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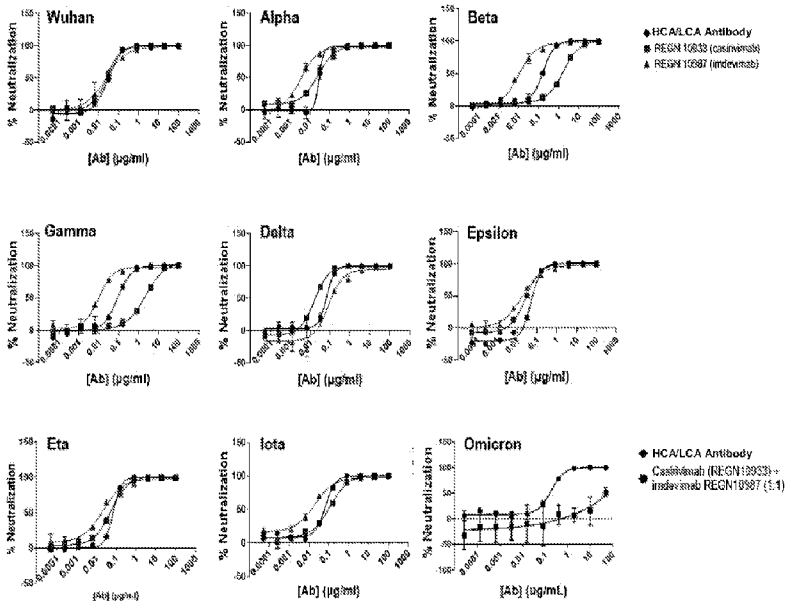
(54) Title: COMPOSITIONS AND METHODS AGAINST A VIRUS

FIG. 3



(57) Abstract: COVID-19 is the deadliest respiratory virus pandemic since 1918 and the latest of several coronavirus epidemics and pandemics in recent years. Despite the unprecedented response by both the government and private sectors to develop vaccines and therapies, the evolution of SARS-CoV-2 variants resistant to these interventions reveals a crucial need for therapeutics that maintain their efficacy against current and future mutant variants. The disclosure herein provides a SARS-CoV-2 neutralizing antibody, the HCA/LCA antibody, with potent activity against all variants tested including the Omicron variant. The HCA/LCA antibody also displays potent neutralizing activity against SARS-CoV. The presently disclosed HCA/LCA antibody can provide a therapeutic effect against the current SARS-CoV-2 variants and can maintain efficacy against future variants and novel coronaviruses.

[Continued on next page]

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COMPOSITIONS AND METHODS AGAINST A VIRUS

CROSS-REFERENCE

[0001] This application claims priority to U.S. Provisional Patent Application 63/306,276, filed February 03, 2022; U.S. Provisional Patent Application 63/316,262, filed March 03, 2022, and International Application No. PCT/CN2022/081104, filed March 16, 2022, each of which is incorporated herein by reference in its entirety.

BACKGROUND

[0002] The coronavirus disease 2019 (COVID-19) pandemic is the deadliest caused by a respiratory virus since the 1918 Influenza pandemic, with over 5.3 million deaths as of December 2021 (Johns Hopkins University COVID-19 Dashboard). The first known case of COVID-19 occurred in Wuhan, China in December of 2019 (Zhou, 2020), the causative agent of which was determined to be a novel human coronavirus subsequently named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). SARS-CoV-2 is an enveloped, positive-strand RNA virus in the betacoronavirus genus (Xu, 2020), which also includes the human coronaviruses MERS-CoV and SARS-CoV. SARS-CoV is approximately 80% genetically identical to SARS-CoV-2 and shares angiotensin-converting enzyme 2 (ACE2) as the host receptor to which the spike (S) glycoprotein of both viruses bind (Zhou, 2020). The spike protein exists as a homotrimer on the envelope of the virus with each spike protein monomer comprised of an S1 domain involved in binding to the ACE2 host receptor and an S2 domain, which mediates the fusion of the viral and cellular membranes (Yuan, 2020). The S1 domain consists of an N-terminal domain (NTD), two C-terminal subdomains (SD1 and SD2), and a receptor-binding domain (RBD) in between (Yuan, 2020). The RBD itself is defined as the region between two cysteine residues (C336 and C525) forming a disulfide bridge and dynamically changes confirmation from an “up” state to a “down” state, with only the “up” state being able to bind to ACE2 (Yuan, 2020; Niu, 2021).

[0003] While there has been an intense global effort to develop vaccines against SARS-CoV-2 and three vaccines that have received emergency use authorization (EUA) by the US FDA, from Moderna (Baden, 2021), Pfizer/BioNTech (Polack, 2020), and Johnson & Johnson (Sadoff, 2021) have been shown to be approximately 95% effective for the Moderna and Pfizer/BioNTech vaccines and 67% for the Johnson & Johnson vaccine in preventing infection, their ability to establish lasting long-term protective immunity has not been demonstrated and their efficacy against the Omicron variant is likely weakened (Callaway, 2021; Planas, 2021). In addition, vaccination may not be safe or effective in certain patient populations such as those with vaccine

allergies or are immunocompromised. As such, there is a need to develop therapeutics to prevent and treat COVID-19. Among the most promising class of SARS-CoV-2-targeting therapeutics are neutralizing antibodies (nAbs), many of which can block the spike protein-ACE2 interaction and prevent the virus from infecting host cells. To date, several antibody-based SARS-CoV-2-targeting therapeutics have been given EUA by the US FDA, including COVID-19 convalescent plasma as well as monoclonal nAbs or nAb cocktails from Regeneron, Lilly, and GSK/Vir (FDA emergency use authorizations for COVID-19).

[0004] Although nAbs show great promise in the treatment and prophylaxis of COVID-19 (Hurt, 2021), a major potential liability of all nAbs is the evolution of mutant variants resistant to nAb therapy (i.e., escape mutants). Although affecting therapeutic nAbs, the evolution of escape mutants is thought to be largely driven by natural evolution of the virus under selective pressure of the host immune response and not by the selective pressure of antiviral therapies, as acute respiratory infections are normally cleared in immunocompetent individuals receiving such therapies (Holmes, 2021). As a therapeutic involving multiple neutralizing antibodies binding distinct epitopes (i.e., a "cocktail") would be more resistant to mutant escape as multiple mutation events at different epitopes could be involved to render a multiple antibody therapeutic ineffective, a cocktail strategy is currently being pursued by multiple biotechnology companies, including a two nAb cocktail approach by Regeneron, Lilly, and Brii. Brii's cocktail is currently in clinical trials (clinicaltrials.gov; NCT04787211). Regeneron's cocktail of casarivimab (REGN10933) and imdevimab (REGN10987), currently under EUA, has been demonstrated to reduce the generation of escape mutants in vitro compared to either single nAb (Baum, 2020) and this cocktail has been successful in clinical trials (Weinrich, 2021). However, the Regeneron cocktail displays a 20-fold reduction in neutralization potency against the Beta variant of SARS-CoV-2 (Wang, 2021) and a recent study that examined the effect of all possible amino acid mutations in the RBD showed that a single E406W mutation almost completely eliminated the neutralization potency of the Regeneron nAb cocktail (Starr, 2021). Lilly has developed two antibodies used in combination therapy which have received EUA, bamlanivimab and etesevimab. However, one of the antibodies, bamlanivimab, is ineffective against multiple mutant variants including Beta (Wang, 2021) and consequently, its monotherapy EUA was revoked by the US FDA (FDA news release, April 16, 2021). Moreover, the Regeneron and Lilly nAbs, among others, are ineffective against the Omicron variant (Cao, 2021; Planas, 2021). Taken together, these findings suggest that the existing therapeutic antibody cocktail strategy alone may not provide adequate resistance to the evolution of escape mutants.

[0005] Another promising strategy to combat the emergence of escape mutants is the use of nAbs that recognize conserved epitopes of SARS-CoV-2 shared by other coronaviruses. Since

conserved epitopes are believed to occur in protein regions that can play a role for some aspect of the viral reproductive cycle, mutations in conserved epitopes are likely to reduce the evolutionary fitness of a virus and would be less likely to become prevalent in the overall viral population (Ekiert, 2009; Ekiert 2011). This conserved epitope approach is being pursued by, among others, GSK/Vir with the nAb sotrovimab (Pinto, 2020). Sotrovimab, sold under the brand name Xevudy, is a human neutralizing monoclonal antibody with activity against severe acute respiratory syndrome coronavirus 2, known as SARS-CoV-2.

SUMMARY

[0006] The current COVID-19 pandemic is the third caused by a novel coronavirus within the last 20 years which suggests the likelihood that other novel coronavirus pandemics can arise in the near future (DeFrancesco, 2020). Neutralizing antibodies (nAbs) with conserved epitope binding and broad activity against not only SARS-CoV-2 but other viruses in the betacoronavirus genus could play a crucial role in the early response to future coronavirus pandemics. Indeed, the US National Institutes of Health has recommended that stockpiling broadly acting nAbs should be a pillar of future pandemic preparedness (Therapeutic Neutralizing Monoclonal Antibodies: Report of a Summit sponsored by Operation Warp Speed and the National Institutes of Health).

[0007] The past and potential future vulnerabilities of the current nAbs being used under EUA highlights the need for more effective nAb-based therapies. Here we describe the development of a nAb therapeutic approach that uses an antibody, the HCA/LCA antibody, derived from the B cells of a convalescent COVID-19 patient. Demonstrated herein is an HCA/LCA antibody has broad neutralizing activity against recently circulating mutant variants of SARS-CoV-2 including the Omicron variant. In addition, given neutralization of a related betacoronavirus (SARS-CoV), it is possible that the HCA/LCA antibody can neutralize future variants of SARS-CoV-2 as well as novel betacoronaviruses yet to evolve.

[0008] The present disclosure is based upon development of a neutralizing antibody (nAb). This antibody comprises a heavy chain, “heavy chain A” (HCA), and a light chain, “light chain A” (LCA). This antibody, referred to herein as the HCA/LCA antibody, can serve as a therapeutic for various clades of coronaviruses. The HCA/LCA antibody comprises a neutralizing antibody with potent activity against all current SARS-CoV-2 variants of concern, including Omicron, as well as neutralizing activity against SARS-CoV.

[0009] In some embodiments, provided herein is a method for preventing or treating a SARS-CoV infection or a SARS-CoV-2 infection in a subject comprising administering to the subject an agent capable of independently i) binding SARS-CoV and ii) blocking SARS-CoV-2 binding to angiotensin-converting enzyme 2 (ACE2).

[00010] In some embodiments, the agent is capable of binding SARS-CoV spike protein. In further embodiments, the agent is capable of binding SARS-CoV spike protein S1 domain.

[00011] In some embodiments, the agent is capable of blocking SARS-CoV-2 spike protein from binding to ACE2. In further embodiments of the method, the agent is capable of blocking SARS-CoV-2 spike protein S1 domain from binding to ACE2. In some embodiments, the agent is capable of blocking SARS-CoV-2 spike protein S1 domain receptor binding domain (RBD) from binding to ACE2.

[00012] In some embodiments of the method, the agent is capable of specifically binding the SARS-CoV or SARS-CoV-2.

[00013] In some embodiments, provided herein is a method for method for preventing or treating a SARS-CoV-2 infection in a subject comprising administering to the subject an agent capable of binding bind SARS- CoV-2 spike protein S1 domain, wherein the ability to bind SARS- CoV-2 spike protein S1 domain is reduced by a mutation at position 378, 408, or 414. In some embodiments, the mutation is K378A, R408A, or Q414A.

[00014] Some embodiments of the present disclosure provide a method for preventing or treating a SARS-CoV-2 infection in a subject, wherein the SARS-CoV-2 comprises a spike protein with one or more of A67V, Δ69-70, T95I, Δ211/L212I, ins214EPE, G339D, S371L, S373P, S375F, N440K, G446S, S477N, E484A, Q493R, G496S, Q498R, Y505H, T547K, N679K, N764K, D796Y, N856K, Q954H, N969K, or L981F, comprising administering to the subject an agent capable of neutralizing the infection with a half maximal inhibitory concentration (IC50) of less than 0.4 μg/mL or an IC90 of less than 1 μg/mL.

[00015] In some embodiments, the SARS-CoV-2 comprises a spike protein comprising A67V, Δ69-70, T95I, G142D/Δ143-145, Δ211/L212I, ins214EPE. G339D, S371L, S373P, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493R, G496S, Q498R, N501Y, Y505H, T547K, D614G, H655Y, N679K, P681H, N764K, D796Y, N856K, Q954H, N969K, and L981F.

[00016] Additionally provided herein is a method for preventing or treating a SARS-CoV-2 infection in a subject comprising administering to the subject an agent capable of independently neutralizing SARS-CoV-2 B.1.1.529 (Omicron), SARS-CoV-2 (Epsilon), SARS-CoV-2 (Iota), SARS-CoV-2 (Eta), SARS-CoV-2 (Delta), SARS-CoV-2 (Gamma), SARS-CoV-2 (Beta), and SARS-CoV-2 (Alpha) infections with an average IC50 of less than 900 ng/mL.

[00017] The present disclosure further provides a method for preventing or treating a SARS-CoV infection in a subject comprising administering to the subject an agent capable of neutralizing the SARS-CoV with an IC50 of less than 0.05 μg/mL.

[00018] In some embodiments of the methods provided herein, the agent comprises an antibody or antigen-binding fragment thereof. In some embodiments, the antibody or antigen-binding

fragment thereof is a chimeric antigen receptor (CAR). In some embodiments, the subject is a human, dog, cat, cow, or horse.

[00019] In some embodiments of the above methods, the agent does not specifically bind MERS-CoV spike protein S1 domain. In some embodiments, the agent is capable of neutralizing SARS-CoV-2 variants Wuhan, Alpha, Beta, Gamma, Delta, Epsilon, Eta, Iota, or Omicron.

[00020] In some embodiments, the methods provided herein comprise administering an additional agent. In some cases, the agent and the additional agent interact synergistically in neutralizing the infection. In some cases, the agent and the additional agent interact additively in neutralizing the infection. In some cases, the agent and the additional agent interact antagonistically in neutralizing the infection.

[00021] Further provided herein is a method comprising contacting a cell comprising an infection with SARS-CoV-2 with an agent, wherein the SARS-CoV-2 comprises a spike protein with one or more of A67V, Δ69-70, T95I, Δ211/L212I, ins214EPE, G339D, S371L, S373P, S375F, N440K, G446S, S477N, E484A, Q493R, G496S, Q498R, Y505H, T547K, N679K, N764K, D796Y, N856K, Q954H, N969K, and L981F, wherein the agent capable of neutralizing the infection with a half maximal inhibitory concentration (IC50) of less than 0.4 μg/mL or an IC90 of less than 1 μg/mL.

[00022] In further embodiments, the SARS-CoV-2 comprises a spike protein comprising A67V, Δ69-70, T95I, G142D/Δ143-145, Δ211/L212I, ins214EPE. G339D, S371L, S373P, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493R, G496S, Q498R, N501Y, Y505H, T547K, D614G, H655Y, N679K, P681H, N764K, D796Y, N856K, Q954H, N969K, and L981F.

[00023] Also provided herein is a method comprising contacting a cell comprising an infection with SARS-CoV-2 with agent capable of independently neutralizing SARS-CoV-2 B.1.1.529 (Omicron), SARS-CoV-2 (Epsilon), SARS-CoV-2 (Iota), SARS-CoV-2 (Eta), SARS-CoV-2 (Delta), SARS-CoV-2 (Gamma), SARS-CoV-2 (Beta), and SARS-CoV-2 (Alpha) with an average IC50 of less than 900 ng/mL.

[00024] Further provided herein is method comprising contacting a cell comprising a SARS-CoV infection or a SARS-CoV-2 infection with an agent capable of independently i) binding SARS-CoV and ii) blocking SARS-CoV-2 binding to angiotensin-converting enzyme 2 (ACE2). In some embodiments, the agent is capable of binding SARS-CoV spike protein. In further embodiments, the agent is capable of binding SARS-CoV spike protein S1 domain.

[00025] In further embodiments of the methods provided herein, the agent is capable of blocking SARS-CoV-2 spike protein from binding to ACE2. In some, the agent is capable of blocking SARS-CoV-2 spike protein S1 domain from binding to ACE2. In some embodiments, the agent is capable of blocking SARS-CoV-2 spike protein S1 domain receptor binding domain (RBD)

from binding to ACE2. In further embodiments, the agent is capable of specifically binding the SARS-CoV or SARS-CoV-2.

[00026] The present disclosure further provides a method comprising contacting a cell comprising an infection with SARS-CoV with an agent capable of neutralizing the infection with an IC50 of less than 0.05 μg/mL.

[00027] Also provided in the present disclosure is a method comprising binding an agent SARS-CoV-2 spike protein S1 domain, wherein an ability of the agent to bind SARS- CoV-2 spike protein S1 domain is reduced by a mutation at position 378, 408, or 414. In some embodiments, wherein the mutation is K378A, R408A, or Q414A.

[00028] In one or more of the above embodiments, the agent comprises an antibody or antigen-binding fragment thereof. In some embodiments, the antibody or antigen-binding fragment thereof is a chimeric antigen receptor (CAR).

[00029] In one or more of the above embodiments, the subject is a human, dog, cat, cow, or horse.

[00030] The present disclosure provides an agent capable of capable of neutralizing a SARS-CoV-2 infection with a half maximal inhibitory concentration (IC50) of less than 0.4 μg/mL or an IC90 of less than 1 μg/mL, wherein the SARS-CoV-2 comprises a spike protein with one or more of A67V, Δ69-70, T95I, Δ211/L212I, ins214EPE, G339D, S371L, S373P, S375F, N440K, G446S, S477N, E484A, Q493R, G496S, Q498R, Y505H, T547K, N679K, N764K, D796Y, N856K, Q954H, N969K, or L981F, relative to SEQ ID NO: 1.

[00031] In some embodiments of the agent, the SARS-CoV-2 comprises a spike protein comprising A67V, Δ69-70, T95I, G142D/Δ143-145, Δ211/L212I, ins214EPE. G339D, S371L, S373P, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493R, G496S, Q498R, N501Y, Y505H, T547K, D614G, H655Y, N679K, P681H, N764K, D796Y, N856K, Q954H, N969K, and L981F, relative to SEQ ID NO: 1.

[00032] Herein provided is also agent capable of independently neutralizing SARS-CoV-2 B.1.1.529 (Omicron), SARS-CoV-2 (Epsilon), SARS-CoV-2 (Iota), SARS-CoV-2 (Eta), SARS-CoV-2 (Delta), SARS-CoV-2 (Gamma), SARS-CoV-2 (Beta), and SARS-CoV-2 (Alpha) infections in a subject with an average IC50 of less than 900 ng/mL.

[00033] The present disclosure provides an agent capable of independently i) binding SARS-CoV and ii) blocking SARS-CoV-2 binding to angiotensin-converting enzyme 2 (ACE2). In some embodiments, the agent is capable of binding SARS-CoV spike protein. In further embodiments, the agent of claim 39, wherein the agent is capable of binding SARS-CoV spike protein S1 domain.

[00034] In some embodiments provided herein, the agent is capable of blocking SARS-CoV-2 spike protein from binding to ACE2. In some embodiments, the agent of claim 41, wherein the agent is capable of blocking SARS-CoV-2 spike protein S1 domain from binding to ACE2. In some embodiments of the present disclosure, the agent is capable of blocking SARS-CoV-2 spike protein S1 domain receptor binding domain (RBD) from binding to ACE2.

[00035] In one or more embodiments, the agent is capable of specifically binding the SARS-CoV or SARS-CoV-2.

[00036] The present disclosure also includes an agent capable of neutralizing the SARS-CoV with an IC50 of less than 0.05 μg/mL.

[00037] An agent that specifically binds SARS- CoV-2 spike protein S1 domain, wherein an ability of the agent to bind SARS- CoV-2 spike protein S1 domain is reduced by a mutation at position 378, 408, or 414.

[00038] In some embodiments, the mutation is K378A, R408A, or Q414A.

[00039] In some embodiments of the agents provided in the present disclosure, the agent comprises an antibody or antigen-binding fragment thereof. In further embodiments, the antibody or antigen-binding fragment thereof is a chimeric antigen receptor (CAR).

[00040] Also provided in the present disclosure is a pharmaceutical composition comprising the agent of any of the above embodiments and a pharmaceutically acceptable carrier.

[00041] The present disclosure further describes a nucleic acid molecule encoding the agent from any of the above embodiments. In some embodiments, the present disclosure describes a vector comprising the nucleic acid of the nucleic acid molecule encoding the agent. In further embodiments, provided herein is a host cell comprising the vector.

[00042] The present disclosure also provides a kit comprising the agent of any one of the above embodiments and instructions.

[00043] The present disclosure further provides a method of inactivating one or more strains of a virus, wherein the virus comprises SARS-CoV, SARS-CoV-2, or a variant of SARS-CoV or SARS-CoV-2, the method comprising: administering a first agent, wherein the first agent binds to a first epitope of the virus, and administering a second agent, wherein the second agent binds to a second epitope, wherein at least said first epitope comprises an amino acid sequence that is conserved in the one or more strains of the virus.

[00044] In some embodiments, provided herein is a method for preventing or treating a SARS-CoV infection or a SARS-CoV-2 infection in a subject comprising administering to the subject two or more agents, wherein the one or more agents are capable of independently i) binding SARS-CoV and ii) blocking SARS-CoV-2 binding to angiotensin-converting enzyme 2 (ACE2). In some cases, the two or more agents interact synergistically in neutralizing the SARS-CoV

infection or the SARS-CoV-2 infection. In some cases, the two or more agents comprise sotrovimab.

[00045] Further provided herein is a pharmaceutical composition comprising two or more agents capable of independently i) binding SARS-CoV and ii) blocking SARS-CoV-2 binding to angiotensin-converting enzyme 2 (ACE2). The pharmaceutical composition can comprise two or more agents that act synergistically.

[00046] The present disclosure methods comprising i) contacting a cell infected with a virus with a first agent, wherein the first agent binds to a first epitope of the virus, wherein said first epitope is conserved in variants of the virus, and ii) contacting the cell with a second agent, wherein the second agent binds to a second epitope of the virus; wherein the virus comprises SARS-CoV or SARS-CoV-2. In some embodiments, the second agent binds the second conserved epitope, optionally wherein the first conserved epitope and the second conserved epitope are in a spike protein, optionally wherein the first conserved epitope and the second conserved epitope are in a spike protein S1 domain, optionally wherein the first conserved epitope and the second conserved epitope are in a spike protein S1 domain receptor binding domain. In some embodiments, the second agent binds the non-conserved epitope, optionally wherein the first conserved epitope and the non-conserved epitope are in a spike protein, optionally wherein the first conserved epitope and the non-conserved epitope are in a spike protein S1 domain, optionally wherein the first conserved epitope and the non-conserved epitope are in a spike protein S1 domain receptor binding domain. In some embodiments, a first agent and a second agent of the two or more agents comprise an antibody or antigen-binding fragment thereof, optionally wherein the antibody or antigen-binding fragment thereof is a chimeric antigen receptor (CAR).

[00047] In some embodiments of the methods provided herein, the agent comprises an antibody, or antigen-binding fragment thereof, comprising (a) a heavy chain complementarity determining region (CDR)1 (HCDR1), HCDR2, and HCDR3 and/or a light chain CDR1 (LCDR1), LCDR2 and LCDR3, wherein the HCDR1, the HCDR2, and the HCDR3 comprise amino acid sequences set forth in SEQ ID NO: 6, SEQ ID NO: 7, and SEQ ID NO: 8, respectively, and the LCDR1, the LCDR2, and the LCDR3 comprise the amino acid sequences set forth in SEQ ID NO: 9, SEQ ID NO: 10, and SEQ ID NO: 11, respectively; (b) a heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 12, or an amino acid sequence comprising at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence set forth in SEQ ID NO: 12 and/or 2) a light chain comprising the amino acid sequence set forth in SEQ ID NO: 15, or an amino acid sequence comprising at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence set forth in SEQ ID NO: 15; or (c) a heavy chain variable region (VH) comprising the

amino acid sequence set forth in SEQ ID NO: 13, or an amino acid sequence comprising at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence set forth in SEQ ID NO: 13 and/or 2) a light chain variable region (VL) comprising the amino acid sequence set forth in SEQ ID NO: 16, or an amino acid sequence comprising at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence set forth in SEQ ID NO: 16.

[00048] In some embodiments of the methods provided herein, the first agent comprises an antibody, or antigen-binding fragment thereof, comprising (a) a heavy chain complementarity determining region (CDR)1 (HCDR1), HCDR2, and HCDR3 and/or a light chain CDR1 (LCDR1), LCDR2 and LCDR3, wherein the HCDR1, the HCDR2, and the HCDR3 comprise amino acid sequences set forth in SEQ ID NO: 6, SEQ ID NO: 7, and SEQ ID NO: 8, respectively, and the LCDR1, the LCDR2, and the LCDR3 comprise the amino acid sequences set forth in SEQ ID NO: 9, SEQ ID NO: 10, and SEQ ID NO: 11, respectively; (b) a heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 12, or an amino acid sequence comprising at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence set forth in SEQ ID NO: 12 and/or 2) a light chain comprising the amino acid sequence set forth in SEQ ID NO: 15, or an amino acid sequence comprising at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence set forth in SEQ ID NO: 15; or (c) a heavy chain variable region (VH) comprising the amino acid sequence set forth in SEQ ID NO: 13, or an amino acid sequence comprising at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence set forth in SEQ ID NO: 13 and/or 2) a light chain variable region (VL) comprising the amino acid sequence set forth in SEQ ID NO: 16, or an amino acid sequence comprising at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence set forth in SEQ ID NO: 16; and the second agent comprises (d) a heavy chain complementarity determining region (CDR)1 (HCDR1), HCDR2, and HCDR3 and/or a light chain CDR1 (LCDR1), LCDR2 and LCDR3, wherein the HCDR1, the HCDR2, and the HCDR3 comprise amino acid sequences set forth in SEQ ID NO: 20, SEQ ID NO: 21, and SEQ ID NO: 22, respectively, and the LCDR1, the LCDR2, and the LCDR3 comprise the amino acid sequences set forth in SEQ ID NO: 23, SEQ ID NO: 24, and SEQ ID NO: 25, respectively; (e) 1) a heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 18, or an amino acid sequence comprising at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence set forth in SEQ ID NO: 18 and/or 2) a light chain comprising the amino acid sequence set forth in SEQ ID NO: 19, or an amino acid sequence comprising at least 80%, 85%,

90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence set forth in SEQ ID NO: 19; or (f) 1) a heavy chain variable region (VH) comprising the amino acid sequence set forth in SEQ ID NO: 26, or an amino acid sequence comprising at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence set forth in SEQ ID NO: 26 and/or 2) a light chain variable region (VL) comprising the amino acid sequence set forth in SEQ ID NO: 28, or an amino acid sequence comprising at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence set forth in SEQ ID NO: 28.

[00049] In some embodiments of the methods provided herein, an agent of the two or more agents comprises an antibody, or antigen-binding fragment thereof, comprising (a) a heavy chain complementarity determining region (CDR)1 (HCDR1), HCDR2, and HCDR3 and/or a light chain CDR1 (LCDR1), LCDR2 and LCDR3, wherein the HCDR1, the HCDR2, and the HCDR3 comprise amino acid sequences set forth in SEQ ID NO: 6, SEQ ID NO: 7, and SEQ ID NO: 8, respectively, and the LCDR1, the LCDR2, and the LCDR3 comprise the amino acid sequences set forth in SEQ ID NO: 9, SEQ ID NO: 10, and SEQ ID NO: 11, respectively; (b) a heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 12, or an amino acid sequence comprising at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence set forth in SEQ ID NO: 12 and/or 2) a light chain comprising the amino acid sequence set forth in SEQ ID NO: 15, or an amino acid sequence comprising at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence set forth in SEQ ID NO: 15; or (c) a heavy chain variable region (VH) comprising the amino acid sequence set forth in SEQ ID NO: 13, or an amino acid sequence comprising at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence set forth in SEQ ID NO: 13 and/or 2) a light chain variable region (VL) comprising the amino acid sequence set forth in SEQ ID NO: 16, or an amino acid sequence comprising at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence set forth in SEQ ID NO: 16.

