, LCDR2, and LCDR3 (anti-SARS CoV-2 Spike protein ...antibodies, Col. 2, Lns. 58-60; heavy and/or light chain amino acid sequences set forth herein (e.g., CDR-H1, CDR-H2, CDR- H3, CDR-L1, CDR-L2 and/or CDR-L3), Col. 22, Lns. 44-43), a method of treating or preventing a SARS-CoV-2 infection in a subject (anti-SARS-CoV-2-Spike protein (SARS-CoV-2-S) antibodies and their use for treating or preventing viral infection, Col. 1, Lns. 65-67; a method for treating or preventing infection with a coronavirus, Col. 3, Lns. 65-66); a kit for treating or preventing a SARS-CoV-2 infection in a subject (anti-SARS-CoV-2-Spike protein (SARS-CoV-2-S) antibodies and their use for treating or preventing viral infection, Col. 1, Lns. 65-67; a method for treating or preventing infection with a coronavirus, Col. 3, Lns. 65-66; a kit comprising the antibody, Col. 3, Ln. 39).

The inventions listed in Groups I+ therefore lack unity under Rule 13 because they do not share a same or corresponding special technical features.