[00050] Further provided herein is a method comprising contacting a cell infected with a SARS-CoV-2 virus with a first agent and a second agent, wherein the contacting provides a combination index (CI) value of less than 1 at a neuralization level of at least 60%. In some cases, the CI value is less than 0.85 at a neutralization level of at least 60%. In some cases, the CI value is less than 0.6 at a neutralization level of at least 80%. In some embodiments, the first agent binds a first conserved epitope of the SARS-CoV-2 virus, and the second agent binds a second conserved epitope of the SARS-CoV-2 virus, optionally wherein the first conserved epitope and the second

conserved epitope are in spike protein, optionally wherein the first conserved epitope and the second conserved epitope are in a spike protein S1 domain, optionally wherein the first conserved epitope and the second conserved epitope are in a spike protein S1 domain receptor binding domain.

[00051] In some embodiments, the SARS-CoV-2 comprises a spike protein with one or more of A67V, Δ69-70, T95I, G142D/Δ143-145, Δ211/L212I, ins214EPE, G339D, S371L, S373P, S373F, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493R, G496S, Q498R, N501Y, Y505H, T547K, D614G, H655Y, N679K, P681H, N764K, D796Y, N856K, Q954H, N969K, or L981F.

[00052] Also provided herein is a method comprising contacting a cell infected with a SARS-CoV virus with a first agent and a second agent, wherein the contacting provides a CI value of less than 1 at a neuralization level of at least 40%. In some cases, the contacting provides a CI value is less than 0.7 at a neutralization level of at least 60%. In some cases, the contacting provides a CI value is less than 0.5 at a neutralization level of at least 80%.

[00053] In some embodiments provided herein, the first agent binds a first conserved epitope of the SARS-CoV virus, and the second agent binds a second conserved epitope of the SARS-CoV virus, optionally wherein the first conserved epitope and the second conserved epitope are in spike protein, optionally wherein the first conserved epitope and the second conserved epitope are in a spike protein S1 domain, optionally wherein the first conserved epitope and the second conserved epitope are in a spike protein S1 domain receptor binding domain. In some embodiments, the present disclosure provides a method comprising contacting a cell infected with a SARS-CoV virus with a first agent and a second agent, wherein the contacting provides a CI value of less than 1 at a neutralization level of at least 20%. In some cases, the contacting provides a CI value of less than 0.6 at a neutralization level of at least 20%. In some cases, the contacting provides a CI value of less than 0.5 at a neutralization level of at least 40%.

[00054] In some embodiments, the first agent binds a conserved epitope of the SARS-CoV virus, and the second agent binds a non-conserved epitope of the SARS-CoV virus, optionally wherein the conserved epitope and the non-conserved epitope are in spike protein, optionally wherein the conserved epitope and the non-conserved epitope are in a spike protein S1 domain, optionally wherein the conserved epitope and the non-conserved epitope are in a spike protein S1 domain receptor binding domain.

[00055] Further provided herein is a method of preventing or treating a SARS-CoV infection or a SARS-CoV-2 infection in a subject comprising administering to the subject two or more agents, wherein the two or more agents are each capable of independently i) binding SARS-CoV and ii) blocking SARS-CoV-2 binding to angiotensin-converting enzyme 2 (ACE2). In some

embodiments, the two or more agents interact synergistically in neutralizing the SARS-CoV infection or the SARS-CoV-2 infection. In some embodiments, the two or more agents comprise sotrovimab.

[00056] The present disclosure provides a pharmaceutical composition comprising two or more agents, each capable of independently i) binding SARS-CoV and ii) blocking SARS-CoV-2 binding to angiotensin-converting enzyme 2 (ACE2). In some cases, the first agent and the second agent comprise an antibody or antigen-binding fragment thereof, optionally wherein the antibody or antigen-binding fragment thereof is a chimeric antigen receptor (CAR).

[00057] Provided herein is a composition comprising a i) first antibody or antigen-binding fragment thereof and ii) a second antibody or antigen-binding fragment thereof, wherein the composition is capable of a combination index (CI) of less than 1, 0.9, 0.8, 0.7, 0.6, or 0.5 for neutralizing an infection with a pseudotyped virus with a SARS-CoV-2 spike protein at a percent neutralization level of at least 20%, at least 40%, at least 60%, or at least 80%.

[00058] The first antibody or antigen-binding fragment thereof can comprise a heavy chain complementarity determining region (CDR)1 (HCDR1), HCDR2, and HCDR3 and/or a light chain CDR1 (LCDR1), LCDR2 and LCDR3, wherein the HCDR1, the HCDR2, and the HCDR3 comprise amino acid sequences set forth in SEQ ID NO: 6, SEQ ID NO: 7, and SEQ ID NO: 8, respectively, and the LCDR1, the LCDR2, and the LCDR3 comprise the amino acid sequences set forth in SEQ ID NO: 9, SEQ ID NO: 10, and SEQ ID NO: 11, respectively; a heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 12, or an amino acid sequence comprising at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence set forth in SEQ ID NO: 12 and/or 2) a light chain comprising the amino acid sequence set forth in SEQ ID NO: 15, or an amino acid sequence comprising at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence set forth in SEQ ID NO: 15; or a heavy chain variable region (VH) comprising the amino acid sequence set forth in SEQ ID NO: 13, or an amino acid sequence comprising at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence set forth in SEQ ID NO: 13 and/or 2) a light chain variable region (VL) comprising the amino acid sequence set forth in SEQ ID NO: 16, or an amino acid sequence comprising at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence set forth in SEQ ID NO: 16.

INCORPORATION BY REFERENCE

[00059] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

BRIEF DESCRIPTION OF THE DRAWINGS

[00060] In order to better understand various exemplary embodiments, reference is made to the accompanying drawings, wherein:

[00061] Figure 1 depicts Luminex spike mutant binding. The charts show binding strength as demonstrated by Luminex binding assay. The left axis of each heat map represents the concentration of antibody dilution, the bottom axis describes the spike protein (with mutations indicated) that are used for each column, and the right axis represents the intensity of binding in relative light units (RLU).

[00062] Figure 2 provides the results of an antibody ACE2-competition ELISA using indicated antibodies at concentrations given by the horizontal axis. For REGN-COV-2, casarivimab and imdevimab were added at an equimolar ratio summing to the concentration given on the horizontal axis.

[00063] Figure 3 provides a comparison of pseudovirus neutralization activity of the HCA/LCA antibody and casarivimab and imdevimab. Using a SAR-CoV-2 spike pseudotyped viral neutralization assay, the neutralizing activity of each antibody against the indicated SARS-CoV-2 viral variants or SARS-CoV was determined.

[00064] Figure 4 provides a comparison of pseudovirus neutralization activity of the HCA/LCA antibody and sotrovimab. Using a SAR-CoV-2 spike pseudotyped viral neutralization assay, the neutralizing activity of each antibody against the indicated SARS-CoV-2 viral variants or SARS-CoV was determined. An X indicates that antibody concentration was not tested.

[00065] Figure 5 provides curves comparing percent neutralization by each antibody to the concentration of each antibody present, in terms of μg/mL, which demonstrates the potency of the HCA/LCA antibody relative to other neutralizing antibodies. Using a SAR-CoV spike pseudotyped viral neutralization assay, the neutralizing activity of each antibody against the SARS-CoV was determined.

DETAILED DESCRIPTION OF THE DISCLOSURE

[00066] The following definitions supplement those in the art and are directed to the current application and are not to be imputed to any related or unrelated case, e.g., to any commonly owned patent or application. Although any methods and materials similar or equivalent to those

described herein can be used in the practice for testing of the present disclosure, the preferred materials and methods are described herein. Accordingly, the terminology used herein is for the purpose of describing particular embodiments only and is not intended to be limiting.

[00067] The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described.

[00068] Although various features of the present disclosure can be described in the context of a single embodiment, the features can also be provided separately or in any suitable combination. Conversely, although the present disclosure can be described herein in the context of separate embodiments for clarity, the present disclosure can also be implemented in a single embodiment.

Definitions

[00069] In this application, the use of the singular includes the plural unless specifically stated otherwise. It must be noted that, as used in the specification, the singular forms "a," "an" and "the" include plural referents unless the context clearly dictates otherwise. In this application, the use of "or" means "and/or" unless stated otherwise. Furthermore, use of the term "including" as well as other forms, such as "include", "includes," and "included," is not limiting.

[00070] Reference in the specification to "some embodiments," "an embodiment," "one embodiment" or "other embodiments" means that a particular feature, structure, or characteristic described in connection with the embodiments is included in at least some embodiments, but not necessarily all embodiments, of the present disclosure.

[00071] As used in this specification and claim(s), the words "comprising" (and any form of comprising, such as "comprise" and "comprises"), "having" (and any form of having, such as "have" and "has"), "including" (and any form of including, such as "includes" and "include") or "containing" (and any form of containing, such as "contains" and "contain") are inclusive or open-ended and do not exclude additional, un-recited elements or method steps. It is contemplated that any embodiment discussed in this specification can be implemented with respect to any method or composition of the present disclosure, and vice versa. Furthermore, compositions of the present disclosure can be used to achieve methods of the present disclosure.

[00072] The term "about" or "approximately" means within an acceptable error range for the particular value as determined by one of ordinary skill in the art, which will depend in part on how the value is measured or determined, i.e., the limitations of the measurement system. For example, "about" can mean within 1 or more than 1 standard deviation, per the practice in the art. Alternatively, "about" can mean a range of up to 20%, up to 10%, up to 5%, or up to 1% of a given value. In another example, the amount "about 10" includes 10 and any amounts from 9 to 11.

[00073] In yet another example, the term "about" in relation to a reference numerical value can also include a range of values plus or minus 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, or 1% from that value. Alternatively, particularly with respect to biological systems or processes, the term "about" can mean within an order of magnitude, preferably within 5-fold, and more preferably within 2-fold, of a value. Where particular values are described in the application and claims, unless otherwise stated the term "about" meaning within an acceptable error range for the particular value should be assumed.

[00074] As used herein, the term "antibody" refers to an immunoglobulin (Ig) whether natural or partly or wholly synthetically produced. The term also covers any polypeptide or protein having a binding domain which is, or is homologous to, an antigen-binding domain. The term further includes "antigen-binding fragments" or "functional fragment thereof", or "fragment of an antibody", "antibody fragment", "functional fragment of an antibody" and other interchangeable terms for similar binding fragments such as described below. An antibody includes, for example, monoclonal antibodies, chimeric antibodies, humanized antibodies, human antibodies, recombinant antibodies, chemically engineered antibodies, deimmunized antibodies, affinity-matured antibodies, multispecific antibodies (for example, bispecific antibodies and polyreactive antibodies), heteroconjugate antibodies, antibody fragments, and combinations thereof (e.g., a monoclonal antibody that is also deimmunized, a humanized antibody that is also deimmunized, etc.). An antibody can be, for example, murine, chimeric, humanized, heteroconjugate, bispecific, diabody, triabody, or tetrabody. The antigen binding fragment can include, for example, Fab', F(ab')2, Fab, Fv, rlgG, scFv, hcAbs (heavy chain antibodies), a single domain antibody, VHH, VNAR, sdAbs, or nanobody. The phrases "antibody of the present disclosure" or "antibodies of the present disclosure" can refer to the HCA/LCA antibody disclosed herein, or an antigen-binding fragment thereof.

[00075] The terms "fragment of an antibody," "antibody fragment," "functional fragment of an antibody," "antigen-binding portion," "antigen-binding fragment," or their grammatical equivalents are used interchangeably herein to mean one or more fragments or portions of an antibody that retain the ability to specifically bind to an antigen (see, generally, Holliger et al., Nat. Biotech., 23(9): 1126-1129 (2005)). The antibody fragment desirably comprises, for example, one or more CDRs, the variable region (or portions thereof), the constant region (or portions thereof), or combinations thereof. Examples of antibody fragments include, but are not limited to, (i) a Fab fragment, which is a monovalent fragment consisting of the VL, VH, CL, and CHI domains; (ii) a F(ab')2 fragment, which is a bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the stalk region; (iii) a Fv fragment consisting of the VL and VH domains of a single arm of an antibody; (iv) a single chain Fv (scFv), which is a

monovalent molecule consisting of the two domains of the Fv fragment (i.e., VL and VH) joined by a synthetic linker which enables the two domains to be synthesized as a single polypeptide chain (see, e.g., Bird et al., Science, 242: 423-426 (1988); Huston et al., Proc. Natl. Acad. Sci. USA, 85: 5879-5883 (1988); and Osbourn et al., Nat. Biotechnol., 16: 778 (1998)) and (v) a diabody, which is a dimer of polypeptide chains, wherein each polypeptide chain comprises a VH connected to a VL by a peptide linker that is too short to allow pairing between the VH and VL on the same polypeptide chain, thereby driving the pairing between the complementary domains on different VH-VL polypeptide chains to generate a dimeric molecule having two functional antigen binding sites. Antibody fragments are known in the art and are described in more detail in, e.g., U.S. Pat. No. 8,603,950. Other antibody fragments can include variable fragments of heavy chain antibodies (VHH).

[00076] "Heavy chain variable region" or "VH" with regard to an antibody can refer to the fragment of the heavy chain that can contain three CDRs interposed between flanking stretches known as framework regions; these framework regions are generally more highly conserved than the CDRs and can form a scaffold to support the CDRs.

[00077] "Light chain variable region" or "VL" with regard to an antibody can refer to the fragment of the light heavy chain that can contain three CDRs interposed between flanking stretches known as framework regions; these framework regions are generally more highly conserved than the CDRs and can form a scaffold to support the CDRs.

[00078] An "Fv" or "Fv fragment" can consist of only the light chain variable domain (VL) and heavy chain variable domain (VH) of a "single arm" of an immunoglobulin. Thus an "Fv" can be the minimum antibody fragment which contains a complete antigen-recognition and binding site. A "two- chain" Fv fragment can consist of a dimer of one heavy- and one light-chain variable domain in tight, non-covalent association. A single-chain Fv species (scFv) includes a VH and a VL domain of an immunoglobulin, with these domains being present in a single polypeptide chain in which they are covalently linked to each other by a linker peptide. Typically, in a scFv fragment the variable domains of the light and heavy chain can associate in a dimeric structure analogous to that in a two-chain Fv species. In single chain Fv fragments, it is possible to either have the variable domain of the light chain arranged at the N-terminus of the single polypeptide chain, followed by the linker and the variable domain of the heavy chain arranged at the C-terminus of the polypeptide chain or vice versa, having the variable domain of the heavy chain arranged on the N-terminus and the variable domain of the light chain at the C-terminus with the linker peptide arranged in between. The linker peptide can be any flexible linker known in the art, for example, made from glycine and serine residues. It is also possible to additionally stabilize the domain association between the VH and the VL domain by introducing disulfide

bonds into conserved framework regions (see Reiter et al. Stabilization of the Fv fragments in recombinant immunotoxins by disulfide bonds engineered into conserved framework regions, Biochemistry 1994, 33, 6551-5459). Such scFv fragments are also known as disulfide-stabilized scFv fragments (ds-scFv).

[00079] A "multispecific antibody" can be an antibody that can bind simultaneously to at least two targets that are of different structure, e.g., two different antigens, two different epitopes on the same antigen, or a hapten and/or an antigen or epitope. A "multivalent antibody" can be an antibody that can bind simultaneously to at least two targets that are of the same or different structure. The HCA/LCA antibodies described herein can be multispecific antibodies or multivalent antibodies. Valency indicates how many binding arms or sites the antibody has to a single antigen or epitope; i.e., monovalent, bivalent, trivalent or multivalent. The multivalency of the antibody means that it can take advantage of multiple interactions in binding to an antigen, thus increasing the avidity of binding to the antigen. Specificity indicates how many antigens or epitopes an antibody is able to bind; i.e., monospecific, bispecific, trispecific, multispecific. Using these definitions, a natural antibody, e.g., an IgA, is bivalent because it has two binding arms but is monospecific because it binds to one epitope. Multispecific, multivalent antibodies are constructs that have more than one binding region of different specificity.

[00080] A "bispecific antibody" can be an antibody that can bind simultaneously to two targets which are of different structure. Bispecific antibodies (bsAb) and bispecific antibody fragments (bsFab) can have at least one arm that specifically binds to, for example, a CD47, and at least one other arm that specifically binds to an antigen produced by or associated with a diseased cell, tissue, organ or pathogen, for example a tumor-associated antigen. of bispecific antibodies can be produced using molecular engineering.

[00081] The term "monoclonal antibodies," as used herein, can refer to antibodies that are produced by a single clone of B-cells and bind to the same epitope. In contrast, "polyclonal antibodies" refer to a population of antibodies that are produced by different B -cells and bind to different epitopes of the same antigen. A whole antibody can typically consist of four polypeptides: two identical copies of a heavy (H) chain polypeptide and two identical copies of a light (L) chain polypeptide. Each of the heavy chains can contain one N-terminal variable (VH) region and three C-terminal constant (CHI, CH2 and CH3) regions, and each light chain can contain one N-terminal variable (VL) region and one C- terminal constant (CL) region. The variable regions of each pair of light and heavy chains can form the antigen binding site of an antibody. The VH and VL regions can have a similar general structure, with each region comprising four framework regions, whose sequences can be relatively conserved. The framework regions can be connected by three complementarity determining regions (CDRs). The

three CDRs, known as CDR1, CDR2, and CDR3, can form the "hypervariable region" of an antibody, which can be responsible for antigen binding.

[00082] As used herein a "chimeric antibody" can be an antibody that comprises an amino acid sequence derived from two different species or, or two different sources, and includes synthetic molecules. By way of nonlimiting example, a chimeric antibody can be an antibody that comprises a non-human CDR and a human variable region framework or constant or Fc region, an antibody with binding domains from two different monoclonal antibodies, or an antibody comprising a mutation of one or more amino acid residues to increase or decrease biological activity or binding of a part of the antibody. In certain embodiments, recombinant antibodies are produced from a recombinant DNA molecule or synthesized. In certain embodiments, the antibodies described herein are a polypeptide(s) encoded by one or more polynucleotides.

[00083] As used herein, "recognize" can refer to the association or binding between an antigen binding domain and an antigen. As used herein, an "antigen" can refer to an antigenic substance that can trigger an immune response in a host. An antigenic substance can be a molecule, such as a costimulatory molecule that can trigger an immune response in a host.

[00084] As used herein, an "antibody construct" can refer to a construct that contains an antigen binding domain and an Fc domain.

[00085] As used herein, a "binding domain" can refer to an antibody or non-antibody domain.

[00086] As used herein, an "antigen binding domain" can refer to a binding domain from an antibody or from a non-antibody that can bind to an antigen. An antigen binding domain can be a tumor antigen binding domain or a binding domain that can bind to an antigen (such as a molecule) on an antigen presenting cell. Antigen binding domains can be numbered when there is more than one antigen binding domain in a given conjugate or antibody construct (e.g., first antigen binding domain, second antigen binding domain, third antigen binding domain, etc.). Different antigen binding domains in the same conjugate or construct can target the same antigen or different antigens (e.g., first antigen binding domain that can bind to a tumor antigen, second antigen binding domain that can bind to a molecule on an antigen presenting cell (APC antigen), and third antigen binding domain that can bind to an APC antigen). The term "antigen binding domain" can refer to a fragment of an antibody that comprises the area which specifically binds to an epitope, and is complementary to part or all of an antigen. An antigen binding domain can be provided by, for example, one or more antibody variable domains (also called antibody variable regions). Particularly, an antigen binding domain can comprise an antibody light chain variable region (VL) and an antibody heavy chain variable region (VH).

[00087] As used herein, the term "antigen" can mean a molecule or portion of a molecule that can react with a recognition site on an antibody. The term "antigen" can also include a molecule

or a portion of a molecule that can, either by itself or in conjunction with an adjuvant or carrier, elicit an immune response (also called an "immunogen"). The term "antigen" as used herein can include molecules or portions of molecules (epitopes) that can elicit production of antibodies or that can bind to antibodies. The term includes materials that react strongly and with high specificity, and also includes materials that react weakly and/or with low affinity to an antibody.

[00088] The term "epitope," as used herein, can refer to an antigenic determinant that interacts with a specific antigen binding site in the variable region of an antibody molecule known as a paratope. A single antigen can have more than one epitope. Thus, different antibodies can bind to different areas on an antigen and can have different biological effects. Epitopes can be either conformational or linear. A conformational epitope can be produced by spatially juxtaposed amino acids from different segments of the linear polypeptide chain. A linear epitope can be produced by adjacent amino acid residues in a polypeptide chain. In certain circumstance, an epitope can include moieties of saccharides, phosphoryl groups, or sulfonyl groups on the antigen. Various techniques known to persons of ordinary skill in the art can be used to determine whether an antigen-binding domain of an antibody interacts with one or more amino acids within a polypeptide or protein. Exemplary techniques include, e.g., routine cross-blocking assay such as that described Antibodies, Harlow and Lane (Cold Spring Harbor Press, Cold Spring Harb., NY), alanine scanning mutational analysis, peptide blots analysis (Reineke, 2004, Methods Mol Biol 248:443-463), and peptide cleavage analysis. In addition, methods such as epitope excision, epitope extraction and chemical modification of antigens can be employed (Tomer, 2000, Protein Science 9:487-496). Another method that can be used to identify the amino acids within a polypeptide with which an antigen-binding domain of an antibody interacts is hydrogen/deuterium exchange detected by mass spectrometry. In general terms, the hydrogen/deuterium exchange method can involve deuterium-labeling the protein of interest, followed by binding the antibody to the deuterium-labeled protein. Next, the protein/antibody complex can be transferred to water to allow hydrogen- deuterium exchange to occur at all residues except for the residues protected by the antibody (which remain deuterium-labeled). After dissociation of the antibody, the target protein can be subjected to protease cleavage and mass spectrometry analysis, thereby revealing the deuterium-labeled residues, which correspond to the specific amino acids with which the antibody interacts. See, e.g., Ehring (1999) Analytical Biochemistry 267(2):252-259; Engen and Smith (2001) Anal. Chem. 73:256A-265A. X-ray crystallography of the antigen/antibody complex can also be used for epitope mapping purposes.

[00089] As used herein, an "antibody antigen binding domain" can refer to a binding domain from an antibody that can bind to an antigen.

[00090] As used herein, an "Fc domain" can refer to an Fc domain from an antibody or from a non- antibody that can bind to an Fc receptor. As used herein, an "Fc domain" and an "Fc comprising domain" can be used interchangeably.

[00091] As used herein, a "target binding domain" can refer to a construct that contains an antigen binding domain from an antibody or from a non-antibody that can bind to an antigen.

[00092] As used herein, the abbreviations for the natural 1- enantiomeric amino acids can be conventional and can be as follows: alanine (A, Ala); arginine (R, Arg); asparagine (N, Asn); aspartic acid (D, Asp); cysteine (C, Cys); glutamic acid (E, Glu); glutamine (Q, Gin); glycine (G, Gly); histidine (H, His); isoleucine (I, He); leucine (L, Leu); lysine (K, Lys); methionine (M, Met); phenylalanine (F, Phe); proline (P, Pro); serine (S, Ser); threonine (T, Thr); tryptophan (W, Trp); tyrosine (Y, Tyr); valine (V, Val). Unless otherwise specified, X can indicate any amino acid. In some aspects, X can be asparagine (N), glutamine (Q), histidine (H), lysine (K), or arginine (R).

[00093] The phrase "pharmaceutically acceptable" can be refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

[00094] The phrase "pharmaceutically acceptable excipient" or "pharmaceutically acceptable carrier" as used herein can mean a pharmaceutically acceptable material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, solvent or encapsulating material. Each carrier can be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not injurious to the patient. Some examples of materials which can serve as pharmaceutically acceptable carriers include: (1) sugars, such as lactose, glucose and sucrose; (2) starches, such as corn starch and potato starch; (3) cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; (4) powdered tragacanth; (5) malt; (6) gelatin; (7) talc; (8) excipients, such as cocoa butter and suppository waxes; (9) oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; (10) glycols, such as propylene glycol; (11) polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; (12) esters, such as ethyl oleate and ethyl laurate; (13) agar; (14) buffering agents, such as magnesium hydroxide and aluminum hydroxide; (15) alginic acid; (16) pyrogen-free water; (17) isotonic saline; (18) Ringer's solution; (19) ethyl alcohol; (20) phosphate buffer solutions; and (21) other non-toxic compatible substances employed in pharmaceutical formulations.

[00095] The term IC (e.g., IC50) can refer to the maximal inhibitory concentration of antibody. Given a titration curve, potency of an antibody is typically quantified as the inhibitory concentration (IC), defined as the antibody concentration at which the viral replication has been reduced by 50% (IC50), 80% (IC80), 90% (IC90), etc., relative to the absence of the antibody. In the present disclosure, this term can be used with reference to the neutralization potency of antibodies.

[00096] The term "conservative amino acid substitution" or "conservative mutation" can refer to the replacement of one amino acid by another amino acid with a common property. A functional way to define common properties between individual amino acids is to analyze the normalized frequencies of amino acid changes between corresponding proteins of homologous organisms (Schulz, G. E. and Schirmer, R. H., Principles of Protein Structure, Springer-Verlag, New York (1979)). According to such analyses, groups of amino acids can be defined where amino acids within a group exchange preferentially with each other, and therefore resemble each other most in their impact on the overall protein structure (Schulz, G. E. and Schirmer, R. H., supra). Examples of conservative mutations include amino acid substitutions of amino acids within the sub groups above, for example, lysine for arginine and vice versa such that a positive charge can be maintained; glutamic acid for aspartic acid and vice versa such that a negative charge can be maintained; serine for threonine such that a free -OH can be maintained; and glutamine for asparagine such that a free -NH2 can be maintained. Alternatively or additionally, the therapeutic IgA antibodies can comprise the amino acid sequence of the reference protein with at least one non-conservative amino acid substitution.

[00097] As used herein, the term "Complementarity Determining Regions" (CDRs, i.e., CDR1, CDR2, and CDR3) can refer to the amino acid residues of an antibody variable domain that play a role in antigen binding. Each variable domain can have one, two, orthree CDR regions identified as CDR1, CDR2 and CDR3. The CDRs of variable heavy chain can be CDR-H1, CDR-H2 and CDR-H3. The CDRs of variable light chain can be CDR-L1, CDR-L2 and CDR-L3. Exemplary hypervariable loops can occur at amino acid residues 26-32 (LI), 50-52 (L2), 91-96 (L3), 26-32 (HI), 53-55 (H2), and 96-101 (H3). (Chothia and Lesk, J. Mol. Biol. 196:901-917 (1987)). Exemplary CDRs (CDR-L1, CDR-L2, CDR-L3, CDR-H1, CDR-H2, and CDR-H3) can occur at amino acid residues 24-34 of L1, 50-56 of L2, 89-97 of L3, 31-35 of H1, 50-65 of H2, and 95-102 of H3 (Rabat et al., Sequences of Proteins of Immunological Interest, 5th ed. (1991)). Thus, the HVs can be comprised within the corresponding CDRs and references herein to the "hypervariable loops" of VH and VL domains can be interpreted as also encompassing the corresponding CDRs, and vice versa, unless otherwise indicated. The more highly conserved regions of variable domains can be called the framework region (FR), as defined below. The

variable domains of native heavy and light chains can each comprise four FRs (FR1, FR2, FR3 and FR4, respectively), which can largely adopt a [beta]-sheet configuration, connected by the three hypervariable loops. The hypervariable loops in each chain can be held together in close proximity by the FRs and, with the hypervariable loops from the other chain, contribute to the formation of the antigen-binding site of antibodies. Structural analysis of antibodies can reveal the relationship between the sequence and the shape of the binding site formed by the complementarity determining regions (Chothia et al., J. Mol. Biol. 227: 799- 817 (1992)); Tramontano et al., J. Mol. Biol, 215: 175-182 (1990)). Despite their high sequence variability, five of the six loops can adopt just a small repertoire of main-chain conformations, called "canonical structures." These conformations can be first of all determined by the length of the loops and secondly by the presence of key residues at certain positions in the loops and in the framework regions that determine the conformation through their packing, hydrogen bonding or the ability to assume unusual main-chain conformations.

[00098] A "variable region" of an antibody can refer to the variable region of the antibody light chain or the variable region of the antibody heavy chain, either alone or in combination. The variable regions of the heavy and light chain can each consist of four framework regions (FR) connected by three complementarity determining regions (CDRs) also known as hypervariable regions. The CDRs in each chain can be held together in close proximity by the FRs and, with the CDRs from the other chain, contribute to the formation of the antigen binding site of antibodies. There are at least two techniques for determining CDRs: (1) an approach based on cross-species sequence variability (i.e., Rabat et al. Sequences of Proteins of Immunological Interest, (5th ed., 1991, National Institutes of Health, Bethesda Md.)); and (2) an approach based on crystallographic studies of antigen-antibody complexes (Ahazikani et al (1997) J. Molec. Biol. 273:927-948)). A CDR can refer to CDRs defined by either approach or by a combination of both approaches.

[00099] A "constant region" of an antibody can refer to the constant region of the antibody light chain, i.e, a light chain constant region or the constant region of the antibody heavy chain, i.e., a heavy chain constant region either alone or in combination. The constant region does not vary with respect to antigen specificity.

[000100] As used herein, the term "heavy chain region" can include amino acid sequences derived from the constant domains of an immunoglobulin heavy chain. A polypeptide comprising a heavy chain region can comprises at least one of: a CH1 domain, a hinge (e.g., upper, middle, and/or lower hinge region) domain, a CH2 domain, a CH3 domain, or a variant or fragment thereof. In an embodiment, an antibody or an antigen binding fragment thereof can comprise the Fc region of an immunoglobulin heavy chain (e.g., a hinge portion, a CH2 domain, and a CH3

domain). In another embodiment, an antibody or an antigen-binding fragment thereof lacks at least a region of a constant domain (e.g., part of a CH2 domain). In certain embodiments, at least one of the constant domains are derived from a human immunoglobulin heavy chain. For example, in one preferred embodiment, the heavy chain region comprises a fully human hinge domain. In other preferred embodiments, the heavy chain region comprises a fully human Fc region (e.g., hinge, CH2 and CH3 domain sequences from a human immunoglobulin). In certain embodiments, the constituent constant domains of the heavy chain region are from different immunoglobulin molecules. For example, a heavy chain region of a polypeptide can comprise a domain derived from an IgA molecule and a hinge region derived from an IgAl or IgA2 molecule. In other embodiments, the constant domains are chimeric domains comprising regions of different immunoglobulin molecules. For example, a hinge can comprise a first region from an IgAl molecule and a second region from an IgA2 molecule. As set forth above, it will be understood by one of ordinary skill in the art that the constant domains of the heavy chain region can be modified such that they vary in amino acid sequence from the naturally occurring (wild-type) immunoglobulin molecule. That is, the polypeptides disclosed herein can comprise alterations or modifications to one or more of the heavy chain constant domains (CH1, hinge, CH2 or CH3) and/or to the light chain constant domain (CL). Exemplary modifications include additions, deletions or substitutions of one or more amino acids in one or more domains.

[000101] The antibodies of the present disclosure can comprise a CDR3 region that is a length of at least about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 amino acids in length. The antibodies or antigen-binding fragment thereof of the present disclosure can comprise a CDR3 region that is at least about 18 amino acids in length.

[000102] As used herein, the term “hinge region” can include the region of a heavy chain molecule that joins the CH1 domain to the CH2 domain. The hinge region can comprise approximately 25 residues and can be flexible, thus allowing the two N-terminal antigen binding regions to move independently. Hinge regions can be subdivided into three distinct domains: upper, middle, and lower hinge domains (Roux et al. J. Immunol. 1998 161:4083).

[000103] The term “antibody heavy chain,” can refer to the larger of the two types of polypeptide chains present in antibody molecules in their naturally occurring conformations, and which normally determines the class to which the antibody belongs.

[000104] The term “antibody light chain,” can refer to the smaller of the two types of polypeptide chains present in antibody molecules in their naturally occurring conformations. Kappa (“ic”) and lambda (“l”) light chains can refer to antibody light chain isotypes.

[000105] An antibody or antigen-binding fragment thereof can “specifically bind” or “preferentially bind” to a target if it binds with greater affinity and/or avidity than it binds to

epitopes on unrelated polypeptides. The specificity of an antibody or antigen-binding fragment or portion thereof can be determined based on affinity and/or avidity. Methods to determine such specific binding are also well known in the art. According to certain embodiments of the present disclosure, the antibodies or antigen-binding fragment thereof can bind to a human cancer antigen but not to a cancer antigen from other species. Alternatively, the antibodies or antigen-binding fragment thereof, in certain embodiments, can bind to human cancer antigen and to cancer antigen from one or more non -human species. For example, the antibodies or antigen-binding fragment thereof can bind to human cancer antigen and can bind or not bind, as the case may be, to one or more of mouse, rat, guinea pig, hamster, gerbil, pig, cat, dog, rabbit, goat, sheep, cow, horse, camel, cynomolgus, marmoset, rhesus or chimpanzee cancer antigen.

[000106] The term "recombinant human antibody", as used herein, can include all human antibodies that are prepared, expressed, created or isolated by recombinant means, such as (a) antibodies isolated from an animal (e.g., a mouse) that is transgenic or transchromosomal for human immunoglobulin genes or a hybridoma prepared therefrom (described further below), (b) antibodies isolated from a host cell transformed to express the human antibody, e.g., from a transfectoma, (c) antibodies isolated from a recombinant, combinatorial human antibody library, and (d) antibodies prepared, expressed, created or isolated by any other means that involve splicing of human immunoglobulin gene sequences to other DNA sequences. Such recombinant human antibodies can have variable regions in which the framework and CDR regions are derived from immunoglobulin sequences. In certain embodiments, however, such recombinant human antibodies can be subjected to in vitro mutagenesis (or, when an animal transgenic for human Ig sequences is used, in vivo somatic mutagenesis) and thus the amino acid sequences of the VH and VL regions of the recombinant antibodies are sequences that, while derived from and related to human immunoglobulin VH and VL sequences, may not naturally exist within the human antibody germline repertoire in vivo.

[000107] In some embodiments, the antibodies or a functional fragment thereof disclosed herein (e.g., comprising the one or modifications disclosed herein in the IgA heavy chain constant region), have at least 2%, 3%, 4%, 5%, 7%, 8%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or at least 100% of one or more improved property, compared to a corresponding WT IgA antibody or a corresponding WT IgG antibody.

[000108] The term "Fab" as used herein can refer to a region of an antibody composed of one constant and one variable domain of each of the heavy and the light chains (monovalent antigen-binding fragment), but wherein the heavy chain is truncated such that it lacks the CH2 and CH3 domain (i.e., VH, CH1, VL, and CL), and can also lack some or all of the hinge region. It can be produced by digestion of a whole antibody with the enzyme papain. Fab can refer to this

region in isolation, or this region in the context of a full-length antibody, immunoglobulin construct or Fab fusion protein.

[000109] The term Fab' as used herein can refer to a region obtained by treating a whole antibody with pepsin, followed by reduction, to yield a molecule consisting of an intact light chain and a portion of a heavy chain comprising a VH and a single constant domain. Two Fab' fragments can be obtained per antibody treated in this manner.

[000110] An "scFv" can be an antibody fragment comprising the VFI and VL domains of an antibody, wherein these domains are present in a single polypeptide chain. See, for example, U.S. Pat. Nos. 4,946,778, 5,260,203, 5,455,030, and 5,856,456. Generally, the Fv polypeptide can further comprise a polypeptide linker between the VH and VL domains that enables the scFv to form the desired structure for antigen-binding. For a review of scFv see Pluckthun (1994) The Pharmacology of Monoclonal Antibodies vol 113 ed. Rosenburg and Moore (Springer-Verlag, New York) pp 269-315. The VFI and VL domain complex of Fv fragments can also be stabilized by a disulfide bond (US Pat. No. 5,747,654).

[000111] The terms "disease", "disorder", or "condition" are used interchangeably herein and can refer to any alternation in state of the body or of some of the organs, interrupting or disturbing the performance of the functions and/or causing symptoms such as discomfort, dysfunction, distress, or even death to the person afflicted or those in contact with a person. A disease or disorder can also be related to a distemper, ailing, ailment, malady, disorder, sickness, illness, complaint, or affectation.

[000112] The term "in need thereof" when used in the context of a therapeutic or prophylactic treatment, can mean having a disease, being diagnosed with a disease, or being in need of preventing a disease, e.g., for one at risk of developing the disease. Thus, a subject in need thereof can be a subject in need of treating or preventing a disease, disorder, or condition.

[000113] As used herein, the terms "treat," "treatment," "treating," or "amelioration" can refer to therapeutic treatments, wherein the object is to reverse, alleviate, ameliorate, inhibit, slow down or stop the progression or severity of a condition associated with, a disease or disorder. The term "treating" can include reducing or alleviating at least one adverse effect or symptom of a condition, disease or disorder, such as, but not limited to, a viral infection. "Treatment" can include not just the improvement of symptoms or clinical markers, but also a cessation of at least slowing of progress or worsening of symptoms that would be expected in absence of treatment. Treatment can also refer to the prevention of a disease or condition. For example, treatment can comprise preventing a viral infection. As used herein, "preventing" a disease, disorder, or condition can include reducing the contraction of a disease, disorder, or condition or slowing the progression of symptoms associated with a disease, disorder, or condition.

[000114] As used herein, the term "administering," can refer to the placement of a compound (e.g., an antibody or antigen binding fragment thereof as disclosed herein) into a subject by a method or route that results in at least partial delivery of the agent at a desired site. Pharmaceutical compositions comprising an antibody or antigen binding fragment thereof, disclosed herein can be administered by any appropriate route which results in an effective treatment in the subject, including but not limited to intravenous, intraarterial, injection or infusion directly into a tissue parenchyma, etc. Where necessary or desired, administration can include, for example, intracerebroventricular ("icv") administration, intranasal administration, intracranial administration, intracelial administration, intracerebellar administration, or intrathecal administration. In some embodiments, administration is performed orally, intralesionally, by intravenous therapy or by subcutaneous, intramuscular, intraarterial, intravenous, intracavitary, intracranial, or intraperitoneal injection.

[000115] As used herein, the terms "protein", "peptide" and "polypeptide" are used interchangeably to designate a series of amino acid residues connected to each other by peptide bonds between the alpha-amino and carboxy groups of adjacent residues. The terms "protein", "peptide" and "polypeptide" can refer to a polymer of amino acids, including modified amino acids (e.g., phosphorylated, glycated, glycosylated, etc.) and amino acid analogs, regardless of its size or function. "Protein" and "polypeptide" can be used in reference to relatively large polypeptides, whereas the term "peptide" can be used in reference to small polypeptides, but usage of these terms in the art can overlap. The terms "protein", "peptide" and "polypeptide" are used interchangeably herein when referring to a gene product and fragments thereof. These terms encompass, e.g., native and artificial proteins, protein fragments and polypeptide analogs (such as muteins, variants, and fusion proteins) of a protein sequence as well as post-translationally, or otherwise covalently or non-covalently, modified proteins. A peptide, polypeptide, or protein can be monomeric or polymeric. A polypeptide can have the amino acid sequence of naturally occurring polypeptide from any mammal. Such native sequence polypeptide can be isolated from nature or can be produced by recombinant or synthetic means. In some embodiments, the polypeptide is a "variant". "Variant" can mean a biologically active polypeptide having at least about 80% amino acid sequence identity with the native sequence polypeptide after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity, and not considering any conservative substitutions as part of the sequence identity. Such variants include, for instance, polypeptides wherein one or more amino acid residues are added, or deleted, at the N- or C -terminus of the polypeptide. In some embodiments, a variant will have at least about 80% amino acid sequence identity. In some embodiments, a variant will have at least about 90% amino acid sequence identity. In some embodiments, a variant will have at least about

95% amino acid sequence identity with the native sequence polypeptide. A "derivative" of a polypeptide is a polypeptide (e.g., an antibody) that has been chemically modified, e.g., via conjugation to another chemical moiety (such as, for example, polyethylene glycol or albumin, e.g., human serum albumin), phosphorylation, and glycosylation.

[000116] The term "fusion protein" as used herein can refer to a polypeptide that comprises an amino acid sequence of an antibody or fragment thereof and an amino acid sequence of a heterologous polypeptide (i.e., an unrelated polypeptide).

[000117] The terms "synthetic polynucleotide," "synthetic gene" or "synthetic polypeptide," as used herein, can mean that the corresponding polynucleotide sequence or portion thereof, or amino acid sequence or portion thereof, is derived, from a sequence that has been designed, or synthesized de novo, or modified, compared to an equivalent naturally-occurring sequence. Synthetic polynucleotides (antibodies or antigen-binding fragments) or synthetic genes can be prepared by methods known in the art, including but not limited to, the chemical synthesis of nucleic acid or amino acid sequences. Synthetic genes can be different from naturally-occurring genes, either at the amino acid, or polynucleotide level, (or both) and can be located within the context of synthetic expression control sequences. Synthetic gene polynucleotide sequences, may not necessarily encode proteins with different amino acids, compared to the natural gene; for example, they can also encompass synthetic polynucleotide sequences that incorporate different codons but which encode the same amino acid (i.e., the nucleotide changes represent silent mutations at the amino acid level).

Agents, e.g., Antibodies and Antigen-Binding Fragments Thereof

[000118] Provided herein are agents, e.g., antibodies and antigen-binding fragments thereof, that can bind to SARS-CoV and/or SARS-CoV-2. The agents, e.g., antibodies and antigen-binding fragments thereof, can bind a SAR-CoV-2 spike protein, e.g., spike protein S1 domain, e.g., spike protein S1 domain receptor binding domain (RBD). In some cases, the agents, e.g., antibodies and antigen-binding fragments thereof, can bind a SARS-CoV spike protein, e.g., spike protein S1 domain, e.g., spike protein S1 domain receptor binding domain (RBD). In some cases, the present disclosure is based upon development of a neutralizing antibody (nAb). The antibody can comprise a heavy chain, "heavy chain A" (HCA) having the amino acid sequence set forth in SEQ ID NO: 12, and a light chain, "light chain A" (LCA) having the amino acid sequence set forth in SEQ ID NO: 15. This antibody, referred to herein as the HCA/LCA antibody, or an antigen-binding fragment thereof, can serve as a therapeutic for various clades of coronaviruses. The HCA/LCA antibody was derived from the B cells of a convalescent COVID-19 patient, and can serve as the basis of a therapeutic treatment for a subject in need thereof. The HCA/LCA antibody comprises a neutralizing antibody with potent activity against all current

SARS-CoV-2 variants of concern, including Omicron, as well as neutralizing activity against SARS-CoV. The ability of the HCA/LCA antibody to neutralize a related coronavirus can be recognized based on the present disclosure. *See* **FIG. 4, FIG. 5, TABLE 4, TABLE 5**.

[000119] Also provided herein are agents, e.g., antibodies or antigen-binding fragments thereof, that comprise a heavy chain complementarity determining region (CDR)1 (HCDR1), HCDR2, and HCDR3 and/or a light chain CDR1 (LCDR1), LCDR2 and LCDR3, wherein the HCDR1, the HCDR2, and the HCDR3 comprise amino acid sequences set forth in SEQ ID NO: 6, SEQ ID NO: 7, and SEQ ID NO: 8, respectively, and the LCDR1, the LCDR2, and the LCDR3 comprise the amino acid sequences set forth in SEQ ID NO: 9, SEQ ID NO: 10, and SEQ ID NO: 11, respectively. The sequences of the domains for the HCA antibodies are provided in **TABLE 8**.

[000120] The agents, e.g., antibodies or antigen-binding fragments thereof, provided herein can comprise 1, 2, or 3 of an HCDR1 comprising the amino acid sequence set forth in SEQ ID NO: 6, an HCDR2 comprising the amino acid sequence set forth in SEQ ID NO: 7, and an HCDR3 comprising the amino acid sequence set forth in SEQ ID NO: 8.

[000121] The agents, e.g., antibodies or antigen-binding fragments thereof, provided herein can comprise 1, 2, or 3 of an LCDR1 comprising the amino acid sequence set forth in SEQ ID NO: 9, an HCDR2 comprising the amino acid sequence set forth in SEQ ID NO: 10, and an HCDR3 comprising the amino acid sequence set forth in SEQ ID NO: 11.

[000122] The agents, e.g., antibodies or antigen-binding fragments thereof, provided herein can comprise a first polypeptide comprising 1, 2, or 3 of an HCDR1 comprising the amino acid sequence set forth in SEQ ID NO: 6, an HCDR2 comprising the amino acid sequence set forth in SEQ ID NO: 7, and an HCDR3 comprising the amino acid sequence set forth in SEQ ID NO: 8 and a second polypeptide comprising 1, 2, or 3 of an LCDR1 comprising the amino acid sequence set forth in SEQ ID NO: 9, an HCDR2 comprising the amino acid sequence set forth in SEQ ID NO: 10, and an HCDR3 comprising the amino acid sequence set forth in SEQ ID NO: 11.

[000123] The agents, e.g., antibodies or antigen-binding fragments thereof, can comprise 1, 2, or 3 an HCDRs, each with at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to any one of the amino acid sequences set forth in SEQ ID NO: 6, 7, or 8.

[000124] The agents, e.g., antibodies or antigen-binding fragments thereof, can comprise 1, 2, or 3 LCDRs, each with at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to any one of the amino acid sequences set forth in SEQ ID NO: 9, 10, or 11.

[000125] The agents, e.g., antibodies or antigen-binding fragments thereof, can comprise a heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 12, or an amino acid sequence comprising at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence set forth in SEQ ID NO: 12.

[000126] The agents, e.g., antibodies or antigen-binding fragments thereof provided herein, can comprise a heavy chain variable region (VH) comprising the amino acid sequence set forth in SEQ ID NO: 13, or an amino acid sequence comprising at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence set forth in SEQ ID NO: 13.

[000127] The agents, e.g., antibodies provided herein can comprise a heavy chain constant region having the amino acid sequence set forth in SEQ ID NO: 14, or an amino acid sequence comprising at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence set forth in SEQ ID NO: 14.

[000128] The agents, e.g., antibodies or antigen-binding fragments thereof, provided herein can comprise a light chain comprising the amino acid sequence set forth in SEQ ID NO: 15, or an amino acid sequence comprising at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence set forth in SEQ ID NO: 15.

[000129] The agents, e.g., antibodies or antigen-binding fragments thereof, provided herein can comprise a light chain variable region (VL) comprising the amino acid sequence set forth in SEQ ID NO: 16, or an amino acid sequence comprising at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence set forth in SEQ ID NO: 16.

[000130] The agents, e.g., antibodies provided herein can comprise a light chain constant region having the amino acid sequence set forth in SEQ ID NO: 17, or an amino acid sequence comprising at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence set forth in SEQ ID NO: 17.

[000131] The agents, e.g., antibodies or an antigen-binding fragments thereof provided herein can comprise a light chain variable region (VL) comprising the amino acid sequence set forth in SEQ ID NO: 16, or an amino acid sequence comprising at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence set forth in SEQ ID NO: 16.

[000132] The agents, e.g., antibodies or antigen-binding fragments thereof, provided herein can comprise 1) a heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 12, or an amino acid sequence comprising at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence set forth in SEQ ID NO:

12 and 2) a light chain comprising the amino acid sequence set forth in SEQ ID NO: 15, or an amino acid sequence comprising at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence set forth in SEQ ID NO: 15.

[000133] The agents, e.g., antibodies or antigen-binding fragments thereof, provided herein can comprise 1) a heavy chain variable region (VH) comprising the amino acid sequence set forth in SEQ ID NO: 13, or an amino acid sequence comprising at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence set forth in SEQ ID NO: 13 and 2) a light chain variable region (VL) comprising the amino acid sequence set forth in SEQ ID NO: 16, or an amino acid sequence comprising at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence set forth in SEQ ID NO: 16.

Table 8. HCA Antibody Domain Sequences

SEQ ID NO:	Name	Type	Sequence
12	HCA Heavy Chain	PROTEIN	EVQLVESGGGLVQPGRSLRLSCAASGFTFDESAMHWVR QAPGEGLEWVSGISWNSGRIAYADSVRGRFTISRDNAKN SLYLQMNSLRAEDTALYFCALTTSGWFSFDYWGQGTLV TVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEP VTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSL GTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAP ELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPE VKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV YTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPE NNYK
13	HCA Variable Heavy Chain	PROTEIN	EVQLVESGGGLVQPGRSLRLSCAASGFTFDESAMHWVR QAPGEGLEWVSGISWNSGRIAYADSVRGRFTISRDNAKN SLYLQMNSLRAEDTALYFCALTTSGWFSFDYWGQGTLV TVSS
14	HCA Constant Domain	PROTEIN	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQT YICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLG GPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN

SEQ ID NO:	Name	Type	Sequence
			WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDW LNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPP SRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK TTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEA LHNHYTQKSLSLSPGK
6	HCA HCDR1	PROTEIN	GFTFDESA
7	HCA HCDR2	PROTEIN	ISWNSGRI
8	HCA HCDR3	PROTEIN	ALTTSGWFSFDY
15	LCA Light Chain	PROTEIN	SYVLTQPPSVSVAPGKTARITCGGNNIGSKSVHWYQQKP GQAPVPVIYYDSDRPSGIPERFSGSNSGNTATLTISRVEVG DEADYYCQVWDSSSDRAVFGGGTTLTVLGQPKAAPSVT LFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVK AGVETTTPSKQSNNKYAASSYLSLTPEQWKSHKSYSCQV THEGSTVEKTVAPTECS
16	LCA Variable Light Chain	PROTEIN	SYVLTQPPSVSVAPGKTARITCGGNNIGSKSVHWYQQKP GQAPVPVIYYDSDRPSGIPERFSGSNSGNTATLTISRVEVG DEADYYCQVWDSSSDRAVFGGGTTLTVL
9	LCA LCDR1	PROTEIN	NIGSKS
10	LCA LCDR2	PROTEIN	YDS
11	LCA LCDR3	PROTEIN	QVWDSSSDRAV
17	LCA constant region	PROTEIN	GQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTV AWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQ WKSHKSYSCQVTHEGSTVEKTVAPTECS

[000134] The agents, e.g., antibodies or antigen-binding fragments thereof provided herein, e.g., the HCA/LCA antibody, or an antigen-binding fragment thereof, can neutralize a SARS-CoV infection in a cell. The agents, e.g., antibodies or antigen-binding fragments thereof, e.g., the HCA/LCA antibody, or an antigen-binding fragment thereof, can have a neutralization IC_{50} value of, e.g., about 0.01 μg/mL, about 0.02 μg/mL, about 0.03 μg/mL, about 0.04 μg/mL, about 0.05 μg/mL, about 0.06 μg/mL, or about 0.07 μg/mL against SARS-CoV infection or infection with a virus pseudotyped with a SARS-CoV spike protein (see e.g., **Table 4**). The agents, e.g., antibodies or antigen-binding fragments thereof, e.g., the HCA/LCA antibody or antigen-binding fragment thereof, can have a neutralization IC_{50} value of from about 0.003 μg/mL to about 0.3 μg/mL, or from about 0.01 μg/mL to about 0.1 μg/mL against a SARS-CoV infection or infection with a virus pseudotyped with a SARS-CoV spike protein. The agents, e.g., antibodies or antigen-binding fragments thereof, e.g., the HCA/LCA antibody or an antigen-binding fragment thereof, can have a neutralization IC_{50} value of less than 0.01 μg/mL, 0.02 μg/mL, 0.03 μg/mL, 0.04 μg/mL, 0.05 μg/mL, 0.06 μg/mL, or 0.07 μg/mL against a SARS-CoV infection or infection with a virus pseudotyped with a SARS-CoV spike protein.

[000135] The agents, e.g., antibodies or antigen-binding fragments thereof provided herein, e.g., the HCA/LCA antibody, or an antigen-binding fragment thereof, can have a neutralization IC_{90} value of, e.g., about 0.1 μg/mL, about 0.15 μg/mL, about 0.2 μg/mL, about 0.233 μg/mL, about 0.25 μg/mL, about 0.3 μg/mL, or about 0.4 μg/mL against SARS-CoV infection or infection with a virus pseudotyped with a SARS-CoV spike protein (see e.g., **Table 5**). The agents, e.g., antibodies or antigen-binding fragments thereof, e.g., the HCA/LCA antibody or an antigen-binding fragment thereof can have a neutralization IC_{90} value of from about 0.02 μg/mL to about 0.5 μg/mL, or from about 0.1 μg/mL to about 0.3 μg/mL against a SARS-CoV infection or infection with a virus pseudotyped with a SARS-CoV spike protein. The agents, e.g., antibodies or antigen-binding fragments thereof, e.g., HCA/LCA antibody or an antigen-binding fragment thereof, can have a neutralization IC_{90} value of less than 0.9 μg/mL, 0.5 μg/mL, 0.4 μg/mL, 0.3 μg/mL, 0.2 μg/mL, 0.1 μg/mL, 0.09 μg/mL, 0.07 μg/mL, or 0.05 μg/mL against a SARS-CoV infection or infection with a virus pseudotyped with a SARS-CoV spike protein.

[000136] The agents, e.g., antibodies or antigen-binding fragments thereof, e.g., the HCA/LCA antibody or an antigen-binding fragment thereof, can neutralize a SARS-CoV-2 infection in a cell or infection with a virus pseudotyped with a SARS-CoV-2 spike protein. The agents, e.g., antibodies or antigen-binding fragments thereof, e.g., the HCA/LCA antibody or antigen-binding fragment thereof, can have a neutralization IC_{50} value of, e.g., about 0.002 μg/mL, about 0.005 μg/mL, about 0.075 μg/mL, about 0.01 μg/mL, about 0.02 μg/mL, about 0.03 μg/mL, about 0.04 μg/mL, about 0.05 μg/mL, about 0.06 μg/mL, about 0.07 μg/mL, about

0.08 μg/mL, about 0.09 μg/mL, about 0.1 μg/mL, about 0.11 μg/mL, about 0.12 μg/mL, 0.13 μg/mL, 0.14 μg/mL, 0.15 μg/mL, 0.16 μg/mL, 0.17 μg/mL, 0.18 μg/mL, 0.19 μg/mL, 0.2 μg/mL, 0.23 μg/mL, 0.25 μg/mL, 0.3 μg/mL, 0.4 μg/mL, 0.5 μg/mL, 0.6 μg/mL, 0.7 μg/mL, 0.8 μg/mL, 0.9 μg/mL, 1.0 μg/mL, or 2.0 μg/mL against SARS-CoV-2 infection or infection with a virus pseudotyped with a SARS-CoV-2 spike protein (see e.g., **Table 4**). The agents, e.g., antibodies or antigen-binding fragments thereof, e.g., the HCA/LCA antibody or antigen-binding fragment thereof, can have a neutralization IC_{50} value of from about 0.003 μg/mL to about 2.0 μg/mL, from about 0.01 μg/mL to about 0.5 μg/mL, or from about 0.01 μg/mL to about 0.2 μg/mL against a SARS-CoV-2 infection or infection with a virus pseudotyped with a SARS-CoV-2 spike protein. The agents, e.g., antibodies or antigen-binding fragments thereof, e.g., the HCA/LCA antibody or antigen-binding fragment thereof, can have a neutralization IC_{50} value of less than 0.005 μg/mL, 0.01 μg/mL, 0.02 μg/mL, 0.03 μg/mL, 0.04 μg/mL, 0.05 μg/mL, 0.06 μg/mL, 0.07 μg/mL, 0.08 μg/mL, 0.09 μg/mL, 0.1 μg/mL, 0.2 μg/mL, 0.3 μg/mL, 0.4 μg/mL, 0.5 μg/mL, 0.6 μg/mL, 0.7 μg/mL, 0.8 μg/mL, or 0.9 μg/mL against a SARS-CoV-2 infection or infection with a virus pseudotyped with a SARS-CoV-2 spike protein. In some cases, the agent, e.g., antibody or antigen-binding fragment thereof, e.g., HCA/LCA antibody or antigen-binding fragment thereof, can neutralize the SARS-CoV-2 virus, wherein the SARS-CoV-2 virus (or pseudotyped virus with a SARS-CoV-2 spike protein) comprises a variant (or the spike protein comprises a spike protein from the variant) e.g., as disclosed in **Table 4**, e.g., SARS-CoV-2 B.1.1.529 (Omicron) or one or more mutations of Omicron (see e.g., Table 2), SARS-CoV-2 (Epsilon) or one or more mutations of Epsilon (see e.g., Table 2), SARS-CoV-2 (Iota) or one or more mutations of Iota (see e.g., Table 2), SARS-CoV-2 (Eta) or one or more mutations of Eta (see e.g., Table 2), SARS-CoV-2 (Delta) or one or more mutations of Delta (see e.g., Table 2), SARS-CoV-2 (Gamma) or one or more mutations of Gamma (see e.g., Table 2), SARS-CoV-2 (Beta) or one or more mutations of Beta (see e.g., Table 2), and SARS-CoV-2 (Alpha), or a one or more mutations of Alpha (see e.g., Table 2).

[000137] The agents, e.g., antibodies or antigen-binding fragments thereof, e.g., the HCA/LCA antibody or antigen-binding fragment thereof, can have a neutralization IC_{90} value of, e.g., about 0.1 μg/mL, about 0.15 μg/mL, about 0.2 μg/mL, about 0.233 μg/mL, about 0.25 μg/mL, about 0.3 μg/mL, about 0.4 μg/mL, about 0.5 μg/mL, about 0.6 μg/mL, about 0.7 μg/mL, about 0.8 μg/mL, or about 0.9 μg/mL against SARS-CoV infection or infection with a virus pseudotyped with a SARS-CoV spike protein (see e.g., **Table 5**). The agents, e.g., antibodies or antigen-binding fragments thereof, e.g., the HCA/LCA antibody, or fragment thereof, can have a neutralization IC_{90} value of from about 0.02 μg/mL to about 2.3 μg/mL, or from about 0.1 μg/mL to about 0.3 μg/mL against a SARS-CoV infection or infection with a virus pseudotyped with a

SARS-CoV spike protein. The agents, e.g., antibodies or antigen-binding fragments thereof, e.g., the HCA/LCA antibody, or antigen-binding fragment thereof, can have a neutralization IC_{90} value of less than 2.0 μg/mL, 1.8 μg/mL, 1.5 μg/mL, 1.3 μg/mL, 1.0 μg/mL, 0.9 μg/mL, 0.5 μg/mL, 0.4 μg/mL, 0.3 μg/mL, 0.2 μg/mL, 0.1 μg/mL, or 0.09 μg/mL against a SARS-CoV infection or infection with a pseudotyped virus with a SARS-CoV spike protein.

[000138] An agents, e.g., antibodies or antigen-binding fragments thereof, e.g., the HCA/LCA antibody, or an antigen-binding fragment thereof, can have a neutralization IC_{90} value of, e.g., about 0.005 μg/mL, about 0.01 μg/mL, about 0.02 μg/mL, about 0.03 μg/mL, about 0.04 μg/mL, about 0.05 μg/mL, about 0.06 μg/mL, about 0.07 μg/mL, about 0.08 μg/mL, about 0.09 μg/mL, about 0.1 μg/mL, about 0.2 μg/mL, about 0.3 μg/mL, about 0.4 μg/mL, about 0.5 μg/mL, about 0.6 μg/mL, about 0.7 μg/mL, about 0.8 μg/mL, about 0.9 μg/mL, about 1.0 μg/mL, about 1.1 μg/mL, about 1.2 μg/mL, about 1.3 μg/mL, about 1.4 μg/mL, about 1.5 μg/mL, about 2 μg/mL, about 3 μg/mL, about 4 μg/mL, about 5 μg/mL, about 6 μg/mL, about 7 μg/mL, or about 8 μg/mL against SARS-CoV-2 infection or infection with a pseudotyped virus with a SARS-CoV-2 spike protein (see e.g., **Table 5**). The agents, e.g., antibodies or antigen-binding fragments thereof, e.g., the HCA/LCA antibody, or an antigen-binding fragment thereof, can have a neutralization IC_{90} value of from about 0.005 μg/mL to about 8 μg/mL, from about 0.01 μg/mL to about 1.0 μg/mL, or from about 0.01 μg/mL to about 0.3 μg/mL against a SARS-CoV-2 infection or infection with a pseudotyped virus with a SARS-CoV-2 spike protein. The agents, e.g., antibodies or antigen-binding fragments thereof, e.g., the HCA/LCA antibody, or an antigen-binding fragment thereof, can have a neutralization IC_{90} value of less than 8 μg/mL, 7 μg/mL, 6 μg/mL, 5 μg/mL, 4 μg/mL, 3 μg/mL, 2 μg/mL, 1 μg/mL, 0.9 μg/mL, 0.8 μg/mL, 0.7 μg/mL, 0.6 μg/mL, 0.5 μg/mL, 0.4 μg/mL, 0.3 μg/mL, 0.2 μg/mL, 0.1 μg/mL, 0.09 μg/mL, 0.08 μg/mL, 0.07 μg/mL, 0.06 μg/mL, 0.05 μg/mL, 0.04 μg/mL, 0.03 μg/mL, 0.02 μg/mL, 0.01 μg/mL, 0.009 μg/mL, 0.008 μg/m, 0.007 μg/mL, 0.006 μg/mL, or 0.005 μg/mL against a SARS-CoV-2 infection or infection with a pseudotyped virus with a SARS-CoV-2 spike protein. In some cases, the agents, e.g., antibodies or antigen-binding fragments thereof, e.g., HCA/LCA antibody, or an antigen-binding fragment thereof, can neutralize the SARS-CoV-2 virus or a pseudotyped virus with a SARS-CoV-2 spike protein, wherein the SARS-CoV-2 virus comprises a variant (or the spike protein comprises a spike protein from the variant), e.g., as disclosed in **Table 4**, e.g., SARS-CoV-2 B.1.1.529 (Omicron) or one or more mutations of Omicron (see e.g., Table 2), SARS-CoV-2 (Epsilon) or one or more mutations of Epsilon (see e.g., Table 2), SARS-CoV-2 (Iota) or one or more mutations of Iota (see e.g., Table 2), SARS-CoV-2 (Eta) or one or more mutations of Eta (see e.g., Table 2), SARS-CoV-2 (Delta) or one or more mutations of Delta (see e.g., Table 2), SARS-CoV-2 (Gamma) or one or more mutations of Gamma (see e.g.,

Table 2), SARS-CoV-2 (Beta) or one or more mutations of Beta (see e.g., Table 2), and SARS-CoV-2 (Alpha), or a one or more mutations of Alpha (see e.g., Table 2).

[000139] The agents, e.g., antibodies or antigen-binding fragments thereof, e.g., the HCA/LCA antibody, or an antigen-binding fragment thereof, can have a neutralization IC_{50} value of about 0.06 μg/mL, 0.07 μg/mL, 0.08 μg/mL, or 0.09 μg/mL against the SARS-CoV-2 Gamma variant or a pseudotyped virus comprising a spike protein from SARS-CoV-2 Gamma, or one or more mutations found in the Gamma variant (see e.g., Table 2). The agents, e.g., antibodies or antigen-binding fragments thereof, e.g., the HCA/LCA antibody, or an antigen-binding fragment thereof, can have a neutralization IC_{50} value of from about 0.15 μg/mL to about 0.21 μg/mL against the SARS-CoV-2 Beta variant or a pseudotyped virus comprising a spike protein from SARS-CoV-2 Beta, or one or more mutations found in the Beta variant (see e.g., Table 2). The agents, e.g., antibodies or antigen-binding fragments thereof, e.g., the HCA/LCA antibody, or antigen-binding fragment thereof, can have an IC_{50} from about 0.17 μg/mL to about 0.46 μg/mL against the Omicron variant or a pseudotyped virus comprising a spike protein from SARS-CoV-2 Omicron, or one or more mutations found in the Omicron variant (see e.g., Table 2).

[000140] Provided herein are agents, e.g., SARS-CoV-2 neutralizing antibody comprising a heavy chain antibody fragment and a light chain antibody fragment. Agents, e.g., antibodies or antigen-binding fragments thereof of the present disclosure can demonstrate broad SARS-CoV-2 variant coverage (including Omicron), and ability to neutralize SARS-CoV. The agents, e.g., antibodies or antigen-binding fragments thereof, e.g., the HCA/LCA antibody or antigen-binding fragment thereof disclosed herein can demonstrate a broad neutralizing ability within SARS-CoV-2 variants. The agents, e.g., antibodies or antigen-binding fragments thereof, e.g., the HCA/LCA antibody or an antigen-binding fragment thereof can serve as an effective therapeutic for treatment or prophylaxis of SARS-CoV-2 infection. The agents, e.g., antibodies or antigen-binding fragments thereof, e.g., the HCA/LCA antibody or antigen-binding fragment thereof can neutralize the related coronavirus SARS-CoV. Given its cross-species viral neutralization, the agents provided herein, e.g., antibodies or antigen-binding fragments thereof, e.g., HCA/LCA antibody or antigen-binding fragment thereof, can serve as a frontline therapeutic against yet to evolve coronaviruses.

[000141] In some aspects, the HCA/LCA antibody comprises a nAb having several advantages over many existing SARS-CoV-2 nAb therapeutics. Unlike casarivimab and imdevimab, the HCA/LCA antibody can neutralize all current and past SARS-CoV-2 variants tested, including Omicron, and functionally demonstrated by the neutralization of the related coronavirus SARS-CoV. Both the HCA/LCA antibody and sotrovimab can neutralize all of the SARS-CoV-2 variants tested as well as SARS-CoV, although the HCA/LCA antibody did so

with a mean 10.3-fold greater potency for SARS-CoV-2 variants and 2.1-fold greater potency for SARS-CoV than sotrovimab (see **FIG. 4, FIG. 5, TABLE 4, TABLE 5**).

[000142] The presently disclosed agents, e.g., SARS-CoV-2 neutralizing antibody, e.g., the HCA/LCA antibody, can demonstrate broad SARS-CoV-2 variant coverage (including Omicron), and ability to neutralize SARS-CoV. Agents, e.g., antibodies and antigen-binding fragments of the present disclosure can bind epitopes within the receptor binding motif (RBM). The broad neutralizing ability of the HCA/LCA antibody within SARS-CoV-2 variants can indicate that the HCA/LCA antibody, or antigen binding fragment thereof, can be an effective therapeutic for treatment or prophylaxis of SARS-CoV-2 infection. Additionally, given its cross-species viral neutralization, the HCA/LCA antibody, or antigen-binding fragment thereof, can also serve as a frontline therapeutic against yet to evolve coronaviruses.

[000143] The agents, e.g., antibody or antigen-binding fragment thereof, e.g., the HCA/LCA antibody, or antigen-binding fragment thereof, provided herein can be generated via generated by single B cell cloning or phage display library screening. DNA encoding the monoclonal antibody can be readily isolated and sequenced using conventional procedures (e.g., by using oligonucleotide probes that are capable of binding specifically to genes encoding the heavy and light chains of the antibody). In certain embodiments, DNA encoding the monoclonal antibody is isolated and sequenced using high throughput next generation sequencing techniques. The encoding DNA can also be obtained by synthetic methods.

[000144] The agents, e.g., antibodies or antigen-binding fragments thereof, e.g., the HCA/LCA antibody, or antigen-binding fragment thereof, provided herein can be effective in any number of neutralization assays (e.g., VSV, MLV, Lentiviral). The agents, e.g., antibodies or antigen-binding fragments thereof, e.g., antibodies of the present disclosure, and antigen-binding fragments thereof, can bind the receptor binding motif (RBM) epitopes within the receptor binding motif (RBM). The agents, e.g., antibodies or antigen-binding fragments thereof, e.g., the HCA/LCA antibody, or antigen-binding fragment thereof, can specifically bind SARS-CoV spike protein S1 domain. The agents, e.g., antibodies or antigen-binding fragments thereof, e.g., the HCA/LCA antibody, or antigen-binding fragment thereof, can block SARS-CoV-2 spike protein receptor binding domain (RBD) binding to angiotensin-converting enzyme 2 (ACE2).

[000145] In some aspects, the agents, e.g., antibodies, e.g., antibodies described herein can comprise multispecific antibodies, including but not limited to bispecific antibodies or trispecific antibodies, for example. In certain aspects, the antibodies described herein are bispecific antibodies. For example, bispecific antibodies or multispecific antibodies of the present disclosure can comprise a first antigen-binding fragment, and a second antigen-binding fragment capable of neutralizing SARS-CoV-2, wherein each antigen-binding fragment binds to a distinct

epitope. In some embodiments, the first antigen-binding fragment binds to a non-RBD and/or non-NTD region of spike protein of SARS-CoV-2.

[000146] The agents, e.g., antibodies or antigen-binding fragments thereof, e.g., the HCA/LCA antibody or antigen-binding fragment thereof, can be administered alone or in combination with one or more other agents to treat coronaviruses. The agents, e.g., antibodies or antigen-binding fragments thereof, e.g., the HCA/LCA antibody or antigen-binding fragment thereof, can be effective in any number of neutralization assays (e.g., VSV, MLV, Lentiviral). The agents, e.g., antibodies or antigen-binding fragments thereof, e.g., HCA/LCA antibody,or antigen-binding fragment thereof, can bind epitopes within the receptor binding motif (RBM), indicating a lower susceptibility to mutant escape. The agents, e.g., antibodies or antigen-binding fragments thereof, e.g., HCA/LCA or antigen-binding fragment thereof, can provide potent neutralization activity against coronavirus strains of various clades. For example, the agents, e.g., antibodies or antigen-binding fragments thereof, e.g., the HCA/LCA antibody or antigen-binding fragment thereof, can neutralize strains in the Clade 1/2 (SARS-Cov-2), including but not limited to, the following strains: SARS-CoV-2 Omicron, SARS-CoV-2 Gamma, SARS-CoV-2 P.1, SARS-CoV-2 Delta, SARS-CoV-2 Kappa, SARS-CoV-2 Beta, SARS-CoV-2 Alpha, SARS-CoV-2 Eta, SARS-CoV-2 B.1.526, SARS-CoV-2 Epsilon, SARS-CoV-2 B.1.1.28, SARS-CoV-2 B.1.1.1 strains, or strains with one or more mutations found in these strains. The agents, e.g., antibodies or antigen-binding fragments thereof, e.g., HCA/LCA or antigen-binding fragment thereof, can neutralize strains in the Clade 1, including but not limited to, the following strains: SARS Urbani, LYRa11, RS4084, RsSHC014, RS7327, WIV-1, RS4321. The agents, e.g., antibodies or antigen-binding fragments thereof, e.g., HCA/LCA or an antigen-binding fragment thereof, can neutralize strains in Clade 2, including but not limited to, the following strains: ZC45, ZXC21, JL2012, RF4092, YN2013, HuB2013, Shaanxi2011, HeB2013, 273-2005, Rf1, Yunnan2011, RS4081, 279-2005, AS6526, RS4237, RS4247, RP3, GX2013, HKU3-13, HKU3-8, Longquan140. The agents, e.g., antibodies or antigen-binding fragments thereof, e.g., HCA/LCA or antigen-binding fragment thereof, can neutralize strains in Clade 3, including but not limited to, the following strains: BM48-31.

[000147] In some aspects, the present disclosure provides a composition comprising a combination of one or more agents, e.g., antibodies or antigen-binding fragments thereof. For example, in some embodiments, a composition disclosed herein comprises two, 3, 4, 5, 6, 7, 8, 9, 10 or more antibodies. In certain embodiments, the two or more of the antibodies can bind to SARS-CoV-2 in a non-competing manner. In certain embodiments, the combination comprises a first antibody comprising a first heavy chain CDR 1 (HCDR1), a first HCDR2 and a first HCDR3. In certain embodiments, the first antibody further comprises a first light chain CDR1

(LCDR1), a first LCDR2 and first LCDR2. In certain embodiments, the combination further comprises a second antibody comprising a second heavy chain CDR 1 (HCDR1), a second HCDR2 and a second HCDR3. In certain embodiments, the second antibody further comprises a second light chain CDR1 (LCDR1), a second LCDR2 and a second LCDR2. In some embodiments, the first antibody is the HCA/LCA antibody described herein.

[000148] Provided herein are combinations (e.g., mixtures) of antibodies that can bind to SARS-CoV or SARS-CoV-2 strain to neutralize the virus. For example, the present disclosure provides an antibody (e.g., HCA/LCA antibody, or antigen-binding fragment thereof), having an IC_{50} of about 0.03 μg/mL, 0.04 μg/mL, 0.05 μg/mL, 0.06 μg/mL, or 0.07 μg/mL against the SARS-CoV strain or a pseudotyped virus comprising a SARS-CoV spike protein. Further provided are antibodies that neutralize SARS-CoV-2 or variants thereof. For example, for the Gamma variant or a pseudotyped virus comprising a SARS-CoV-2 Gamma spike protein, antibodies of the present disclosure can have a neutralization IC_{50} of about 0.06 μg/mL, 0.07 μg/mL, 0.08 μg/mL, or 0.09 μg/mL. For the Beta variant or a pseudotyped virus comprising a SARS-CoV-2 Beta spike protein, the antibodies can have a neutralization IC_{50} from about 0.15 μg/mL to about 0.21 μg/mL. For the Omicron variant or a pseudotyped virus comprising a SARS-CoV-2 Omicron spike protein, the antibodies can have a neutralization IC_{50} from about 0.17 μg/mL to about 0.46 μg/mL. In some embodiments, the agents, e.g., antibodies or antigen-binding fragments thereof, e.g., the HCA/LCA antibody or antigen-binding fragment thereof, are administered in the form of a cocktail of monoclonal antibodies. For example, an agent provided herein, e.g., the HCA/LCA antibody or antigen-binding fragment thereof, can be administered in combination with one or more of (e.g., 1, 2, 3, 4, or 5 of) bamlanivimab, etesevimab, sotrovimab, casirivimab, imdevimab, and/or HCB/LCB, or an antigen-binding fragment of any of the foregoing. One or more of the agents provided herein can be combined with HCB/LCB, an antibody comprising heavy chain B (HCB) (the sequence set forth in SEQ ID NO: 18 and light chain B (LCB) (the sequence set forth in SEQ ID NO: 19. The sequences of the domains for the HCB antibodies are provided in **TABLE 9**.

[000149] One or more of the agents provided herein can be combined with another agent, e.g., antibodies or antigen-binding fragments thereof, that can comprise a heavy chain complementarity determining region (CDR)1 (HCDR1), HCDR2, and HCDR3 and/or a light chain CDR1 (LCDR1), LCDR2 and LCDR3, wherein the HCDR1, the HCDR2, and the HCDR3 comprise amino acid sequences set forth in SEQ ID NO: 20, SEQ ID NO: 21, and SEQ ID NO: 22, respectively, and the LCDR1, the LCDR2, and the LCDR3 comprise the amino acid sequences set forth in SEQ ID NO: 23, SEQ ID NO: 24, and SEQ ID NO: 25, respectively.

[000150] One or more of the agents provided herein can be combined with another agent, e.g., antibody or antigen-binding fragment thereof, that can comprise 1, 2, or 3 of an HCDR1 comprising the amino acid sequence set forth in SEQ ID NO: 20, an HCDR2 comprising the amino acid sequence set forth in SEQ ID NO: 21, and an HCDR3 comprising the amino acid sequence set forth in SEQ ID NO: 22.

[000151] One or more of the agents provided herein can be combined with another agent, e.g., antibody or antigen-binding fragment thereof, that can comprise 1, 2, or 3 of an LCDR1 comprising the amino acid sequence set forth in SEQ ID NO: 23, an HCDR2 comprising the amino acid sequence set forth in SEQ ID NO: 24, and an HCDR3 comprising the amino acid sequence set forth in SEQ ID NO: 25.

[000152] One or more of the agents provided herein can be combined with another agent, e.g., antibody or antigen-binding fragment thereof, that can comprise a first polypeptide comprising 1, 2, or 3 of an HCDR1 comprising the amino acid sequence set forth in SEQ ID NO: 20, an HCDR2 comprising the amino acid sequence set forth in SEQ ID NO: 21, and an HCDR3 comprising the amino acid sequence set forth in SEQ ID NO: 22 and a second polypeptide comprising 1, 2, or 3 of an LCDR1 comprising the amino acid sequence set forth in SEQ ID NO: 23, an HCDR2 comprising the amino acid sequence set forth in SEQ ID NO: 24, and an HCDR3 comprising the amino acid sequence set forth in SEQ ID NO: 25.

[000153] One or more of the agents provided herein can be combined with another agent, e.g., antibody or antigen-binding fragment thereof, that can comprise an HCDR with at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to any one of the amino acid sequences set forth in SEQ ID NO: 20, 21, or 22.

[000154] One or more of the agents provided herein can be combined with another agent, e.g., antibody or antigen-binding fragment thereof, that can comprise an LCDR with at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to any one of the amino acid sequences set forth in SEQ ID NO: 23, 24, or 25.

[000155] One or more of the agents provided herein can be combined with another agent, e.g., antibody or antigen-binding fragment thereof, that can comprise a heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 18, or an amino acid sequence comprising at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence set forth in SEQ ID NO: 18.

[000156] One or more of the agents provided herein can be combined with another agent, e.g., antibody or antigen-binding fragment thereof, that can comprise a heavy chain variable region (VH) comprising the amino acid sequence set forth in SEQ ID NO: 26, or an amino acid

sequence comprising at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence set forth in SEQ ID NO: 26.

[000157] One or more of the agents provided herein can be combined with another agent, e.g., antibody or antigen-binding fragment thereof, that can comprise a heavy chain constant region having the amino acid sequence set forth in SEQ ID NO: 27, or an amino acid sequence comprising at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence set forth in SEQ ID NO: 27.

[000158] One or more of the agents provided herein can be combined with another agent, e.g., antibody or antigen-binding fragment thereof, that can comprise a light chain comprising the amino acid sequence set forth in SEQ ID NO: 19, or an amino acid sequence comprising at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence set forth in SEQ ID NO: 19.

[000159] One or more of the agents provided herein can be combined with another agent, e.g., antibody or antigen-binding fragment thereof, that can comprise a light chain variable region (VL) comprising the amino acid sequence set forth in SEQ ID NO: 28, or an amino acid sequence comprising at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence set forth in SEQ ID NO: 28.

[000160] One or more of the agents provided herein can be combined with another agent, e.g., antibody or antigen-binding fragment thereof, that can comprise a light chain constant region having the amino acid sequence set forth in SEQ ID NO: 29, or an amino acid sequence comprising at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence set forth in SEQ ID NO: 29.

[000161] One or more of the agents provided herein can be combined with another agent, e.g., antibody or antigen-binding fragment thereof, that can comprise a light chain variable region (VL) comprising the amino acid sequence set forth in SEQ ID NO: 28, or an amino acid sequence comprising at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence set forth in SEQ ID NO: 28.

[000162] One or more of the agents provided herein can be combined with another agent, e.g., antibody or antigen-binding fragment thereof, that can comprise 1) a heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 18, or an amino acid sequence comprising at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence set forth in SEQ ID NO: 18 and 2) a light chain comprising the amino acid sequence set forth in SEQ ID NO: 19, or an amino acid sequence comprising at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence set forth in SEQ ID NO: 19.

[000163] One or more of the agents provided herein can be combined with another agent, e.g., antibody or antigen-binding fragment thereof, that can comprise 1) a heavy chain variable region (VH) comprising the amino acid sequence set forth in SEQ ID NO: 26, or an amino acid sequence comprising at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence set forth in SEQ ID NO: 26 and 2) a light chain variable region (VL) comprising the amino acid sequence set forth in SEQ ID NO: 28, or an amino acid sequence comprising at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence set forth in SEQ ID NO: 28.

Table 9. HCB Antibody Domain Sequences

SEQ ID NO:	Name	Type	Sequence
18	HCB Heavy Chain	PROTEIN	QITLKESGPTLVKPTQTLTLTCTFSGFSLSSSGMGVGWI RQPPGKALEWLALIYWNDDKRYSPSLKSRLTITKDTSK NQVVLTLTNMDPVDTATYYCAHTTLYNNCPFDYWGQ GTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKD YFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVV TVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTH TCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVV DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTY RVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISK AKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDI AVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKS RWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
26	HCB Variable Heavy Chain	PROTEIN	QITLKESGPTLVKPTQTLTLTCTFSGFSLSSSGMGVGWI RQPPGKALEWLALIYWNDDKRYSPSLKSRLTITKDTSK NQVVLTLTNMDPVDTATYYCAHTTLYNNCPFDYWGQ GTLVTVSS
27	HCB Constant Domain	PROTEIN	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGT QTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE LLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPE VKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREP QVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQKSLSLSPGK

SEQ ID NO:	Name	Type	Sequence
20	HCB HCDR1	PROTEIN	GFSLSSSGMG
21	HCB HCDR2	PROTEIN	IYWNDDK
22	HCB HCDR3	PROTEIN	AHTTLYNNCPFDY
19	LCB Light Chain	PROTEIN	SYVLTQPPSVSVAPGKTARITCGGNNIGSYSVHWYQQR PGQAPVLVIYYDSDRPSGIPERFSGSNSGNTATLTISRVE AGDEADYYCQVWDNSSNHPWVFGGGTKLTVLGQPKA APSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWK ADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKS HKSYSCQVTHEGSTVEKTVAPTECS
28	LCB Variable Light Chain	PROTEIN	SYVLTQPPSVSVAPGKTARITCGGNNIGSYSVHWYQQR PGQAPVLVIYYDSDRPSGIPERFSGSNSGNTATLTISRVE AGDEADYYCQVWDNSSNHPWVFGGGTKLTVL
23	LCB LCDR1	PROTEIN	NIGSYS
24	LCB LCDR2	PROTEIN	YDS
25	LCB LCDR3	PROTEIN	QVWDNSSNHPWV
29	LCB constant region	PROTEIN	GQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVT VAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPE QWKSHKSYSCQVTHEGSTVEKTVAPTECS

[000164] The combination of agents, e.g., antibodies or antigen-binding fragments thereof, can have a combination index (CI) less than 1, indicating synergism. For example, at a neutralization level of about 20%, 30%, 40%, 50%, 60%, 70%, 80%, or 90% for SARS-CoV-2 or SARS-CoV (or a pseudotyped virus with a SARS-CoV-2 spike protein or a SARS-CoV spike protein) for each agent, e.g., antibody or antigen-binding fragment thereof, the CI can be about, or less than 0.95, 0.9, 0.85, 0.8, 0.75, 0.7, 0.65, 0.6, 0.55, 0.5, 0.45, 0.4, 0.35, 0.3, 0.25, 0.2, 0.15, or 0.1. The SARS-CoV-2 can be a variant comprising one or more mutations of a variant, e.g.,

Omicron, Beta, or Gamma, or the spike protein can comprise one or more mutations of a variant, e.g., Omicron, Beta, or Gamma.

[000165] The combination of the HCA/LCA antibody and sotrovimab at a neutralization level of 60% for SARS-CoV-2 (or a pseudotyped virus with a SARS-CoV-2 spike protein) can have a CI of about 0.9, 0.8, 0.814, 0.7, 0.6, or 0.5, or a CI of less than 0.9, 0.8, 0.814, 0.7, 0.6, 0.5, or a CI of about 0.07 to about 0.9. The SARS-CoV-2 can be a variant comprising one or more mutations of a variant, e.g., Omicron, or the spike protein can comprise one or more mutations of a variant, e.g., Omicron.

[000166] The combination of the HCA/LCA antibody and sotrovimab at a neutralization level of 80% for SARS-CoV-2 (or a pseudotyped virus with a SARS-CoV-2 spike protein) can have a CI of about 0.9, 0.8, 0.7, 0.6, 0.561, 0.5, 0.45, 0.4, 0.3, or a CI of less than 0.9, 0.8, 0.7, 0.6, 0.561, 0.5, 0.45, 0.4, 0.3, or a CI of about 0.4 to about 0.7. The SARS-CoV-2 can be a variant comprising one or more mutations of a variant, e.g., Omicron, or the spike protein can comprise one or more mutations of a variant, e.g., Omicron.

[000167] The combination of the HCA/LCA antibody and HCB/LCB antibody at a neutralization level of 20%, 40%, 60%, or 80% for SARS-CoV-2 (or a pseudotyped virus with a SARS-CoV-2 spike protein) can have a CI of about 0.9, 0.8, 0.7, 0.6, 0.561, 0.549, 0.519, 0.488, 0.487, 0.454, 0.445, 0.416, 0.4, 0.3, 0.2, 0.1, or a CI of less than 0.9, 0.8, 0.7, 0.6, 0.561, 0.549, 0.519, 0.488, 0.487, 0.454, 0.445, 0.416, 0.4, 0.3, 0.2, 0.1, or a CI of about 0.04 to about 0.6. The SARS-CoV-2 can be variant comprising one or more mutations of a variant, e.g., Beta, or Gamma, or the spike protein can comprise one or more mutations of a variant, e.g., Beta or Gamma.

[000168] The combination of the HCA/LCA antibody and sotrovimab at a neutralization level of 40% for SARS-CoV (or a pseudotyped virus with a SARS-CoV spike protein) can have a CI of about 0.924, 0.8, 0.7, 0.6, 0.5, or a CI of less than 0.924, 0.8, 0.7, 0.6, 0.5, or a CI of about 0.7 to about 0.99.

[000169] The combination of the HCA/LCA antibody and sotrovimab at a neutralization level of 60% for SARS-CoV (or a pseudotyped virus with a SARS-CoV spike protein) can have a CI of about 0.9, 0.8, 0.7, 0.679, 0.6, 0.5, 0.4, 0.3, or a CI of less than 0.9, 0.8, 0.7, 0.679, 0.6, 0.5, 0.4, 0.3, or a CI of about 0.5 to about 0.7.

[000170] The combination of the HCA/LCA antibody and sotrovimab at a neutralization level of 80% for SARS-CoV (or a pseudotyped virus with a SARS-CoV spike protein) can have a CI of about 0.9, 0.8, 0.7, 0.6, 0.5, 0.475, 0.4, 0.3, or a CI of less than 0.9, 0.8, 0.7, 0.6, 0.5, 0.475, 0.4, 0.3, or a CI of about 0.4 to about 0.5.

[000171] In some embodiments, the agents, e.g., antibodies or antigen-binding fragments thereof, e.g., the HCA/LCA antibody or antigen-binding fragment thereof, are administered for the treatment of mild to moderate coronavirus disease 2019 (COVID-19) in adults and pediatric patients, including neonates, with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death. In some cases, the agents, e.g., antibodies or antigen-binding fragments thereof, e.g., the HCA/LCA antibody or antigen-binding fragment thereof are administered for post-exposure prophylaxis of COVID-19. In some cases, the agents, e.g., antibodies or antigen-binding fragments thereof, e.g., the HCA/LCA antibody or antigen-binding fragment thereof are administered for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults and pediatric patients who are 12 years of age and older and weigh at least 40 kg with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death.

[000172] In some cases, the agents, e.g., antibodies or antigen-binding fragments thereof, e.g., the HCA/LCA antibody or antigen-binding fragment thereof, is administered for treatment in adults. In some cases, the agents, e.g., antibodies or antigen-binding fragments thereof, e.g., the HCA/LCA antibody or antigen-binding fragment thereof, are administered for treatment in pediatric individuals. In some cases, the pediatric individuals include neonates. In some cases, the agents, e.g., antibodies or antigen-binding fragments thereof, e.g., the HCA/LCA antibody or antigen-binding fragment thereof are administered in individuals ages 0-2, 3-11, 12-17, 18-25, 26-49, 50-110. In some cases, the agents, e.g., antibodies or antigen-binding fragments thereof, e.g., the HCA/LCA antibody or antigen-binding fragment thereof are administered in individuals who are vaccinated for COVID-19. In some cases, the agents, e.g., antibodies or antigen-binding fragments thereof, e.g., the HCA/LCA antibody or antigen-binding fragment thereof are administered for treatment in individuals who are fully vaccinated for COVID-19. In some cases, the agents, e.g., antibodies or antigen-binding fragments thereof, e.g., the HCA/LCA antibody or antigen-binding fragment thereof are administered in individuals who have received one or more doses of a vaccine, e.g., the mRNA or viral vector vaccine, for SARS-CoV-2. In some cases, the individual has received 1 dose of the vaccine for SARS-CoV-2. In some cases, the individual has received 2 doses of the vaccine for SARS-CoV-2. In some cases, the individual has received three doses of an mRNA vaccine. In some cases, the individual has received four shots of the mRNA vaccine.

[000173] In some cases, the agents, e.g., antibodies or antigen-binding fragments thereof, e.g., the HCA/LCA antibody or antigen-binding fragment thereof are administered for treatment in individuals who are not vaccinated for COVID-19. In some cases, the agents, e.g., antibodies

or antigen-binding fragments thereof, e.g., the HCA/LCA antibody or antigen-binding fragment thereof are administered to individuals who are not expected to mount an adequate immune response to complete SARS-CoV-2 vaccination. For example, in some cases, the individuals have one or more immunocompromising conditions. In some cases, the agents, e.g., antibodies or antigen-binding fragments thereof, e.g., the HCA/LCA antibody or antigen-binding fragment thereof are administered to individuals taking one or more immunosuppressive medications.

[000174] In some cases, the agents, e.g., antibody or antigen-binding fragments thereof, e.g., the HCA/LCA antibody or antigen-binding fragment thereof are administered to individuals who do not have immunocompromising conditions. Additionally, in some cases, the agents, e.g., antibodies or antigen-binding fragments thereof, e.g., the HCA/LCA antibody or antigen-binding fragment thereof are administered to individuals who have been exposed to an individual infected with SARS-CoV-2. In some cases, the agents, e.g., antibodies or antigen-binding fragments thereof, e.g., the HCA/LCA antibody or antigen-binding fragment thereof are administered to individuals who are at risk of exposure to an individual infected with SARS-CoV2 because of occurrence of SARS-CoV-2 infection in other individuals in the same institutional setting. For example, in some cases, the institutional setting comprises a nursing home or a prison. In some cases, the agents, e.g., antibodies or antigen-binding fragments thereof, e.g., the HCA/LCA antibody or antigen-binding fragment thereof are administered to individuals who have been infected with SARS-CoV-2. In some cases the agents, e.g., antibodies or antigen-binding fragments thereof, e.g., the HCA/LCA antibody or antigen-binding fragment thereof are administered to individuals who have not been infected with SARS-CoV-2. In some cases, the agents, e.g., antibodies or antigen-binding fragments thereof, e.g., the HCA/LCA antibody or antigen-binding fragment thereof are administered to individuals who have been infected with SARS-CoV. In some cases, the agents, e.g., antibodies or antigen-binding fragments thereof, e.g., the HCA/LCA antibody or antigen-binding fragment thereof are administered to individuals who have not been infected with SARS-CoV.

[000175] The agents provided herein, e.g., antibodies or antigen-biding fragments thereof, e.g., HCA/LCA or antigen-binding fragment thereof, can comprise one or more modifications that extend the half-life of the agent. The one or more modifications can comprise an LS mutation (M428L/N434S), YTE, AAA (T307A/A380A/N434A), QL (T250Q/M28L), or V308P, or any combination thereof.

Nucleic Acid Molecules Encoding Agents, e.g., Antibodies or Antigen Binding Fragments Thereof

[000176] Using the information provided herein, for example, nucleic acid and amino acid sequences of the agents, e.g., antibodies or antigen-binding fragments thereof, e.g., the HCA/LCA antibody or antigen-binding fragment thereof disclosed herein; a nucleic acid molecule encoding the antibodies or antigen-binding fragments thereof can be easily obtained by a skilled artisan. Nucleic acid molecules of the present disclosure can be in the form of RNA, such as mRNA, hnRNA, tRNA or any other form, or in the form of DNA, including but not limited to, cDNA and genomic DNA obtained by cloning or produced synthetically, or any combinations thereof. The DNA can be triplex, duplex or single-stranded, or any combination thereof. Any portion of at least one strand of the DNA or RNA can be the coding strand, also known as the sense strand, or it can be the antisense strand, also known as the antisense strand. Polynucleotide or nucleic acid molecule, as used interchangeably herein, refer to polymers of nucleotides of any length, and include DNA and RNA. The nucleotides can be deoxyribonucleotides, ribonucleotides, modified nucleotides or bases, and/or their analogs, or any substrate that can be incorporated into a polymer by DNA or RNA polymerase. A nucleic acid molecule can comprise modified nucleotides, such as methylated nucleotides and their analogs. If present, modification to the nucleotide structure can be imparted before or after assembly of the polymer. The sequence of nucleotides can be interrupted by non-nucleotide components.

[000177] A polynucleotide can be further modified after polymerization, such as by conjugation with a labeling component. Other types of modifications include, for example, “caps”, substitution of one or more of the naturally occurring nucleotides with an analog, internucleotide modifications such as, for example, those with uncharged linkages (e.g., methyl phosphonates, phosphotriesters, phosphoamidates, cabamates, etc.) and with charged linkages (e.g., phosphorothioates, phosphorodithioates, etc.), those containing pendant moieties, such as, for example, proteins (e.g., nucleases, toxins, antibodies, signal peptides, ply-L-lysine, etc.), those with intercalators (e.g., acridine, psoralen, etc.), those containing chelators (e.g., metals, radioactive metals, boron, oxidative metals, etc.), those containing alkylators, those with modified linkages (e.g., alpha anomeric nucleic acids, etc.), as well as unmodified forms of the polynucleotide(s). Further, any of the hydroxyl groups ordinarily present in the sugars can be replaced, for example, by phosphonate groups, phosphate groups, protected by standard protecting groups, or activated to prepare additional linkages to additional nucleotides, or can be conjugated to solid supports. The 5' and 3' terminal OH can be phosphorylated or substituted with amines or organic capping group moieties of from 1 to 20 carbon atoms. Other hydroxyls can also be derivatized to standard protecting groups. Polynucleotides can also contain analogous forms of ribose or deoxyribose sugars that are generally known in the art, including, for example,

2'-0-methyl-, 2'-0-allyl, 2'-fluoro- or 2'- azido-ribose, carbocyclic sugar analogs, a-anomeric sugars, epimeric sugars such as arabinose, xyloses or lyxoses, pyranose sugars, furanose sugars, sedoheptuloses, acyclic analogs and abasic nucleoside analogs such as methyl riboside. One or more phosphodiester linkages can be replaced by alternative linking groups. These alternative linking groups include, but are not limited to, embodiments wherein phosphate is replaced by P(0)S("thioate"), P(S)S ("dithioate"),"(0)NR2 ("amidate"), P(0)R, P(0)OR', CO or CH2 ("formacetal"), in which each R or R' is independently H or substituted or unsubstituted alkyl (1-20 C) optionally containing an ether (—O—) linkage, aryl, alkenyl, cycloalkyl, cycloalkenyl or araldyl. Not all linkages in a polynucleotide need be identical. The preceding description applies to all polynucleotides referred to herein, including isolated nucleic acid, RNA and DNA.

[000178] In the context of the present disclosure, the following abbreviations for the commonly occurring nucleic acid bases are used. "A" refers to adenosine, "C" refers to cytosine, "G" refers to guanosine, "T" refers to thymidine, and "U" refers to uridine. In some embodiments, the nucleic acid molecule comprises an isolated nucleic acid. The nucleic acids can be present in whole cells, in a cell lysate, or in a partially purified or substantially pure form. A nucleic acid molecule is isolated when purified away from other cellular components or other contaminants, e.g., other cellular nucleic acids or proteins, by standard techniques, including, but not limited to alkaline/SDS treatment, CsCl banding, column chromatography, agarose gel electrophoresis and others well known in the art. See, F. Ausubel, et al., ed. (1987) Current Protocols in Molecular Biology, Greene Publishing and Wiley Interscience, New York. A nucleic acid according to at least some embodiments of the disclosure can be, for example, DNA or RNA and may or may not contain intronic sequences. In a preferred embodiment, the nucleic acid is a cDNA molecule.

[000179] Another aspect of the present disclosure pertains to nucleic acid molecules comprising nucleic acid sequences that encode the agents, e.g., antibodies or antigen-binding fragments thereof, e.g., the HCA/LCA antibody or antigen-binding fragment thereof,. In some embodiments, the isolated nucleic acid molecule comprises a nucleic acid sequence encoding a modified IgA heavy chain constant region.

[000180] Nucleic acid molecules isolated from the present disclosure can include nucleic acid molecules comprising an open reading frame (ORF), optionally with one or more introns, e.g., but not limited to, at least one specified portion of at least a CDR, as CDR1, CDR2 and / or CDR3 of at least one light chain; nucleic acid molecules comprising the coding sequence of a cancer associated antibody disclosed herein or variable region e.g., variable regions of the light chain; and nucleic acid molecules comprising a nucleotide sequence substantially different from those described above but which, due to the degeneracy of the genetic code, still encode at least

antibody or antigen binding fragment thereof as described herein and / or as it is known in the art. Of course, the genetic code is well known in the art. Therefore, it would be routine for one skilled in the art to generate such degenerate nucleic acid variants encoding specific antibodies of the present disclosure. See for example, Ausubel et al., Supra, and such nucleic acid variants are included in the present disclosure.

[000181] Nucleic acid molecules comprising nucleic acid sequence that encode one or more chains of an antibody are provided herein. In some embodiments, a nucleic acid molecule comprises a nucleic acid sequence that encodes a heavy chain or a light chain of an antibody. In some embodiments, a nucleic acid molecule comprises both a nucleic acid sequence that encodes a heavy chain and a nucleic acid sequence that encodes a light chain, of an antibody. In some embodiments, a first nucleic acid molecule comprises a first nucleic acid sequence that encodes a heavy chain and a second nucleic acid molecule comprises a second nucleic acid sequence that encodes a light chain.

[000182] In some embodiments, the heavy chain and the light chain are expressed from one nucleic acid molecule, or from two separate nucleic acid molecules, as two separate polypeptides. In some embodiments, such as when an antibody is an scFv, a single nucleic acid sequence encodes a single polypeptide comprising both a heavy chain and a light chain linked together.

[000183] In some embodiments, a nucleic acid sequence encoding a heavy chain or light chain of an antibody disclosed herein comprises a nucleic acid sequence that encodes at least one of the CDRs provided herein. In some embodiments, a nucleic acid sequence encoding a heavy chain or light chain of an antibody disclosed herein comprises a sequence that encodes at least 3 of the CDRs provided herein. In some embodiments, a nucleic acid sequence encoding a heavy chain or light chain of an antibody comprises a sequence that encodes at least 6 of the CDRs provided herein. In some embodiments, a nucleic acid sequence encoding a heavy chain or light chain of an antibody comprises a nucleotide sequence that encodes a leader sequence, which, when translated, is located at the N terminus of the heavy chain or light chain.

[000184] Nucleic acid molecules can be constructed using recombinant DNA techniques conventional in the art. In some embodiments, a nucleic acid molecule is placed in an expression vector that is suitable for expression in a selected host cell.

[000185] The present disclosure also provides vectors comprising isolated nucleotides or isolated polynucleotides encoding the antibodies disclosed herein. In certain embodiments, the polynucleotide provided herein encodes the antibodies, at least one promoter (e.g., SV40, CMV, EF-1α) operably linked to the nucleic acid sequence, and at least one selection marker. Examples of vectors include, but are not limited to, retrovirus (including lentivirus), adenovirus, adeno-associated virus, herpesvirus (e.g. herpes simplex virus), poxvirus, baculovirus, papillomavirus,

papovavirus (e.g. SV40), lambda phage, and M13 phage, plasmid pcDNA3.3, pMD18-T, pOptivec, pCMV, pEGFP, pIRES, pQD-Hyg-GSeu, pALTER, pBAD, pcDNA, pCal, pL, pET, pGEMEX, pGEX, pCI, pEGFT, pSV2, pFUSE, pVITRO, pVIVO, pMAL, pMONO, pSELECT, pUNO, pDUO, Psg5L, pBABE, pWPXL, pBI, p15TV-L, pPro18, pTD, pRS10, pLexA, pACT2.2, pCMV-SCRIPT.RTM., pCDM8, pCDNA1.1/amp, pcDNA3.1, pRc/RSV, PCR 2.1, pEF-1, pFB, pSG5, pXT1, pCDEF3, pSVSPORT, pEF-Bos etc.

[000186] Vectors comprising nucleic acid molecules that encode the antibodies or antigen binding fragment herein are provided. Vectors comprising nucleic acid molecules that encode the agents, e.g., antibodies or antigen-binding fragments thereof, e.g., the HCA/LCA antibody or antigen-binding fragment thereof be effective in any number of neutralization assays (e.g., VSV, MLV, Lentiviral). Such vectors include, but are not limited to, DNA vectors, phage vectors, viral vectors, retroviral vectors, etc. In one embodiment, the nucleic acid coding for the light chain and that coding for the heavy chain are isolated separately by the procedures outlined above. In one embodiment, the isolated nucleic acid encoding the light chain and that coding for the heavy chain can be inserted into separate expression plasmids, or together in the same plasmid, so long as each is under suitable promoter and translation control. In some embodiments, the heavy chain and light chain are expressed as part of a single polypeptide, such as, for example, when the antibody is an scFv.

[000187] In some embodiments, a first vector comprises a nucleic acid molecule that encodes a heavy chain and a second vector comprises a nucleic acid molecule that encodes a light chain. In some embodiments, the first vector comprises the HCA or HCB and the second vector comprises the LCA or LCB. In some embodiments, the first vector and second vector are transfected into host cells in similar amounts (such as similar molar amounts or similar mass amounts). In some embodiments, a mole- or mass-ratio of between 5: 1 and 1:5 of the first vector and the second vector is transfected into host cells. In some embodiments, a mass ratio of between 1:1 and 1:5 for the vector encoding the heavy chain and the vector encoding the light chain is used. In some embodiments, a mass ratio of 1:2 for the vector encoding the heavy chain and the vector encoding the light chain is used.

[000188] Laboratory Manual, Stockton Press, NY. Delivery of a therapeutic antibody to appropriate cells can be effected via gene therapy ex vivo, in situ, or in vivo by use of any suitable approach known in the art, including by use of physical DNA transfer methods (e.g., liposomes or chemical treatments) or by use of viral vectors (e.g., adenovirus, adeno-associated virus, or a retrovirus). For example, for in vivo therapy, a nucleic acid encoding the desired antibody, either alone or in conjunction with a vector, liposome, or precipitate can be injected directly into the subject, and in some embodiments, can be injected at the site where the

expression of the antibody compound is desired. For ex vivo treatment, the subject's cells are removed, the nucleic acid is introduced into these cells, and the modified cells are returned to the subject either directly or, for example, encapsulated within porous membranes which are implanted into the patient. See, e.g., U.S. Pat. Nos. 4,892,538 and 5,283,187. There are a variety of techniques available for introducing nucleic acids into viable cells. The techniques vary depending upon whether the nucleic acid is transferred into cultured cells in vitro, or in vivo in the cells of the intended host. Techniques suitable for the transfer of nucleic acid into mammalian cells in vitro include the use of liposomes, electroporation, microinjection, cell fusion, DEAE-dextran, and calcium phosphate precipitation. A commonly used vector for ex vivo delivery of a nucleic acid is a retrovirus.

[000189] The term "host cell" as used herein can refer to the particular subject cell transfected with a nucleic acid molecule and the progeny or potential progeny of such a cell. Progeny of such a cell may not be identical to the parent cell transfected with the nucleic acid molecule due to mutations or environmental influences that may occur in succeeding generations or integration of the nucleic acid molecule into the host cell genome.

[000190] Other in vivo nucleic acid transfer techniques include transfection with viral vectors (such as adenovirus, Herpes simplex I virus, or adeno-associated virus) and lipid-based systems. The nucleic acid and transfection agent are optionally associated with a microparticle. Exemplary transfection agents include calcium phosphate or calcium chloride co-precipitation, DEAE-dextran-mediated transfection, quaternary ammonium amphiphile DOTMA ((dioleoyloxypropyl) trimethylammonium bromide, commercialized as Lipofectin by GIBCO-BRL))(Felgner et al, (1987) Proc. Natl. Acad. Sci. USA 84, 7413-7417; Malone et al. (1989) Proc. Natl Acad. Sci. USA 86 6077-6081); lipophilic glutamate diesters with pendent trimethylammonium heads (Ito et al. (1990) Biochem. Biophys. Acta 1023, 124-132); the metabolizable parent lipids such as the cationic lipid dioctadecylamido glycylspermine (DOGS, Transfectam, Promega) and dipalmitoylphosphatidyl ethanolamylspermine (DPPES)(J. P. Behr (1986) Tetrahedron Lett. 27, 5861- 5864; J. P. Behr et al. (1989) Proc. Natl. Acad. Sci. USA 86, 6982-6986); metabolizable quaternary ammonium salts (DOTB, N-(l-[2,3-dioleoyloxy]propyl)-N,N,N-trimethylammonium methylsulfate (DOTAP)(Boehringer Mannheim), polyethyleneimine (PEI), dioleoyl esters, ChoTB, ChoSC, DOSC)(Leventis et al. (1990) Biochim. Inter. 22, 235-241); 3beta[N-(N',N'-dimethylaminoethane)- carbamoyljcholesterol (DC-Chol), dioleoylphosphatidyl ethanolamine (DOPE)/3beta[N-(N',N' dimethylaminoethane)-carbamoyl] cholesterolDC-Chol in one to one mixtures (Gao ct al., (1991) Biochim. Biophys. Acta 1065, 8-14), spermine, spermidine, lipopolyamines (Behr et al., Bioconjugate Chem, 1994, 5: 382-389), lipophilic polylysines (LPLL) (Zhou et al., (1991) Biochim. Biophys. Acta 939, 8-18), [[(1, 1,3,3

tetramethylbutyl)cresoxy]ethoxy]ethyl]dimethylbnzylammonium hydroxide (DEBDA hydroxide) with excess phosphatidylcholine/cholesterol (Balias et al., (1988) Biochim. Biophys. Acta 939, 8-18), cetyltrimethylammonium bromide (CTAB)/DOPE mixtures (Pinnaduwage et al, (1989) Biochim. Biophys. Acta 985, 33-37), lipophilic diester of glutamic acid (TMAG) with DOPE, CTAB, DEBDA, didodecylammonium bromide (DDAB), and stearylamine in admixture with phosphatidylethanolamine (Rose et al., (1991) Biotechnique 10, 520-525), DDAB/ DOPE (TransfectACE, GIBCO BRL), and oligogalactose bearing lipids. Exemplary transfection enhancer agents that increase the efficiency of transfer include, for example, DEAE-dextran, polybrene, lysosome-disruptive peptide (Ohmori N I et al, Biochem Biophys Res Commun Jun. 27, 1997; 235(3):726-9), chondroitan-based proteoglycans, sulfated proteoglycans, polyethylenimine, polylysine (Pollard H et al. J Biol Chem, 1998 273 (13):7507- 11), integrin-binding peptide CYGGRGDTP, linear dextran nonasaccharide, glycerol, cholesteryl groups tethered at the 3'-terminal internucleoside link of an oligonucleotide (Letsinger, R. L. 1989 Proc Natl Acad Sci USA 86: (17):6553-6), lysophosphatide, lysophosphatidylcholine, lysophosphatidylethanolamine, and 1 -oleoyl lysophosphatidylcholine.

[000191] In some situations, it can be desirable to deliver the nucleic acid with an agent that directs the nucleic acid containing vector to target cells. Such “targeting” molecules include antibodies specific for a cell-surface membrane protein on the target cell, or a ligand for a receptor on the target cell. Where liposomes are employed, proteins which bind to a cell-surface membrane protein associated with endocytosis can be used for targeting and/or to facilitate uptake. Examples of such proteins include capsid proteins and fragments thereof tropic for a particular cell type, antibodies for proteins which undergo internalization in cycling, and proteins that target intracellular localization and enhance intracellular half-life. In other embodiments, receptor-mediated endocytosis can be used. Such methods are described, for example, in Wu et al., 1987 or Wagner et al., 1990. For review of the currently known gene marking and gene therapy protocols, see Anderson 1992. See also WO 93/25673 and the references cited therein.

Chimeric antigen receptor

[000192] In one aspect, the disclosure herein, provides a neutralizing antibody-derived chimeric antigen receptor comprising, an antigen binding fragment, disclosed herein, a transmembrane domain, and an intracellular signaling domain. For example, an antibody-derived chimeric antigen receptor can comprise an HCA/LCA or HCB/LCB antibody-derived chimeric antigen receptor, or any one or more of the CDRs (HCDRs and/or LCDRs), heavy chain, heavy chain variable region (VH), light chains, or light chain variable regions (LH) disclosed herein. In some embodiments of the present disclosure, the antigen binding fragments of these neutralizing

antibody-derived CARs bind to SARS-CoV or SARS-CoV-2 spike protein domains. The term "chimeric antigen receptor" (CAR) as used herein refers to an engineered receptor, which grafts an arbitrary specificity onto an immune effector cell. CARs can have an extracellular domain (ectodomain), which can comprise an antigen-binding domain, a transmembrane domain, and an intracellular (endodomain) domain. The term "signaling domain" refers to the functional portion of a protein which acts by transmitting information within the cell to regulate cellular activity via defined signaling pathways by generating second messengers or functioning as effectors by responding to such messengers.

[000193] An "intracellular signaling domain," as the term is used herein, can refer to an intracellular portion of a molecule. The intracellular signaling domain generates a signal that promotes an immune effector function of the CAR containing cell, e.g., a CART cell. Examples of immune effector function, e.g., in a CART cell, include cytolytic activity and helper activity, including the secretion of cytokines. In an embodiment, the intracellular signaling domain can comprise a primary intracellular signaling domain. Exemplary primary intracellular signaling domains include those derived from the molecules responsible for primary stimulation, or antigen dependent simulation. In an embodiment, the intracellular signaling domain can comprise a costimulatory intracellular domain. Exemplary costimulatory intracellular signaling domains include those derived from molecules responsible for costimulatory signals, or antigen independent stimulation. For example, in the case of a CART, a primary intracellular signaling domain can comprise a cytoplasmic sequence of a T cell receptor, and a costimulatory intracellular signaling domain can comprise cytoplasmic sequence from co-receptor or costimulatory molecule. A primary intracellular signaling domain can comprise a signaling motif which is known as an immunoreceptor tyrosine-based activation motif or IT AM. Examples of IT AM containing primary cytoplasmic signaling sequences include, but are not limited to, those derived from CD3 zeta, FcR gamma, FcR beta, CD3 gamma, CD3 delta, CD3 epsilon, CD5, CD22, CD79a, CD79b, and CD66d DAP10 and DAP 12.

[000194] The term "costimulatory molecule" can refer to the cognate binding partner on a T cell that specifically binds with a costimulatory ligand, thereby mediating a costimulatory response by the T cell, such as, but not limited to, proliferation. Costimulatory molecules are cell surface molecules other than antigen receptors or their ligands that can be used for an efficient immune response. Costimulatory molecules include, but are not limited to, an MHC class I molecule, BTLA and a Toll ligand receptor, as well as 0X40, CD2, CD27, CD28, CD5, ICAM-1, LFA-1 (CDl la/CD18) and 4-1BB (CD137).

[000195] A costimulatory intracellular signaling domain can be derived from the intracellular portion of a costimulatory molecule. A costimulatory molecule can be represented in

the following protein families: TNF receptor proteins, Immunoglobulin-like proteins, cytokine receptors, integrins, signaling lymphocytic activation molecules (SLAM proteins), and activating NK cell receptors. Examples of such molecules include CD27, CD28, 4-1BB (CD137), 0X40, GITR, CD30, CD40, ICOS, BAFFR, HVEM, lymphocyte function-associated antigen-1 (LFA-1), CD2, CD7, LIGHT, NKG2C, SLAMF7, NKp80, CD160, B7-H3, and a ligand that specifically binds with CD83, and the like.

[000196] The intracellular signaling domain can comprise the entire intracellular portion, or the entire native intracellular signaling domain, of the molecule from which it is derived, or a functional fragment thereof.

[000197] In another aspect, the antigen binding fragment comprises a humanized antibody or antibody fragment. In one embodiment, the antigen binding fragment comprises one or more (e.g., one, two, or all three) light chain complementary determining region 1 (LC-CDR1), light chain complementary determining region 2 (LC-CDR2), and light chain complementary determining region 3 (LC-CDR3) of an antibody described herein, and one or more (e.g., one, two, or all three) heavy chain complementary determining region 1 (HC-CDR1), heavy chain complementary determining region 2 (HC-CDR2), and heavy chain complementary determining region 3 (HC-CDR3) of an antibody described herein.

Transmembrane domain

[000198] With respect to the transmembrane domain, in various embodiments, a CAR can be designed to comprise a transmembrane domain that is attached to the extracellular domain of the CAR. A transmembrane domain can include one or more additional amino acids adjacent to the transmembrane region, e.g., one or more amino acid associated with the extracellular region of the protein from which the transmembrane was derived (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 up to 15 amino acids of the extracellular region) and/or one or more additional amino acids associated with the intracellular region of the protein from which the transmembrane protein is derived (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 up to 15 amino acids of the intracellular region). In one aspect, the transmembrane domain is one that is associated with one of the other domains of the CAR is used. In some instances, the transmembrane domain can be selected or modified by amino acid substitution to avoid binding of such domains to the transmembrane domains of the same or different surface membrane proteins, e.g., to minimize interactions with other members of the receptor complex. In one aspect, the transmembrane domain is capable of homodimerization with another CAR on the CAR T-cell surface. In a different aspect, the amino acid sequence of the transmembrane domain can be modified or substituted so as to minimize interactions with the binding domains of the native binding partner present in the same CAR T-cell.

[000199] The transmembrane domain can be derived either from a natural or from a recombinant source. Where the source is natural, the domain can be derived from any membrane-bound or transmembrane protein. In one aspect the transmembrane domain is capable of signaling to the intracellular domain(s) whenever the CAR has bound to a target. A transmembrane domain, for example, can include at least the transmembrane region(s) of e.g., the alpha, beta or zeta chain of the T-cell receptor, CD28, CD3 epsilon, CD45, CD4, CD5, CD8, CD9, CD16, CD22, CD33, CD37, CD64, CD80, CD86, CD134, CD137, CD154. [0460] In some instances, the transmembrane domain can be attached to the extracellular region of the CAR, e.g., the antigen-binding domain of the CAR, via a hinge, e.g., a hinge from a human protein. For example, in one embodiment, the hinge can be a human Ig (immunoglobulin) hinge, e.g., an IgG4 hinge, or a CD8a hinge. In one aspect, the hinge or spacer comprises an IgG4 hinge.

Cytoplasmic Domain

[000200] The cytoplasmic domain or region of the CAR can include an intracellular signaling domain. An intracellular signaling domain is generally responsible for activation of at least one of the normal effector functions of the immune cell in which the CAR has been introduced. The term "effector function" refers to a specialized function of a cell. Effector function of a T cell, for example, can be cytolytic activity or helper activity including the secretion of cytokines. The term "intracellular signaling domain" refers to the portion of a protein which transduces the effector function signal and directs the cell to perform a specialized function. While usually the entire intracellular signaling domain can be employed, in many cases it is not necessary to use the entire chain. To the extent that a truncated portion of the intracellular signaling domain is used, such truncated portion can be used in place of the intact chain as long as it transduces the effector function signal. The term intracellular signaling domain is thus meant to include any truncated portion of the intracellular signaling domain sufficient to transduce the effector function signal.

[000201] Examples of intracellular signaling domains for use in the CAR of the present disclosure include the cytoplasmic sequences of the T cell receptor (TCR) and co-receptors that act in concert to initiate signal transduction following antigen receptor engagement, as well as any derivative or variant of these sequences and any recombinant sequence that has the same functional capability.

[000202] It is known that signals generated through the TCR alone are insufficient for full activation of the T cell and that a secondary and/or costimulatory signal can also be involved. Thus, T cell activation can be said to be mediated by two distinct classes of cytoplasmic signaling sequences: those that initiate antigen- dependent primary activation through the TCR

(primary intracellular signaling domains) and those that act in an antigen-independent manner to provide a secondary or costimulatory signal (secondary cytoplasmic signaling domain, e.g., a costimulatory domain).

[000203] A primary signaling domain regulates primary activation of the TCR complex either in a stimulatory way, or in an inhibitory way. Primary intracellular signaling domains that act in a stimulatory manner can contain signaling motifs which are known as immunoreceptor tyrosine-based activation motifs or ITAMs.

[000204] Examples of ITAM containing primary intracellular signaling domains that are of particular use herein include those of TCR zeta, FcR gamma, FcR beta, CD3 gamma, CD3 delta, CD3 epsilon, CD5, CD22, CD79a, CD79b, and CD66d. In one embodiment, a CAR comprises an intracellular signaling domain, e.g., a primary signaling domain, of CD3-zeta. In one embodiment, a primary signaling domain comprises a modified ITAM domain, e.g., a mutated ITAM domain which has altered (e.g., increased or decreased) activity as compared to the native ITAM domain. In one embodiment, a primary signaling domain comprises a modified ITAM-containing primary intracellular signaling domain, e.g., an optimized and/or truncated ITAM-containing primary intracellular signaling domain. In an embodiment, a primary signaling domain comprises one, two, three, four or more ITAM motifs.

[000205] The intracellular signaling domain of the CAR can comprise the CD3-zeta signaling domain by itself or it can be combined with any other desired intracellular signaling domain(s) useful in the context of a CAR of the invention. For example, the intracellular signaling domain of the CAR can comprise a CD3 zeta chain portion and a costimulatory signaling domain. The costimulatory signaling domain refers to a portion of the CAR comprising the intracellular domain of a costimulatory molecule. A costimulatory molecule is a cell surface molecule other than an antigen receptor or its ligands that can play a role for an efficient response of lymphocytes to an antigen. Examples of such molecules include CD27, CD28, 4-1BB (CD137), 0X40, CD30, CD40, PD-1, ICOS, lymphocyte function-associated antigen-1 (LFA-1), CD2, CD7, LIGHT, NKG2C, B7-H3, and a ligand that specifically binds with CD83, and the like. For example, CD27 costimulation has been demonstrated to enhance expansion, effector function, and survival of human CART cells in vitro and augments human T cell persistence and antitumor activity in vivo (Song et al. Blood. 2012; 119(3) :696-706).

[000206] The intracellular signaling sequences within the cytoplasmic portion of a CAR provided herein can be linked to each other in a random or specified order. Optionally, a short oligo- or polypeptide linker, for example, between 2 and 10 amino acids (e.g., 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acids) in length can form the linkage between intracellular signaling sequence. In

one embodiment, a glycine-serine doublet can be used as a suitable linker. In one embodiment, a single amino acid, e.g., an alanine, a glycine, can be used as a suitable linker.

[000207] In one aspect, the intracellular signaling domain is designed to comprise two or more, e.g., 2, 3, 4, 5, or more, costimulatory signaling domains. In an embodiment, the two or more, e.g., 2, 3, 4, 5, or more, costimulatory signaling domains, are separated by a linker molecule, e.g., a linker molecule described herein. In one embodiment, the intracellular signaling domain comprises two costimulatory signaling domains. In some embodiments, the linker molecule is a glycine residue. In some embodiments, the linker is an alanine residue.

[000208] In some embodiments, CAR does not actually recognize the entire antigen; instead, it binds to only a portion of the antigen's surface, an area called the antigenic determinant or epitope. In some embodiments, a CAR described herein include (including functional portions and functional variants thereof) glycosylated, amidated, carboxylated, phosphorylated, esterified, N-acylated, cyclized via, e.g., a disulfide bridge, or converted into an acid addition salt and/or optionally dimerized or polymerized, or conjugated.

Pharmaceutical Compositions and Dosage

[000209] Disclosed herein, in certain embodiments, are pharmaceutical compositions comprising a therapeutic agent disclosed herein for administration in a subject.

[000210] In some instances, pharmaceutical compositions comprising one or more fo the agents provided herein, e.g., antibodies or antigen-binding fragments thereof, e.g., HCA/LCA antibody or antigen-binding fragment thereof can be formulated in a conventional manner using one or more physiologically acceptable carriers including excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. Proper formulation can be dependent upon the route of administration chosen. A summary of pharmaceutical compositions described herein is found, for example, in Remington: The Science and Practice of Pharmacy, Nineteenth Ed (Easton, Pa.: Mack Publishing Company, 1995); Hoover, John E., Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pennsylvania 1975; Liberman, H.A. and Lachman, L., Eds., Pharmaceutical Dosage Forms, Marcel Decker, New York, N.Y., 1980; and Pharmaceutical Dosage Forms and Drug Delivery Systems, Seventh Ed. (Lippincott Williams & Wilkins 1999).

[000211] Pharmaceutical compositions are optionally manufactured, such as, by way of example only, by means of mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or compression processes.

[000212] In certain embodiments, compositions can also include one or more pH adjusting agents or buffering agents, including acids such as acetic, boric, citric, lactic, phosphoric and hydrochloric acids; bases such as sodium hydroxide, sodium phosphate, sodium borate, sodium

citrate, sodium acetate, sodium lactate and tris-hydroxymethylaminomethane; and buffers such as citrate/dextrose, sodium bicarbonate and ammonium chloride. Such acids, bases and buffers are included in an amount required to maintain pH of the composition in an acceptable range.

[000213] In other embodiments, compositions can also include one or more salts in an amount required to bring osmolality of the composition into an acceptable range. Such salts include those having sodium, potassium or ammonium cations and chloride, citrate, ascorbate, borate, phosphate, bicarbonate, sulfate, thiosulfate or bisulfite anions; suitable salts include sodium chloride, potassium chloride, sodium thiosulfate, sodium bisulfite and ammonium sulfate.

[000214] The pharmaceutical compositions described herein can be formulated into any suitable dosage form, including but not limited to, aqueous oral dispersions, liquids, gels, syrups, elixirs, slurries, suspensions and the like, for oral ingestion by an individual to be treated, solid oral dosage forms, aerosols, controlled release formulations, fast melt formulations, effervescent formulations, lyophilized formulations, tablets, powders, pills, dragees, capsules, delayed release formulations, extended release formulations, pulsatile release formulations, multiparticulate formulations, and mixed immediate release and controlled release formulations. In some embodiments, the pharmaceutical compositions are formulated into capsules. In some embodiments, the pharmaceutical compositions are formulated into solutions (for example, for IV administration). In some cases, the pharmaceutical composition is formulated as an infusion. In some cases, the pharmaceutical composition is formulated as an injection.

[000215] The pharmaceutical solid dosage forms described herein optionally include a compound described herein and one or more pharmaceutically acceptable additives such as a compatible carrier, binder, filling agent, suspending agent, flavoring agent, sweetening agent, disintegrating agent, dispersing agent, surfactant, lubricant, colorant, diluent, solubilizer, moistening agent, plasticizer, stabilizer, penetration enhancer, wetting agent, anti-foaming agent, antioxidant, preservative, or one or more combination thereof.

[000216] In still other aspects, using standard coating procedures, such as those described in Remington's Pharmaceutical Sciences, 20th Edition (2000), a film coating is provided around the compositions. In some embodiments, the compositions are formulated into particles (for example for administration by capsule) and some or all of the particles are coated. In some embodiments, the compositions are formulated into particles (for example for administration by capsule) and some or all of the particles are microencapsulated. In some embodiments, the compositions are formulated into particles (for example for administration by capsule) and some or all of the particles are not microencapsulated and are uncoated.

[000217] In certain embodiments, compositions provided herein can also include one or more preservatives to inhibit microbial activity. Suitable preservatives include mercury-

containing substances such as merfen and thiomersal; stabilized chlorine dioxide; and quaternary ammonium compounds such as benzalkonium chloride, cetyltrimethyl ammonium bromide and cetylpyridinium chloride.

[000218] In some cases, one or more agents provided herein, e.g., one or more antibodies or antigen-binding fragments thereof, e.g., HCA/LCA antibody or antigen-binding fragment thereof are given as soon as possible after positive results of direct viral testing and within 10 days of symptom onset. In some cases, an agent provided herein, e.g., an antibody or antigen-binding fragment thereof, e.g., HCA/LCA antibody or antigen-binding fragment thereof is administered in a pharmaceutical preparation comprising the agent and one or more of (e.g., 1, 2, 3, 4, or 5 of) L-histidine, L-histidine monohydrochloride, L-methionine, polysorbate 80, or sucrose.

[000219] The agents provided herein, e.g., antibodies or antigen-binding fragments thereof, e.g., HCA/LCA antibody or antigen-binding fragment thereof can be administered by subcutaneous injection or intravenous infusion. The agents provided herein, e.g., antibodies or antigen-binding fragments thereof, e.g., HCA/LCA antibody or antigen-binding fragment thereof can also be administered to a subject who will experience ongoing exposure to the virus (e.g., SARS-CoV-2 or SARS-CoV-1), and who is not expected to mount an adequate immune response to complete vaccination for the virus. In such cases, after the first administration of one or more agents provided herein, e.g., an antibody or antigen-binding fragment thereof, e.g., HCA/LCA antibody or antigen-binding fragment thereof, administration by subcutaneous injection or intravenous infusion can occur once every 4 weeks for the duration of ongoing exposure.

[000220] In some cases, one or more agents provided herein, e.g., an antibody or antigen-binding fragment thereof, e.g., HCA/LCA antibody or antigen-binding fragment thereof are administered as a single intravenous (IV) infusion of 500 mg. In some cases, one or more agents provided herein, e.g., one or more antibodies or antigen-binding fragments thereof, e.g., HCA/LCA antibody or antigen-binding fragment thereof is provided in a single-dose vial and can be diluted prior to administration. For example, the dose can be diluted using a Polyvinyl chloride (PVC) or polyolegin (PO), sterile, prefilled 50-mL or 100-mL infusion bag containing, e.g., sodium chloride, e.g., 0.9% Sodium Chloride. The dose can be diluted with a PVC, sterile, prefilled 50-mL or 100-mL infusion bag containing dextrose injection, e.g., 5% Dextrose Injection.

EMBODIMENTS

[000221] The following non-limiting embodiments provide illustrative examples of the invention, but do not limit the scope of the invention.

[000222] Embodiment 1. An agent capable of capable of neutralizing a SARS-CoV-2 infection with a half maximal inhibitory concentration (IC50) of less than 0.4 μg/mL or an IC90 of less than 1 μg/mL, wherein the SARS-CoV-2 comprises a spike protein with one or more of A67V, Δ69-70, T95I, Δ211/L212I, ins214EPE, G339D, S371L, S373P, S375F, N440K, G446S, S477N, E484A, Q493R, G496S, Q498R, Y505H, T547K, N679K, N764K, D796Y, N856K, Q954H, N969K, or L981F, wherein the amino acid positions are relative to the amino acid positions as set forth in SEQ ID NO: 1.

[000223] Embodiment 2. The agent of Embodiment 1, wherein the SARS-CoV-2 comprises a spike protein comprising A67V, Δ69-70, T95I, G142D/Δ143-145, Δ211/L212I, ins214EPE. G339D, S371L, S373P, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493R, G496S, Q498R, N501Y, Y505H, T547K, D614G, H655Y, N679K, P681H, N764K, D796Y, N856K, Q954H, N969K, and L981F, wherein the amino acid positions are relative to the amino acid positions as set forth in SEQ ID NO: 1.

[000224] Embodiment 3. An agent capable of independently neutralizing SARS-CoV-2 B.1.1.529 (Omicron), SARS-CoV-2 (Epsilon), SARS-CoV-2 (Iota), SARS-CoV-2 (Eta), SARS-CoV-2 (Delta), SARS-CoV-2 (Gamma), SARS-CoV-2 (Beta), and SARS-CoV-2 (Alpha) infections in a subject with an average IC50 of less than 900 ng/mL.

[000225] Embodiment 4. An agent capable of independently i) binding SARS-CoV and ii) blocking SARS-CoV-2 binding to angiotensin-converting enzyme 2 (ACE2).

[000226] Embodiment 5. The agent of Embodiment 4, wherein the agent is capable of binding SARS-CoV spike protein.

[000227] Embodiment 6. The agent of claim Embodiment 5, wherein the agent is capable of binding SARS-CoV spike protein S1 domain.

[000228] Embodiment 7. The agent of Embodiments 4 through 6, wherein the agent is capable of blocking SARS-CoV-2 spike protein from binding to ACE2.

[000229] Embodiment 8. The agent of Embodiment 7, wherein the agent is capable of blocking SARS-CoV-2 spike protein S1 domain from binding to ACE2.

[000230] Embodiment 9. The agent of Embodiment 8, wherein the agent is capable of blocking SARS-CoV-2 spike protein S1 domain receptor binding domain (RBD) from binding to ACE2.

[000231] Embodiment 10. The agent of any one of Embodiments 4 through 9, wherein the agent is capable of specifically binding the SARS-CoV or SARS-CoV-2.

[000232] Embodiment 11. An agent capable of neutralizing the SARS-CoV with an IC50 of less than 0.05 μg/mL.

[000233] Embodiment 12. An agent that specifically binds SARS- CoV-2 spike protein S1 domain, wherein an ability of the agent to bind SARS- CoV-2 spike protein S1 domain is reduced by a mutation at position 378, 408, or 414, wherein the position 378, 408, or 414 is relative to positions of sequences set forth in SEQ ID NO: 1.

[000234] Embodiment 13. The agent of Embodiment 12, wherein the mutation is K378A, R408A, or Q414A.

[000235] Embodiment 14. The agent of any one of Embodiment 1 through 13, wherein the agent comprises an antibody or antigen-binding fragment thereof.

[000236] Embodiment 15. The agent of Embodiment 14, wherein the antibody or antigen-binding fragment thereof is a chimeric antigen receptor (CAR).

[000237] Embodiment 16. The agent of any one of Embodiments 1-15, wherein the agent comprises an antibody, or antigen-binding fragment thereof, comprising

a. a heavy chain complementarity determining region (CDR)1 (HCDR1), HCDR2, and HCDR3 and/or a light chain CDR1 (LCDR1), LCDR2 and LCDR3, wherein the HCDR1, the HCDR2, and the HCDR3 comprise amino acid sequences set forth in SEQ ID NO: 6, SEQ ID NO: 7, and SEQ ID NO: 8, respectively, and the LCDR1, the LCDR2, and the LCDR3 comprise the amino acid sequences set forth in SEQ ID NO: 9, SEQ ID NO: 10, and SEQ ID NO: 11, respectively;

b. a heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 12, or an amino acid sequence comprising at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence set forth in SEQ ID NO: 12 and/or 2) a light chain comprising the amino acid sequence set forth in SEQ ID NO: 15, or an amino acid sequence comprising at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence set forth in SEQ ID NO: 15; or

c. a heavy chain variable region (VH) comprising the amino acid sequence set forth in SEQ ID NO: 13, or an amino acid sequence comprising at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence set forth in SEQ ID NO: 13 and/or 2) a light chain variable region (VL) comprising the amino acid sequence set forth in SEQ ID NO: 16, or an amino acid sequence comprising at least 80%, 85%, 90%,

91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence set forth in SEQ ID NO: 16.

[000238] Embodiment 17. A pharmaceutical composition comprising the agent of any one of Embodiments 1 through 16 and a pharmaceutically acceptable carrier.

[000239] Embodiment 18. A nucleic acid molecule encoding the agent of any one of Embodiments 1 through 16.

[000240] Embodiment 19. A vector comprising the nucleic acid molecule of Embodiment 18.

[000241] Embodiment 20. A host cell comprising the vector of Embodiment 19.

[000242] Embodiment 21. A kit comprising the agent of any one of Embodiments 1 through 16 and instructions.

EXAMPLES

Preparation of controls

[000243] For these examples, competitor control antibodies Casirivimab and Imdevimab (ProteoGenix, Schiltigheim, France) as well as sotrovimab (Abpro, Woburn, MA, USA) were produced at the aforementioned institutions using the sequence of each antibody as obtained from The United States Adopted Name Council of the American Medical Association.

EXAMPLE 1. ACE2 competition assay

[000244] Given that the HCA/LCA antibody can bind the spike protein RBD (**FIG. 1**), and a major therapeutic mechanism SARS-CoV-2 nAbs is preventing spike protein binding to ACE2, the ability of the HCA/LCA antibody to block the spike protein RBD-ACE2 interaction was compared to casarivimab, imdevimab, and sotrovimab. This ability of the HCA/LCA antibody to block the ACE-2-RBD interaction was confirmed using an in vitro ACE2 competition assay using the indicated mutant variant RBDs (**FIG. 2**). The cocktail of casarivimab and imdevimab (REGN-COV2) also blocked the ACE2-spike protein interaction (**FIG. 2**) consistent with published results (Hansen, 2020). Unlike the other nAbs evaluated in this study, sotrovimab did not compete with ACE2 for spike protein binding, consistent with previous studies evaluating S309, the parental antibody to sotrovimab (**FIG. 2**) (Pinto, 2020).

[000245] The competition reaction was tested by using the SARS-CoV-2 variant inhibitor screening Kit (R&D VANC00) according to the manufacturer's instruction to assess whether the selected antibodies can compete with ACE2 for RBD binding. Briefly, 96 well plates were coated with His-Tag capture antibody and incubated at 4°C overnight then blocked with 1% BSA in

PBS for 1 hour at 37°C. Afterward recombinant SARS-Cov-2 wild type spike protein RBD or mutant variants were immobilized onto His-Tag capture antibody-coated plates for an additional of 1 hour at room temperature. Serial dilutions of the selected antibodies were loaded in duplicates and incubated for 1 hour at room temperature, followed by the addition of biotinylated human ACE2. Then Streptavidin-HRP was added, and the plates were developed using substrate solution, followed by sulfuric acid addition to stop the reaction. The plates were read at 450 nm by SpectraMax iD3 Multi-Mode Microplate Reader manufactured by Molecular Devices to determine the results.

[000246] To calculate the percentage of ACE2 binding, the average nonspecific binding was subtracted from each point and divided by RBD only control value and multiplied by 100: %ACE2 Binding= $[(OD_{sample} - OD_{NSB}) / (OD_{RBD\ only} - OD_{NSB})] \times 100$

[000247] **FIG. 2** provides the results of this assay. ACE2-competition ELISA using indicated antibodies at concentrations given by the horizontal axis. For REGN-COV-2, casarivimab and imdevimab were added at an equimolar ratio summing to the concentration given on the horizontal axis.

[000248] **Results:** This ability of the HCA/LCA antibody to block the ACE-2-RBD interaction was confirmed using an in vitro ACE2 competition assay using the indicated mutant variant RBDs (**FIG. 2**). The cocktail of casarivimab and imdevimab (REGN-COV2) also blocked the ACE2-spike protein interaction (**FIG. 2**) consistent with published results (Hansen, 2020). Unlike the other nAbs evaluated in this study, sotrovimab did not compete with ACE2 for spike protein binding, consistent with previous studies evaluating S309, the parental antibody to sotrovimab (Fig. 2) (Pinto, 2020).

EXAMPLE 2. Bead-based multiplex assay method for SARS-CoV-2 spike protein binding

[000249] Given the failure of many current nAbs to effectively neutralize SARS-CoV-2 mutant variants, the present experiment was used to assess ability of the HCA/LCA antibody to bind SARS-CoV-2 spike protein domains bearing a variety of mutations found in variants of concern or those associated with reduced nAb efficacy or enhanced infectivity, such as N234Q, K417N, N440K, K444R, L452R, E484K, F490L, S494P, and D614G (Li, 2020; Grabowski, 2021; Harvey, 2021; Rani, 2021). In addition, the ability of the HCA/LCA antibody to bind the S1 domain of the spike proteins from MERS-CoV and SARS-CoV was assessed. The expressed sequences of casarivimab, imdevimab, and sotrovimab were used as comparator controls.

[000250] A custom assay was designed using Magplex-Avidin microspheres (Luminex), which were coated in anti-HIS antibody [Biotin] (GenScript A00613, mouse IgG1k clone 6G2A9) at 2.5 ug/mL, washed, and then each microsphere was coated with 2.5 ug/mL of either

SARS-CoV-1 S1-HIS, MERS S1-HIS, and SARS-CoV-2 S1-HIS or SARS-CoV-2 RBD-HIS variant proteins (Sino Biological) to create bead stocks. For the antibody binding assay, test antibodies were diluted in PBS/1% BSA starting at 10 ug/mL (2x concentrations) and then five-fold on U-bottom plates, for a total of eight dilutions. 50 uL/well of antibody was added to a 96-well plate (Greiner Bio-One 655096). A master stock of microspheres was created in PBS/1% BSA to allow 2000 beads/analyte/well, vortexed, and 50 uL/well was added to the assay plate.

[000251] Antibodies were incubated with microspheres for 30 minutes at RT with shaking at 300 rpm; washed 3x with PBS, then Goat anti-Human IgG Fc Secondary Antibody PE, eBioscience (Thermo Fisher Scientific 12-4998-82) with minimal cross-reactivity to bovine/horse/mouse serum proteins), was used at a 1:200 dilution in PBS/1% BSA, used at 100uL/well . After incubating for 30 minutes, wells were washed 3x with PBS, and the plate was read on the Magpix (Luminex) instrument. Median Fluorescence Intensity (MFI) was used to quantify binding of antibodies to each protein in the panel. See **TABLE 1** for the HIS-tagged proteins used in the assay.

[000252] **FIG. 1** provides binding strengths as demonstrated by the Luminex binding assay. The left axis of each heat map represents the concentration of antibody dilution, the bottom axis describes the spike protein (with mutations indicated) that are used for each column, and the right axis represents the intensity of binding in relative light units (RLU). **FIG. 1** supports the conclusion that the HCA/LCA antibody can bind receptor binding domain and neutralize another species of the SARS-CoV-2 virus (e.g., the SARS-CoV of the 2003 epidemic).

[000253] **Results:** All antibodies assessed displayed strong binding activity against all SARS-CoV-2 mutants tested, with the exception of a marked reduction in binding of casarivimab to Beta (Fig. 1), which is consistent with the previously reported reduced neutralization activity of casarivimab to this variant (Wang, 2021). The only antibodies assayed that displayed binding to either SARS-CoV or MERS-CoV were sotrovimab, a nAb derived from a memory B cell screen of a patient infected with SARS-CoV in 2003 (Traggiai, 2004; Rockx, 2008; Rockx, 2010), and the HCA/LCA antibody, both showing binding to SARS-CoV but not MERS-CoV (**FIG. 1**).

Table 1. Multiplex binding assay:

Sino Biological spike protein (S1 or RBD, with C-terminal HIS-tag)

Label in Figure	Sino Biological Catalog#	Product Name	Stock concentration	Magplex Avidin (Luminex) Bead Region	Sino Biological Lot#
MERS S1	40591-V08H	(AFS88936.1)(Met1-	0.25	25	LC14NO0903
SARS S1	40591-V08B1	SARS-CoV S1	0.37	18	MF14AP1801
D614G S1	40591-V08H3	SARS-CoV-2 Spike	3.58	12	MB14JU1490

N234Q S1	40591-V08H11	SARS-CoV-2 Spike	0.29	74	MB14DE0801
Alpha S1	40591-V08H12	SARS-CoV-2 Spike S1	1.4	14	MB15JA1209
Beta S1	40591-V08H10	SARS-CoV-2 Spike	0.25	15	LC15JA2613
N439K S1	40591-V08H9	SARS-CoV-2 Spike	0.25	27	LC15JA2710
Y453F S1	40591-V08H8	SARS-CoV-2 Spike	0.96	33	MC15JA0511
Delta S1	40591-V08H23	SARS-CoV-2 Spike	0.25	78	LC15JU2313
Wuhan RBD WT	40592-V08H	SARS-CoV-2 Spike	0.25	37	LC14JU1207
K417N RBD	40592-V08H59	SARS-CoV-2 Spike	0.25	72	LC15JA1512
N440K RBD	40592-V08H55	SARS-CoV-2 Spike	0.25	76	LC14SE1510
K444R RBD	40592-V08H54	SARS-CoV-2 Spike	0.25	35	LC15JA1911
L452R RBD	40592-V08H28	SARS-CoV-2 Spike	0.15	44	LC14SE1505
E484K RBD	40592-V08H84	SARS-CoV-2 Spike	0.71	39	MC15JA1122
F490L RBD	40592-V08H83	SARS-CoV-2 Spike	0.26	48	MC14DE0602
S494P RBD	40592-V08H18	RBD-His tag (S494P)	0.25	61	LC14SE0301

EXAMPLE 3. Pseudovirus neutralization assays

[000254] Using a SAR-CoV-2 spike pseudotyped viral neutralization assay, the neutralizing activity of each antibody against the indicated SARS-CoV-2 viral variants or SARS-CoV was determined. All antibodies were assayed for neutralization activity against viruses pseudotyped with a variety of SARS-CoV-2 spike proteins including the original Wuhan isolate, all of the current (as of December 2021) WHO variants of concern (Alpha, Beta Gamma, Delta, and Omicron) (**FIG. 3, FIG. 4, TABLE 1, TABLE 2**) and major variants of interest as of September 2021 (Epsilon, Eta, Iota).

[000255] As indicated by **FIG. 3**, the HCA/LCA antibody is capable of neutralizing all WHO SARS-CoV-2 variants of concern and all variants of interest tested. As indicated by **FIG. 4**, the HCA/LCA antibody can bind receptor binding domain and neutralize another species of the SARS-CoV-2 virus (e.g., the SARS-CoV of the 2003 epidemic).

[000256] SARS-CoV-2 antibodies were tested for neutralization of Pseudovirus particles expressing the wild type spike protein of SARS-CoV, SARS-CoV-2, or variants thereof (Integral Molecular, see Attachment 2) according to manufacturer's protocol. Briefly, the recommended amount of particles/well were incubated in DMEM + 10% FBS with varying amounts of serially-diluted antibody for 1 hour at 37°C, and then 20,000 ACE2-HEK293T cells (Integral Molecular,

see attachment 3) were added. Neutralization of infection was assessed using Renilla-Glo Luciferase Assay kit (Promega) after an incubation of 48-72 hours. Results were analyzed in GraphPad PRISM and IC50 values were determined for individual antibodies.

[000257] **TABLE 2** (below) provides pseudoviral particles for neutralization assays expressing coronavirus spike protein. The SARS-CoV-2 ("WT") spike protein, which has GenBank accession number QHD43416.1, had **SEQ ID NO. 1**

(MFVFLVLLPLVSSQCVNLTTRTQLPPAYTNSFTR
GVYYPDKVFRSSVLHSTQDLFLPFFSNVTWFHAIHVSGTNGTKRFDNPVLPFNDGVYFA
STEKSNIIRGWIFGTTLDSKTQSLLIVNNATNVVIKVCEFQFCNDPFLGVYYHKNNKSWM
ESEFRVYSSANNCTFEYVSQPFLMDLEGKQGNFKNLREFVFKNIDGYFKIYSKHTPINLV
RDLPQGFSALEPLVDLPIGINITRFQTLLALHRSYLTPGDSSSGWTAGAAAYYVGYLQPR
TFLLKYNENGTITDAVDCALDPLSETKCTLKSFTVEKGIYQTSNFRVQPTESIVRFPNITNL
CPFGEVFNATRFASVYAWNRKRISNCVADYSVLYNSASFSTFKCYGVSPTKLNDLCFTN
VYADSFVIRGDEVRQIAPGQTGKIADYNYKLPDDFTGCVIAWNSNNLDSKVGGNYNYL
YRLFRKSNKPFERDISTEIYQAGSTPCNGVEGFNCYFPLQSYGFQPTNGVGYQPYRVVVL
SFELLHAATVCGPKKSTNLVKNKCVNFNFNGLTGTGVLTESNKKFLPFQQFGRDIADTT
DAVRDPQTLEILDITPCSFGGVSVITPGTNTSNQVAVLYQDVNCTEVPVAIHADQLTPTW
RVYSTGSVFQTRAGCLIGAEHVNNSYECDIPIGAGICASYQTQTNSPRRARSVASQSIIAY
TMSLGAENSVAYSNNSIAIPTNFTISVTTEILPVSMTKTSVDCTMYICGDSTECSNLLLQY
GSFCTQLNRALTGIVEQDKNTQEVFAQVKQIYKTPPIKDFGGFNFSQILPDPSKPSKRSFIE
DLLFNKVTLADAGFIKQYGDCLGDIAARDLICAQKFNGLTVLPPLLTDEMIAQYTSALLA
GTITSGWTFGAGAALQIPFAMQMAYRFNGIGVTQNVLYENQKLIANQFNSAIGKIQDSLS
STASALGKLQDVVNQNAQALNTLVKQLSSNFGAISSVLNDILSRLDKVEAEVQIDRLITG
RLQSLQTYVTQQLIRAAEIRASANLAATKMSECVLGQSKRVDFCGKGYHLMSFPQSAPH
GVFLHVTYVPAQEKNFTTAPAICHDGKAHFPREGVFVSNGTHWFVTQRNFYEPQIITTD
NTFVSGNCDVVIGIVNNTVYDPLQPELDSFKEELDKYFKNHTSPDVDLGDISGINASVVN
IQKEIDRLNEVAKNLNESLIDLQELGKYEQYIKWPWYIWLGFIAGLIAIVMVTIMLCCMT
SCCSCLKGCCSCGSCCKFDEDDSEPVLKGVKLHYT).

[000258] The SARS-CoV-1 spike protein, which has GenBank accession number AAP13441.1, is the sequence set forth in **SEQ ID NO. 2**

(MFIFLLFLTLTSGSDLDRCTTFDDVQAPNYTQHTS
SMRGVYYPDEIFRSDTLYLTQDLFLPFYSNVTGFHTINHTFGNPVIPFKDGIYFAATEKSN
VVRGWVFGSTMNNKSQSVIIINNSTNVVIRACNFELCDNPFFAVSKPMGTQTHTMIFDN
AFNCTFEYISDAFSLDVSEKSGNFKHLREFVFKNKDGFLYVYKGYQPIDVVRDLPSGFNT
LKPIFKLPLGINITNFRAILTAFSPAQDIWGTSAAAYFVGYLKPTTFMLKYDENGTITDAV

DCSQNPLAELKCSVKSFEIDKGIYQTSNFRVVPSGDVVRFPNITNLCPFGEVFNATKFPSV
YAWERKKISNCVADYSVLYNSTFFSTFKCYGVSATKLNDLCFSNVYADSFVVKGDDVR
QIAPGQTGVIADYNYKLPDDFMGCVLAWNTRNIDATSTGNYNYKYRYLRHGKLRPFER
DISNVPFSPDGKPCTPPALNCYWPLNDYGFYTTTGIGYQPYRVVVLSFELLNAPATVCGP
KLSTDLIKNQCVNFNFNGLTGTGVLTPSSKRFQPFQQFGRDVSDFTDSVRDPKTSEILDIS
PCSFGGVSVITPGTNASSEVAVLYQDVNCTDVSTAIHADQLTPAWRIYSTGNNVFQTQA
GCLIGAEHVDTSYECDIPIGAGICASYHTVSLLRSTSQKSIVAYTMSLGADSSIAYSNNTIA
IPTNFSISITTEVMPVSMAKTSVDCNMYICGDSTECANLLLQYGSFCTQLNRALSGIAAEQ
DRNTREVFAQVKQMYKTPTLKYFGGFNFSQILPDPLKPTKRSFIEDLLFNKVTLADAGF
MKQYGECLGDINARDLICAQKFNGLTVLPPLLTDDMIAAYTAALVSGTATAGWTFGAG
AALQIPFAMQMAYRFNGIGVTQNVLYENQKQIANQFNKAISQIQESLTTTSTALGKLQD
VVNQNAQALNTLVKQLSSNFGAISSVLNDILSRLDKVEAEVQIDRLITGRLQSLQTYVTQ
QLIRAAEIRASANLAATKMSECVLGQSKRVDFCGKGYHLMSFPQAAPHGVVFLHVTYV
PSQERNFTTAPAICHEGKAYFPREGVFVFNGTSWFITQRNFFSPQIITTDNTFVSGNCDVVI
GIINNTVYDPLQPELDSFKEELDKYFKNHTSPDVDLGDISGINASVVNIQKEIDRLNEVAK
NLNESLIDLQELGKYEQYIKWPWYVWLGFIAGLIAIVMVTILLCCMTSCCSCLKGACSCG
SCCKFDEDDSEPVLKGVKLHYT).

[000259] The D614G pseudoviral particle spike protein has the sequence set forth in SEQ ID NO: 1 having mutation of D614G, wherein the positions are relative to the amino acid positions as set forth in SEQ ID NO: 1.

[000260] The Eta (Nigerian) strain spike protein has the sequence set forth in SEQ ID NO: 1 having mutations of Q52R, ΔH69/V70, ΔY144, E484K, D614G, Q677H, F888L, wherein the positions are relative to the amino acid positions as set forth in SEQ ID NO: 1.

[000261] The Iota strain's spike protein sequence has the sequence set forth in SEQ ID NO: 1 having mutations of: L5F, T95I, D253G, E484L, D614G, and A701V, wherein the positions are relative to the amino acids set forth in SEQ ID NO: 1.

[000262] The Beta strain's spike protein sequence has the sequence set forth in SEQ ID NO: 1 having mutations of L18F, D80A, D215G, ΔL242/A243/L244, R246I, K417N, N501Y, E484K, D614G, and A701V, wherein the positions are relative to the amino acids set forth in SEQ ID NO: 1.

[000263] The Indian "double mutant" strain has a spike protein of SEQ ID NO: 1 having mutations of L452R, 484Q, and D614G, wherein the positions are relative to the amino acids set forth in SEQ ID NO: 1.

[000264] The Epsilon variant spike protein sequence has the sequence set forth in SEQ ID NO: 1, which has the following mutations: S13I, W 152C, L452R, and D614G, wherein the positions are relative to the amino acids set forth in SEQ ID NO: 1.

[000265] The Alpha variant's spike protein has the sequence set forth in SEQ ID NO: 1 with the following mutations: ΔH69/V70, ΔY144, N501Y, A570D, D614G, P681H, T716I, S982A, and D1118H, wherein the positions are relative to the amino acids set forth in SEQ ID NO: 1.

[000266] The Gamma variant's spike protein has the sequence set forth in SEQ ID NO: 1 with the following mutations: L18F, T20N, P26S, D138Y, R190S, K417T, E484K, N501Y, D614G, H655Y, T1027I, and V1176F, wherein the positions are relative to the amino acids set forth in SEQ ID NO: 1.

[000267] The Delta variant's spike protein has the sequence set forth in SEQ ID NO: 1 with the following mutations: T19R, G142D, del156/157, R158G, L452R, T478K, D614G, P681R, D950N, wherein the positions are relative to the amino acids set forth in SEQ ID NO: 1.

[000268] The Omicron variant has a spike protein with the sequence set forth in SEQ ID NO: 1 having the following mutations: L18F, T20N, P26S, D138Y, R190S, K417T, E484K, N501Y, D614G, H655Y, T1027I, and V1176F, wherein the positions are relative to the amino acids set forth in SEQ ID NO: 1.

[000269] In some cases, an agent provided herein binds a sequence with at least 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the sequence set forth in SEQ ID NO: 1 or SEQ ID NO: 2.

[000270] In some cases, an agent provided herein binds a sequence with about, at least, or at most 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% identity to the sequence set forth in SEQ ID NO: 1 with one or more of mutations corresponding to A67V, Δ69-70, T95I, Δ211/L212I, ins214EPE, G339D, S371L, S373P, S375F, N440K, G446S, S477N, E484A, Q493R, G496S, Q498R, Y505H, T547K, N679K, N764K, D796Y, N856K, Q954H, N969K, and L981F, wherein the amino acid positions are relative to SEQ ID NO: 1 or SEQ ID NO: 2.

[000271] In some cases, an agent provided herein binds a sequence with about, at least, or at most 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% identity to the sequence set forth in SEQ ID NO: 1 with a mutation corresponding to D614G, wherein the amino acid positions are relative to SEQ ID NO: 1 or SEQ ID NO: 2.

[000272] In some cases, an agent provided herein binds a sequence with about, at least, or at most 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% identity to the sequence set forth in SEQ ID NO: 1 with one or more of mutations corresponding to Q52R,

ΔH69/V70, ΔY144, E484K, D614G, Q677H, and F888L, wherein the amino acid positions are relative to SEQ ID NO: 1 or SEQ ID NO: 2.

[000273] In some cases, an agent provided herein binds a sequence with about, at least, or at most 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% identity to the sequence set forth in SEQ ID NO: 1 with one or more of mutations corresponding to L5F, T95I, D253G, E484L, D614G, and A701V, wherein the amino acid positions are relative to SEQ ID NO: 1 or SEQ ID NO: 2.

[000274] In some cases, an agent provided herein binds a sequence with about, at least, or at most 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% identity to the sequence set forth in SEQ ID NO: 1 with one or more of mutations corresponding to L18F, D80A, D215G, ΔL242/A243/L244, R246I, K417N, N501Y, E484K, D614G, and A701V, wherein the amino acid positions are relative to SEQ ID NO: 1, wherein the amino acid positions are relative to SEQ ID NO: 1 or SEQ ID NO: 2.

[000275] In some cases, an agent provided herein binds a sequence with about, at least, or at most 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% identity to the sequence set forth in SEQ ID NO: 1 with one or more of mutations corresponding to L452R, E484Q, and D614G, wherein the amino acid positions are relative to SEQ ID NO: 1 or SEQ ID NO: 2.

[000276] In some cases, an agent provided herein binds a sequence with about, at least, or at most 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% identity to the sequence set forth in SEQ ID NO: 1 with one or more of mutations corresponding to S13I, W152C, L452R, and D614G, wherein the amino acid positions are relative to SEQ ID NO: 1 or SEQ ID NO: 2.

[000277] In some cases, an agent provided herein binds a sequence with about, at least, or at most 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% identity to the sequence set forth in SEQ ID NO: 1 with one or more of mutations corresponding to ΔH69/V70, ΔY144, N501Y, A570D, D614G, P681H, T716I, S982A, and D1118H, wherein the amino acid positions are relative to SEQ ID NO: 1 or SEQ ID NO: 2.

[000278] In some cases, an agent provided herein binds a sequence with about, at least, or at most 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% identity to the sequence set forth in SEQ ID NO: 1 with one or more of point mutations corresponding to L18F, T20N, P26S, D138Y, R190S, K417T, E484K, N501Y, D614G, H655Y, T1027I, V1176F, wherein the amino acid positions are relative to SEQ ID NO: 1 or SEQ ID NO: 2.

[000279] In some cases, an agent provided herein binds a sequence with about, at least, or at most 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% identity to the

sequence set forth in SEQ ID NO: 1 with one or more of point mutations corresponding to T19R, G142D, del156/157, R158G, L452R, T478K, D614G, P681R, and D950N, wherein the amino acid positions are relative to SEQ ID NO: 1 or SEQ ID NO: 2.

[000280] In some cases, an agent provided herein binds a sequence with about, at least, or at most 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% identity to the sequence set forth in SEQ ID NO: 1 with one or more of point mutations corresponding to A67V, Δ69-70, T95I, G142D /Δ143-145, Δ211/L212I, ins214EPE. G339D, S371L, S373P, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493R, G496S, Q498R, N501Y, Y505H, T547K, D614G, H655Y, N679K, P681H, N764K, D796Y, N856K, Q954H, N969K, and L981F, wherein the amino acid positions are relative to SEQ ID NO: 1 or SEQ ID NO: 2.

[000281] In some cases, an agent provided herein binds a sequence having about, at least, or at most 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% identity to SEQ ID NO: 1 with one or more of mutations at amino acid positions corresponding to Q52R, ΔH69/V70, ΔY144, E484K, D614G, Q677H, F888L, wherein the positions are relative to amino acid positions as set forth in SEQ ID NO: 1 or SEQ ID NO: 2.

[000282] In some cases, an agent provided herein binds a sequence with about, at least, or at most 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identity to SEQ ID NO: 1 or SEQ ID NO: 2 or to a fragment thereof.

Table 2. Pseudoviral particles for neutralization assays expressing coronavirus spike protein

Variant pseudoviral particle	Product (Integral Molecular)	Strain/variant name (Integral Molecular)	WHO	Strain/ Mutations	D614G?
SARS-CoV-1	RVP-801L	SARS-CoV-1 Urbani	-	-	No
SARS-CoV-2 ("WT")	RVP-701L	Wuahn-Hu-1	-	Reference seq (GenBank QHD43416.1)	No
D614G	RVP-702L	D614G B.1, 20A	-	D614G	Yes
Eta (Nigerian)	RVP-723L	Nigerian/European variant B.1.525, 20A/439K	Eta	Q52R, ΔH69/V70, ΔY144, E484K, D614G, Q677H, F888L	Yes
Iota (New York)	RVP-726L	New York variant B.1.536, 20C/484K	Iota	L5F, T95I, D253G, E484L, D614G, A701V	Yes
Beta (South African)	RVP-724L	South African variant Δ3 B.1.351, 20H/501Y.V2	Beta	L18F, D80A, D215G, ΔL242/A243/L244, R246I, K417N, N501Y, E484K, D614G, A701V	Yes
Indian "double mutant"	RVP-727L	Indian variant B.1.617, RBD mutations only ("double mutant")	-	L452R, E484Q, D614G	Yes
Epsilon (California)	RVP-713L	California variant B.1.427/B.1.429, 20C/452R	Epsilon	S13I, W 152C, L452R, D614G	Yes
Alpha (U.K.)	RVP-706L	UK variant B.1.1.7, 20I/501Y.V1	Alpha	ΔH69/V70, ΔY144, N501Y, A570D, D614G, P681H, T716I, S982A, D1118H	Yes
Gamma (Brazil/Japan)	RVP-708L	Brazilian variant P.1, 20J/501Y.V3	Gamma	L18F, T20N, P26S, D138Y, R190S, K417T, E484K, N501Y, D614G, H655Y, T1027I, V1176F	Yes
Delta	RVP-763L	Indian variant 1.617.2	Delta	T19R, G142D, del156/157, R158G, L452R, T478K, D614G, P681R, D950N	Yes

Omicron	RVP-7687L	Omicron Variant B.1.1.529	Omicron	A67V, Δ69-70, T95I, G142D/Δ143-145, Δ211/L212I, ins214EPE. G339D, S371L, S373P, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493R, G496S, Q498R, N501Y, Y505H, T547K, D614G, H655Y, N679K, P681H, N764K, D796Y, N856K, Q954H, N969K, L981F	Yes

[000283] **TABLE 3** provides a depiction of the cell line used for the pseudovirus assays.

Table 3

C-HA102	HsACE2	Stable	Monoclonal	HEK293T

[000284] The neutralization potency of each antibody was typically quantified by the inhibitory concentration (IC) values. These are provided in **FIG. 3** and **FIG. 4**. See **FIG. 3** for the resulting comparison of pseudovirus neutralization activity of the HCA/LCA antibody and casarivimab and imdevimab, which is provided in terms of percent neutralization and concentration of antibody (μg/mL). **FIG. 4** provides the resulting comparison of pseudovirus neutralization activity of the HCA/LCA antibody and sotrovimab, which is also provided in terms of percent neutralization and concentration of (μg/mL). An X indicates that antibody concentration was not tested. **FIG. 5** compares the concentration of each antibody versus percent neutralization. **FIG. 5** highlights the ability of the HCA/LCA antibody to neutralize SARS-CoV.

[000285] **TABLE 4** provides IC_{50} values for SARS-CoV and indicated SARS-CoV-2 variants and fold difference from wild type IC_{50} and fold difference across all covered variants for indicated antibodies compared to the HCA/LCA antibody. **TABLE 5** provides IC_{90} values for SARS-CoV and indicated SARS-CoV-2 variants and fold difference from wild type IC_{90} and fold difference across all covered variants for indicated antibodies compared to the HCA/LCA antibody.

Table 4. Neutralization IC_{50} values of neutralizing antibodies against indicated pseudotyped viruses

		REGN 10933 (casirivimab)		REGN 10987 (imdevimab)		VIR-7831 (sotrovimab)		HCA/LCA antibody	
Virus/ Variant	**WHO designation**	**IC_{50} (μg/mL)**	**Fold difference from Wuhan-Hu-1**	**IC_{50} (μg/mL)**	**Fold difference from Wuhan-Hu-1**	**IC_{50} (μg/mL)**	**Fold difference from Wuhan-Hu-1**	**IC_{50} (μg/mL)**	**Fold difference from Wuhan-Hu-1**
SARS-CoV	-	IC	-	NA	-	0.064	-	0.031	-
Wild type (Wuhan-Hu-1)	-	0.024	-	0.023	-	3.819	-	0.028	-
B.1.1.6, 20I/501Y.V1	Alpha	0.026	1.065	0.003	0.146	0.693	0.181	0.030	1.043

B.1.351, 20H/501Y.V2	Beta	1.733	71.025	0.010	0.429	0.192	0.050	0.162	5.717
P.1, 20J/501Y.V3	Gamma	2.189	89.713	0.010	0.418	0.073	0.019	0.088	3.101
B.1.617.2	Delta	0.016	0.649	0.081	3.494	0.501	0.131	0.065	2.286
B.1.525, 20A/439K	Eta	0.055	2.261	0.022	0.929	NT	-	0.071	2.500
B.1.526, 20C/484K	Iota	0.116	4.750	0.018	0.789	NT	-	0.066	2.338
B.1.427/B.1.429, 20C/452R	Epsilon	0.027	1.092	0.018	0.766	NT	-	0.050	1.764
B.1.1.529	Omicron	NA*	-	NA*	-	0.453	0.119	0.183	6.470

NA: No activity; NT: Not tested; IC: IC50 was not able to be calculated.
*For Omicron, REGN10933 and REGN10987 were not tested as individual antibodies, but were tested as a cocktail at a 1:1 molar ratio for each nAb.

Table 5. Neutralization IC_{90} values of neutralizing antibodies against indicated pseudotyped viruses

		REGN 10933 (casirivimab)		REGN 10987 (imdevimab)		VIR-7831 (sotrovimab)		HCA/LCA antibody	
Virus/ Variant	**WHO designation**	**IC_{90} (µg/mL)**	**Fold difference from Wuhan-Hu-1**	**IC_{90} (µg/mL)**	**Fold difference from Wuhan-Hu-1**	**IC_{90} (µg/mL)**	**Fold difference from Wuhan-Hu-1**	**IC_{90} (µg/mL)**	**Fold difference from Wuhan-Hu-1**
SARS-CoV	-	IC	-	NA	-	-[1]	-	0.233	-
Wild type (Wuhan-Hu-1)	-	.136	-	0.319	-	138.900	-	0.163	-
B.1.1.6, 20I/501Y.V1	Alpha	0.237	1.747	0.029	0.092	12.970	0.093	0.053	0.329
B.1.351, 20H/501Y.V2	Beta	13.940	102.575	0.093	0.290	0.650	0.005	0.696	4.280
P.1, 20J/501Y.V3	Gamma	27.330	201.104	0.060	0.187	0.515	0.004	0.551	3.391
B.1.617.2	Delta	0.098	0.724	0.504	1.579	2.920	0.021	0.179	1.104
B.1.525, 20A/439K	Eta	0.480	3.530	0.275	0.0863	NT	-	0.201	1.239
B.1.526, 20C/484K	Iota	1.217	8.955	0.217	0.680	NT	-	0.237	1.461
B.1.427/B.1.429, 20C/452R	Epsilon	0.189	1.387	0.228	0.714	NT	-	0.176	1.084
B.1.1.529	Omicron	NA*	-	NA*	-	4.915	0.035	0.798	4.908

NA: No activity; NT: Not tested; [1]Sotrovimab did not achieve 90% neutralization for SARS-CoV. IC: IC90 aws not able to be calculated. IC: IC90 was not able to be calculated.
*REGN10933 and REGN10987 were not tested as individual antibodies, but were tested as a cocktail at a 1:1 molar ratio for each nAb.

Results

[000286] All antibodies were assayed for neutralization activity against viruses pseudotyped with a variety of SARS-CoV-2 spike proteins including the original Wuhan isolate, all of the current (as of December 2021) WHO variants of concern (Alpha, Beta Gamma, Delta, and Omicron) (**FIG. 3, FIG. 4, TABLE 4, TABLE 5**) and major variants of interest as of September 2021 (Epsilon, Eta, Iota). Casirivimab displayed a 71-fold reduction in neutralization potency (IC_{50}) against the Beta variant (**TABLE 4**) compared to the original Wuhan virus, consistent with previous data (Wang, 2021), as well as an 89-fold reduced neutralization potency against the Gamma variant (**TABLE 4**). The HCA/LCA antibody, like sotrovimab, displayed neutralization ability against all SARS-CoV-2 variants tested (Fig. 3 and 4, **TABLE 4**, **TABLE 5**) with the HCA/LCA antibody displaying a mean IC_{50} (93 ng/mL) across commonly tested variants 10.3-fold more potent than sotrovimab (mean IC_{50}: 955 ng/mL) and 8.5-fold more potent than casarivimab (mean IC_{50}: 798 ng/mL). While the HCA/LCA antibody is 3.6-fold less potent than imdevimab (mean IC50: 26 ng/mL) among the variants they commonly neutralize, neither casarivimab nor imdevimab are able to neutralize Omicron. However, both the HCA/LCA antibody and sotrovimab neutralize Omicron, with the HCA/LCA antibody being 2.5-fold more potent sotrovimab (IC_{50}: 0.183 vs 0.453 μg/mL, respectively) (**FIG. 4, TABLE 4**). In addition, the HCA/LCA antibody, like sotrovimab, but unlike casarivimab and imdevimab, exhibits neutralization activity against SARS-CoV (**FIG. 5, TABLE 4, TABLE 5**), with the HCA/LCA antibody displaying a 2-fold more potent neutralization IC_{50} for SARS-CoV compared to sotrovimab. As sotrovimab achieved a maximum SARS-CoV neutralization of approximately 75%, a comparison with the IC_{90} of the HCA/LCA antibody could not be made. It should be noted that while casarivimab displayed detectable neutralization against SARS-CoV (**FIG. 5, TABLE 4**), it was at least 500-fold weaker in potency compared to the HCA/LCA antibody (HCA/LCA antibody IC_{50}: 31 ng/mL vs. casarivimab IC_{50}: >16,800 ng/mL) (**FIG. 5, TABLE 4**).

[000287] As both the Lily and Regeneron cocktails have failed against Omicron (Cao, 2021; Planas, 2021) (see also **Example 3, TABLE 4** and **TABLE 5; FIG. 3**), sotrovimab remains the only nAb effective against Omicron currently under EUA. The HCA/LCA antibody and sotrovimab were able to neutralize Omicron. The weak but detectable neutralizing activity observed for casarivimab against SARS-CoV (**FIG. 5**) is curious in light of the lack of observed binding of casarivimab to the SARS-CoV spike protein (**FIG. 2**). It should be pointed out that the maximum concentrations examined were 5 mg/mL and 100 mg/mL for the Luminex binding and pseudovirus neutralization assays, respectively, thus the lack of binding observed in the Luminex assay can be a result of testing insufficiently high concentrations of antibody. However, as the SARS-CoV neutralizing IC_{50} for casarivimab is at least 11-fold less potent than

for soluble ACE2 (data not shown), it is questionable if casarivimab would be an effective therapeutic against SARS-CoV or other related coronaviruses existing or yet to evolve. In contrast, the potent ability of the HCA/LCA antibody to neutralize SARS-CoV is reflected in its 49-fold more potent neutralizing IC_{50} than soluble ACE2 (data not shown).

[000288] As indicated by lentiviral-based SARS-CoV-2 spike protein pseudovirus neutralization system using ACE2-transgenic HEK-293T cells, sotrovimab achieved a mean maximum neutralization of 92% across the SARS-CoV-2 variants tested with activity against most variants being greater than 98% (**FIG. 4**), consistent with published live virus assays and pseudovirus assays performed with VeroE6 cells where maximum neutralization also approached 100% (Chen, 2021; Lempp, 2021). As the use of ACE2-overexpressing cell lines in live virus neutralization assays (Chen, 2021; Lempp, 2021; Planas, 2021) or our lentiviral-based pseudovirus neutralization assay does not appear to adversely affect the efficacy or potency of S309 or sotrovimab, the choice of pseudovirus system (e.g., VSV, MLV, Lentiviral) for neutralization assays appears to be crucial for effective in vitro evaluation of nAbs, especially those binding epitopes outside the RBM. Taken together, the presence of high ACE2-expressing cells throughout the upper and lower respiratory tracks and well as the ability of sotrovimab to potently neutralize virus using target cells expressing high levels of ACE2 suggests that the use of target cell lines with low ACE2 expression instead of underestimating, can be overestimating the potency and efficiency of non-RBM binding antibodies. In practice, so long as the overestimation is modest, the effect on clinical efficacy can be negligible. For sotromivab, the 500mg dose (FDA Fact sheet for sotrovimab) would result in peak plasma concentrations in a 60kg person of approximately 119 µg/mL, which is 40-250-fold higher than reported IC50 values against wild type SARS-CoV-2 from a wide variety of assay formats (Pinto, 2020; Chen, 2021) (**TABLE 4**).

[000289] The weak but detectable neutralizing activity observed for casarivimab against SARS-CoV (**FIG. 5**) is curious in light of the lack of observed binding of casarivimab to the SARS-CoV spike protein (**FIG. 2**). It should be pointed out that the maximum concentrations examined were 5 mg/mL and 100 mg/mL for the Luminex binding and pseudovirus neutralization assays, respectively, thus the lack of binding observed in the Luminex assay can be a result of testing insufficiently high concentrations of antibody. However, as the SARS-CoV neutralizing IC_{50} for casarivimab is at least 11-fold less potent than for soluble ACE2 (data not shown), it is questionable if casarivimab would be an effective therapeutic against SARS-CoV or other related coronaviruses existing or yet to evolve. In contrast, the potent ability of the HCA/LCA antibody to neutralize SARS-CoV is reflected in its 49-fold more potent neutralizing IC_{50} than soluble ACE2 (data not shown).

EXAMPLE 4. Alanine Scanning via shotgun mutagenesis

[000290] SARS-CoV-2 spike protein (Wuhan isolate; accession YP_009724390.1) was used as the reference sequence for numbering the position of amino acid residues.

[000291] Shotgun Mutagenesis epitope mapping services were provided by Integral Molecular (Philadelphia, PA) as previously described (Davidson, 2014). Briefly, a mutation library of the target protein was created by high-throughput, site-directed mutagenesis. Each residue was individually mutated to alanine, with alanine codons mutated to serine. The mutant library was arrayed in 384-well microplates and transiently transfected into HEK-293T cells. Following transfection, cells were incubated with the indicated antibodies at concentrations pre-determined using an independent immunofluorescence titration curve on wild type protein. MAbs were detected using an Alexa Fluor 488-conjugated secondary antibody and mean cellular fluorescence was determined using Intellicyt iQue flow cytometry platform. Mutated residues were identified as playing a role in binding the MAb epitope if they did not support the reactivity of the test MAb but did support the reactivity of the reference MAb. This counterscreen strategy facilitates the exclusion of mutants that are locally misfolded or that have an expression defect.

[000292] Residues identified as playing a role in the HCA/LCA antibody or sotrovimab binding by alanine scanning are listed in **TABLE 6** below. An X in a column associated with an amino acid position indicates that this residue was identified as playing a role in binding of the antibody corresponding to the row that the X is located in.

Table 6: Residues Playing a Role in Binding as Detected by Alanine Scanning

Amino Acid Position*	P337	E340	K378	R408	Q414
HCA/LCA Antibody			X	X	X
Sotrovimab	X	X			

* Amino acid position is relative to position in RBD of SARS-CoV-2

Discussion of Results

[000293] Alanine scanning indicates that K417 provides the only divergence among SARS-CoV-2 variants. Importantly, our current data, including Beta, Gamma and Delta-Plus pseudoviral neutralization (which contain K417N or T mutations) (**FIG. 3, FIG. 4**) and the data from alanine scanning **(K417A)** demonstrate that these mutations do not adversely impact HCA/LCA antibody binding or neutralization. SARS-CoV-2 and related variants are identified as clade 1/2 (Letko, 2020), and require ACE-2 for cellular entry. Interacting residues identified as

playing a role in binding for the HCA/LCA antibody (K378, R408, Q414), as determined by alanine scanning and sotrovimab (P337 and E340) as previously published (Starr, 2021b) on the SARS-CoV-2 Wuhan isolate spike protein showed conservation across all SARS-CoV-2 variants of interest, including Delta and Omicron, as well as past variants of concern. In addition, these identified interacting residues are identical in clade 1 RBD isolates as previously defined (Letko, 2020), including SARS, WIV-1, SHC014. Clade 2 virus RBD sequences do not appear to utilize ACE-2 for cellular entry.

[000294] The recently emerged Omicron variant was rapidly elevated to Variant of Concern status based on the large number of mutations (Stanford University Coronavirus antiviral & Resistance database) that can affect transmissibility, disease severity, or escape from currently available therapeutics (WHO Update on Omicron). Several Omicron mutations also coincide with residues that are involved in binding of both of the antibodies in Regeneron's cocktail to the spike protein, including K417, E484, and Q493 for casarivimab, and N440 and Q446 for imdevimab (Starr, 2021a), which is consistent with the lack of activity of the Regeneron cocktail against Omicron (**FIG. 3, TABLE 4, TABLE 5**), (Cao, 2021; Planas, 2021). There appear to be no significant binding residues for S309 affected by Omicron mutations (Starr, 2021b), as reflected by its retention of neutralizing activity against this variant (**FIG. 4**) (GSK, 2021).

EXAMPLE 5. Drug Combination Study

Background

[000295] The median-effect equation is derived from the mass-action law principle at equilibrium-steady state via mathematical induction and deduction for different reaction sequences and mechanisms and different types of inhibition. This equation serves as the unified theory for the Michaelis-Menten equation, Hill equation, Henderson-Hasselbalch equation, and Scatchard equation. It is shown that dose and effect are interchangeable via defined parameters. This general equation for the single drug effect has been extended to the multiple drug effect equation for n drugs. These equations provide the theoretical basis for the combination index (CI)-isobologram equation that allows quantitative determination of drug interactions, where CI < 1, $= 1$, and > 1 indicate synergism, additive effect, and antagonism, respectively.

[000296] Based on these algorithms, computer software (e.g., Compusyn) has been developed to allow automated simulation of synergism and antagonism at all dose or effect levels. It displays the dose-effect curve, median-effect plot, combination index plot, isobologram, dose-reduction index plot, and polygonogram for in vitro or in vivo studies. This theoretical development, experimental design, and computerized data analysis have facilitated dose-effect analysis for single drug evaluation or carcinogen and radiation risk assessment, as well as for

drug or other entity combinations in a vast field of disciplines of biomedical sciences. For more information, see Chou, Ting-Chao. "Theoretical basis, experimental design, and computerized simulation of synergism and antagonism in drug combination studies." *Pharmacological reviews* vol. 58,3 (2006): 621-81. doi:10.1124/pr.58.3.10.

[000297] Compusyn software generates CI values based on the median-effect curve. Synergism, antagonism, or additivity is only dependent on the potencies and concentrations of the individual reactants. There is no requirement to understand mechanism of synergism, antagonism, or additivity to quantify the effect. Synergy exists where the sum of the activities of the individual antibodies exceeds the combined activity of the combined antibodies. Antagonism is the inverse, whereby the activity of both components combined is lower than that of the most active component. Additivity exists where the interaction results in a combined activity no greater than the sum of the activities of each component.

Procedure

[000298] Each individual antibody was run in a pseudoviral assays to obtain their IC_{50} values. Next, antibodies were mixed together at equipotent (IC_{50}) ratios, and then diluted into several dilutions higher and several dilutions lower. The antibodies included: HCA/LCA Antibody, a non-conserved antibody (the Heavy Chain B/Light Chain B Antibody, or the "HCB/LCB Antibody") and sotrovimab. Sotrovimab comprises a heavy chain having SEQ ID NO: 3
(QVQLVQSGAEVKKPGASVKVSCKASGYPFTSYGISWVRQAPGQGLEWMGWISTY
QGNTNYAQKFQGRVTMTTDTSTTTGYMELRRLRSDDTAVYYCARDYTRGAWFGESLI
GGFDNWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNS
ALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCD
KTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDG
VEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKA
KGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL
DSDGSFFLYSKLTVDKSRWQQGVFSCSVLHEALHSHYTQKSLSLSPGK) and a light chain having an amino acid sequence of SEQ ID NO: 4
(EIVLTQSPGTLSLSPGERATLSCRASQTVSSTSLAWYQQKPG
QAPRLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQHDTSLTFGGGTK
VEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQES
VTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC). The heavy-chain CDR3 of sotrovimab comprises SEQ ID NO: 5 (ARDYTRGAWFGESLIGGFDN).

[000299] To determine CI values, Compusyn software was used. The total concentrations of each antibody or antibodies was entered into the Compusyn software, along with its effect level.

Effect level is a function of percent neutralization. For example, 90% neutralization would correspond to a data entry of 0.9 effect level, or IC_{90}. Using the Chou-Talalay method, Compusyn computes and compares the dose-response curves of the individual antibodies and the combination of Abs and then outputs a combination index (CI) which is a reflection of their pharmacological interaction. Antagonism is indicated by CI values that exceed 1. Additivity is indicated by CI values that are equal to 1. Synergy is indicated by CI values less than 1. his procedure was repeated performed for each combination of antibodies, and CI values were generated.

Results

[000300] **TABLE 7** provides the computed Combination index (CI) values at given neutralization levels of the indicated neutralizing antibody combinations. In **TABLE 7**, CI>1 indicates antagonism, CI<1 indicates synergy, and CI = 1 indicates additivity. Strongly synergistic CI values (CI ≤ 0.75) are in bold. CI values ≥ 1.25 can be considered strongly antagonistic. The combinations included antibodies with conserved epitopes (e.g., sotrovimab, HCA/LCA antibody) combined with the antibodies with an epitope that is not conserved in the SARS-CoV-2 (e.g., the HCB/LCB antibody), and antibodies with conserved epitopes combined with other antibodies with conserved epitopes (e.g., sotrovimab combined with the HCA/LCA antibody).

Table 7: Combination index (CI) values at given neutralization levels of the indicated neutralizing antibody combinations.

		CI at the following percent neutralization levels:			
Virus or Variant Name	***Antibody combination***	**20%**	**40%**	**60%**	**80%**
Omicron	HCA/LCA antibody + sotrovimab	1.713	1.126	0.814	**0.561**
Beta	HCA/LCA antibody + HCB/LCB antibody	**0.561**	**0.519**	**0.488**	**0.454**
Gamma	HCA/LCA antibody + HCB/LCB antibody	**0.549**	**0.487**	**0.416**	**0.445**
SARS-CoV	HCA/LCA antibody + sotrovimab	1.364	0.924	**0.679**	**0.475**

Results

[000301] In some combinations, both the HCA/LCA antibody and the antibody combined with it (e.g., sotrovimab) bind to a conserved epitope of the variant (referred to herein as a conserved/conserved combination). For example, conserved/conserved combination were the

HCA/LCA antibody with sotrovimab in the Omicron strain, and the HCA/LCA antibody with sotrovimab in the SARS-CoV strain.

[000302] In some combinations, the HCA/LCA antibody was combined with an antibody that bound to a nonconserved epitope of the variant (referred to herein as a conserved/nonconserved combination). Examples of conserved/nonconserved combinations include the HCA/LCA antibody combined with the HCB/LCB antibody (see **TABLE 7**). This combination was tested for neutralization of the Beta strain and for neutralization of the Gamma strain. Examples of conserved/conserved combinations include the HCA/LCA antibody combined with sotrovimab, which was tested for the Omicron strain and for the SARS-CoV strain.

[000303] For the Omicron variant, the combination of HCA/LCA antibody and sotrovimab showed synergy at IC60 and strong synergy at IC80. For the SARS-CoV strain, the combination of HCA/LCA antibody and sotrovimab showed an additive effect at IC40, strong synergy at IC60 and stronger synergy at IC80.

[000304] For the Beta variant, HCA/LCA antibody and HCB/LCB antibody showed strong synergy at IC20, IC40, IC60, and IC80, with the strongest being at IC80. For the Gamma variant, HCA/LCA antibody and HCB/LCB antibody showed strong synergy at IC20, IC40, IC60, and IC80, with the strongest being at IC80.

CLAIMS

WHAT IS CLAIMED IS:

1. A method for preventing or treating a SARS-CoV infection or a SARS-CoV-2 infection in a subject comprising administering to the subject an agent capable of independently i) binding SARS-CoV and ii) blocking SARS-CoV-2 binding to angiotensin-converting enzyme 2 (ACE2).
2. The method of claim 1, wherein the agent is capable of binding SARS-CoV spike protein.
3. The method of claim 2, wherein the agent is capable of binding SARS-CoV spike protein S1 domain.
4. The method of claim 1-3, wherein the agent is capable of blocking SARS-CoV-2 spike protein from binding to ACE2.
5. The method of claim 4, wherein the agent is capable of blocking SARS-CoV-2 spike protein S1 domain from binding to ACE2.
6. The method of claim 5, wherein the agent is capable of blocking SARS-CoV-2 spike protein S1 domain receptor binding domain (RBD) from binding to ACE2.
7. The method of any one of claims 1-6, wherein the agent is capable of specifically binding the SARS-CoV or SARS-CoV-2.
8. A method for preventing or treating a SARS-CoV-2 infection in a subject comprising administering to the subject an agent capable of binding bind SARS- CoV-2 spike protein S1 domain, wherein the ability to bind SARS- CoV-2 spike protein S1 domain is reduced by a mutation at position 378, 408, or 414, wherein the position 378, 408, or 414 is relative to positions of sequences set forth in SEQ ID NO: 1.
9. The method of claim 8, wherein the mutation is K378A, R408A, or Q414A.
10. A method for preventing or treating a SARS-CoV-2 infection in a subject, wherein the SARS-CoV-2 comprises a spike protein with one or more of A67V, Δ69-70, T95I, Δ211/L212I, ins214EPE, G339D, S371L, S373P, S375F, N440K, G446S, S477N, E484A, Q493R, G496S, Q498R, Y505H, T547K, N679K, N764K, D796Y, N856K,

Q954H, N969K, or L981F, wherein the position 378, 408, or 414 is relative to positions of sequences set forth in SEQ ID NO: 1, comprising administering to the subject an agent capable of neutralizing the infection with a half maximal inhibitory concentration (IC_{50}) of less than 0.4 μg/mL or an IC_{90} of less than 1 μg/mL.

11. The method of claim 10, wherein the SARS-CoV-2 comprises a spike protein comprising A67V, Δ69-70, T95I, G142D/Δ143-145, Δ211/L212I, ins214EPE. G339D, S371L, S373P, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493R, G496S, Q498R, N501Y, Y505H, T547K, D614G, H655Y, N679K, P681H, N764K, D796Y, N856K, Q954H, N969K, and L981F.
12. A method for preventing or treating a SARS-CoV-2 infection in a subject comprising administering to the subject an agent capable of independently neutralizing SARS-CoV-2 B.1.1.529 (Omicron), SARS-CoV-2 (Epsilon), SARS-CoV-2 (Iota), SARS-CoV-2 (Eta), SARS-CoV-2 (Delta), SARS-CoV-2 (Gamma), SARS-CoV-2 (Beta), and SARS-CoV-2 (Alpha) infections with an average IC_{50} of less than 900 ng/mL.
13. A method for preventing or treating a SARS-CoV infection in a subject comprising administering to the subject an agent capable of neutralizing the SARS-CoV with an IC_{50} of less than 0.05 μg/mL.
14. The method of any one of claims 1-13, wherein the agent comprises an antibody or antigen-binding fragment thereof.
15. The method of claim 14, wherein the antibody or antigen-binding fragment thereof is a chimeric antigen receptor (CAR).
16. The method of any one of claims 1-15, wherein the subject is a human, dog, cat, cow, or horse.
17. The method of any one of claims 1-16, wherein the agent does not specifically bind MERS-CoV spike protein S1 domain.

18. The method of any one of claims 1-17, wherein the agent is capable of neutralizing SARS-CoV-2 variants Wuhan, Alpha, Beta, Gamma, Delta, Epsilon, Eta, Iota, or Omicron.

19. The method of any one of claims 1-18, further comprising administering an additional agent.

20. The method of claim 19, wherein the agent and the additional agent interact synergistically in neutralizing the infection.

21. The method of claim 19, wherein the agent and the additional agent interact additively in neutralizing the infection.

22. The method of claim 19, wherein the agent and the additional agent interact antagonistically in neutralizing the infection.

23. A method comprising contacting a cell comprising an infection with SARS-CoV-2 with an agent, wherein the SARS-CoV-2 comprises a spike protein with one or more of A67V, Δ69-70, T95I, Δ211/L212I, ins214EPE, G339D, S371L, S373P, S375F, N440K, G446S, S477N, E484A, Q493R, G496S, Q498R, Y505H, T547K, N679K, N764K, D796Y, N856K, Q954H, N969K, and L981F, wherein the position 378, 408, or 414 is relative to positions of sequences set forth in SEQ ID NO: 1, and wherein the agent capable of neutralizing the infection with a half maximal inhibitory concentration (IC_{50}) of less than 0.4 μg/mL or an IC_{90} of less than 1 μg/mL.

24. The method of claim 23, wherein the SARS-CoV-2 comprises a spike protein comprising A67V, Δ69-70, T95I, G142D/Δ143-145, Δ211/L212I, ins214EPE. G339D, S371L, S373P, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493R, G496S, Q498R, N501Y, Y505H, T547K, D614G, H655Y, N679K, P681H, N764K, D796Y, N856K, Q954H, N969K, and L981F.

25. A method comprising contacting a cell comprising an infection with SARS-CoV-2 with agent capable of independently neutralizing SARS-CoV-2 B.1.1.529 (Omicron), SARS-CoV-2 (Epsilon), SARS-CoV-2 (Iota), SARS-CoV-2 (Eta), SARS-CoV-2 (Delta), SARS-

CoV-2 (Gamma), SARS-CoV-2 (Beta), and SARS-CoV-2 (Alpha) with an average IC_{50} of less than 900 ng/mL.

26. A method comprising contacting a cell comprising a SARS-CoV infection or a SARS-CoV-2 infection with an agent capable of independently i) binding SARS-CoV and ii) blocking SARS-CoV-2 binding to angiotensin-converting enzyme 2 (ACE2).
27. The method of claim 26, wherein the agent is capable of binding SARS-CoV spike protein.
28. The method of claim 27, wherein the agent is capable of binding SARS-CoV spike protein S1 domain.
29. The method of claim 26-28, wherein the agent is capable of blocking SARS-CoV-2 spike protein from binding to ACE2.
30. The method of claim 29, wherein the agent is capable of blocking SARS-CoV-2 spike protein S1 domain from binding to ACE2.
31. The method of claim 30, wherein the agent is capable of blocking SARS-CoV-2 spike protein S1 domain receptor binding domain (RBD) from binding to ACE2.
32. The method of any one of claims 26-31, wherein the agent is capable of specifically binding the SARS-CoV or SARS-CoV-2.
33. A method comprising contacting a cell comprising an infection with SARS-CoV with an agent capable of neutralizing the infection with an IC_{50} of less than 0.05 μg/mL.
34. A method comprising binding an agent to a SARS- CoV-2 spike protein S1 domain, wherein an ability of the agent to bind the SARS- CoV-2 spike protein S1 domain is reduced by a mutation at position 378, 408, or 414, wherein the position 378, 408, or 414 is relative to positions of sequences set forth in SEQ ID NO: 1.
35. The method of claim 34, wherein the mutation is K378A, R408A, or Q414A.
36. The method of any one of claims 23-34, wherein the agent comprises an antibody or antigen-binding fragment thereof.

37. The method of claim 36, wherein the antibody or antigen-binding fragment thereof is a chimeric antigen receptor (CAR).

38. The method of any one of claims 23-37, wherein the subject is a human, dog, cat, cow, or horse.

39. A method of inactivating one or more strains of a virus, wherein the virus comprises SARS-CoV, SARS-CoV-2, or a variant of SARS-CoV or SARS-CoV-2, the method comprising: administering a first agent, wherein the first agent binds to a first epitope of the virus, and administering a second agent, wherein the second agent binds to a second epitope, wherein at least the first epitope comprises an amino acid sequence that is conserved in the one or more strains of the virus.

40. A method for preventing or treating a SARS-CoV infection or a SARS-CoV-2 infection in a subject comprising administering to the subject two or more agents, wherein the two or more agents are capable of independently i) binding SARS-CoV and ii) blocking SARS-CoV-2 binding to angiotensin-converting enzyme 2 (ACE2).

41. The method of claim 40, wherein the two or more agents interact synergistically in neutralizing the SARS-CoV infection or the SARS-CoV-2 infection.

42. The method of claim 40 or 41, wherein the two or more agents comprise sotrovimab.

43. A pharmaceutical composition comprising two or more agents, each capable of independently i) binding SARS-CoV and ii) blocking SARS-CoV-2 binding to angiotensin-converting enzyme 2 (ACE2).

44. The pharmaceutical composition of claim 43, wherein the two or more agents interact synergistically.

45. A method comprising i) contacting a cell infected with a virus with a first agent, wherein the first agent binds to a first epitope of the virus, wherein the first epitope is conserved in variants of the virus, and ii) contacting the cell with a second agent, wherein the second agent binds to a second epitope of the virus;

wherein the virus comprises SARS-CoV or SARS-CoV-2.

46. The method of claim 45, wherein the second agent binds the second conserved epitope, optionally wherein the first conserved epitope and the second conserved epitope are in a spike protein, optionally wherein the first conserved epitope and the second conserved epitope are in a spike protein S1 domain, optionally wherein the first conserved epitope and the second conserved epitope are in a spike protein S1 domain receptor binding domain.

47. The method of claim 45, wherein the second agent binds the non-conserved epitope, optionally wherein the first conserved epitope and the non-conserved epitope are in a spike protein, optionally wherein the first conserved epitope and the non-conserved epitope are in a spike protein S1 domain, optionally wherein the first conserved epitope and the non-conserved epitope are in a spike protein S1 domain receptor binding domain.

48. The method of any one of claims 43-47, wherein the first agent and the second agent comprise an antibody or antigen-binding fragment thereof, optionally wherein the antibody or antigen-binding fragment thereof is a chimeric antigen receptor (CAR).

49. A method comprising contacting a cell infected with a SARS-CoV-2 virus with a first agent and a second agent, wherein the contacting provides a combination index (CI) value of less than 1 at a neuralization level of at least 60%.

50. The method of claim 49, wherein the CI value is less than 0.85 at a neutralization level of at least 60%.

51. The method of claim 49, wherein the CI value is less than 0.6 at a neutralization level of at least 80%.

52. The method of any one of claims 49-51, wherein the first agent binds a first conserved epitope of the SARS-CoV-2 virus, and the second agent binds a second conserved epitope of the SARS-CoV-2 virus, optionally wherein the first conserved epitope and the second conserved epitope are in spike protein, optionally wherein the first conserved epitope and the second conserved epitope are in a spike protein S1 domain, optionally wherein the

first conserved epitope and the second conserved epitope are in a spike protein S1 domain receptor binding domain.

53. The method of claim 52, wherein the SARS-CoV-2 comprises a spike protein with one or more of A67V, Δ69-70, T95I, G142D/Δ143-145, Δ211/L212I, ins214EPE, G339D, S371L, S373P, S373F, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493R, G496S, Q498R, N501Y, Y505H, T547K, D614G, H655Y, N679K, P681H, N764K, D796Y, N856K, Q954H, N969K, or L981F.

54. A method comprising contacting a cell infected with a SARS-CoV virus with a first agent and a second agent, wherein the contacting provides a CI value of less than 1 at a neuralization level of at least 40%.

55. The method of claim 54, wherein the contacting provides a CI value is less than 0.7 at a neutralization level of at least 60%.

56. The method of claim 54, wherein the contacting provides a CI value is less than 0.5 at a neutralization level of at least 80%.

57. The method of any one of claims 54-56, wherein the first agent binds a first conserved epitope of the SARS-CoV virus, and the second agent binds a second conserved epitope of the SARS-CoV virus, optionally wherein the first conserved epitope and the second conserved epitope are in spike protein, optionally wherein the first conserved epitope and the second conserved epitope are in a spike protein S1 domain, optionally wherein the first conserved epitope and the second conserved epitope are in a spike protein S1 domain receptor binding domain.

58. A method comprising contacting a cell infected with a SARS-CoV virus with a first agent and a second agent, wherein the contacting provides a CI value of less than 1 at a neutralization level of at least 20%.

59. The method of claim 58, wherein the contacting provides a CI value of less than 0.6 at a neutralization level of at least 20%.

60. The method of claim 58, wherein the contacting provides a CI value of less than 0.5 at a neutralization level of at least 40%.

61. The method of any one of claims 58-60, wherein the first agent binds a conserved epitope of the SARS-CoV virus, and the second agent binds a non-conserved epitope of the SARS-CoV virus, optionally wherein the conserved epitope and the non-conserved epitope are in spike protein, optionally wherein the conserved epitope and the non-conserved epitope are in a spike protein S1 domain, optionally wherein the conserved epitope and the non-conserved epitope are in a spike protein S1 domain receptor binding domain.

62. A method of preventing or treating a SARS-CoV infection or a SARS-CoV-2 infection in a subject comprising administering to the subject two or more agents, wherein the two or more agents are each capable of independently i) binding SARS-CoV and ii) blocking SARS-CoV-2 binding to angiotensin-converting enzyme 2 (ACE2).

63. The method of claim 62, wherein the two or more agents interact synergistically in neutralizing the SARS-CoV infection or the SARS-CoV-2 infection.

64. The method of claim 63, wherein the two or more agents comprise sotrovimab.

65. A pharmaceutical composition comprising two or more agents, each capable of independently i) binding SARS-CoV and ii) blocking SARS-CoV-2 binding to angiotensin-converting enzyme 2 (ACE2).

66. The pharmaceutical composition of claim 65, wherein a first agent and a second agent of the two or more agents comprise an antibody or antigen-binding fragment thereof, optionally wherein the antibody or antigen-binding fragment thereof is a chimeric antigen receptor (CAR).

67. The method of any one of claims 1-38, wherein the agent comprises an antibody, or antigen-binding fragment thereof, comprising

    a. a heavy chain complementarity determining region (CDR)1 (HCDR1), HCDR2, and HCDR3 and/or a light chain CDR1 (LCDR1), LCDR2 and LCDR3, wherein

the HCDR1, the HCDR2, and the HCDR3 comprise amino acid sequences set forth in SEQ ID NO: 6, SEQ ID NO: 7, and SEQ ID NO: 8, respectively, and the LCDR1, the LCDR2, and the LCDR3 comprise the amino acid sequences set forth in SEQ ID NO: 9, SEQ ID NO: 10, and SEQ ID NO: 11, respectively;

b. a heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 12, or an amino acid sequence comprising at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence set forth in SEQ ID NO: 12 and/or 2) a light chain comprising the amino acid sequence set forth in SEQ ID NO: 15, or an amino acid sequence comprising at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence set forth in SEQ ID NO: 15; or

c. a heavy chain variable region (VH) comprising the amino acid sequence set forth in SEQ ID NO: 13, or an amino acid sequence comprising at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence set forth in SEQ ID NO: 13 and/or 2) a light chain variable region (VL) comprising the amino acid sequence set forth in SEQ ID NO: 16, or an amino acid sequence comprising at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence set forth in SEQ ID NO: 16.

68. The method of claim 39 or 45-61, wherein the first agent comprises an antibody, or antigen-binding fragment thereof, comprising

a. a heavy chain complementarity determining region (CDR)1 (HCDR1), HCDR2, and HCDR3 and/or a light chain CDR1 (LCDR1), LCDR2 and LCDR3, wherein the HCDR1, the HCDR2, and the HCDR3 comprise amino acid sequences set forth in SEQ ID NO: 6, SEQ ID NO: 7, and SEQ ID NO: 8, respectively, and the LCDR1, the LCDR2, and the LCDR3 comprise the amino acid sequences set forth in SEQ ID NO: 9, SEQ ID NO: 10, and SEQ ID NO: 11, respectively;

b. a heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 12, or an amino acid sequence comprising at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence set forth in SEQ ID NO: 12 and/or 2) a light chain comprising the amino acid sequence set forth in SEQ ID NO: 15, or an amino acid sequence comprising at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence set forth in SEQ ID NO: 15; or

c. a heavy chain variable region (VH) comprising the amino acid sequence set forth in SEQ ID NO: 13, or an amino acid sequence comprising at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence set forth in SEQ ID NO: 13 and/or 2) a light chain variable region (VL) comprising the amino acid sequence set forth in SEQ ID NO: 16, or an amino acid sequence comprising at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence set forth in SEQ ID NO: 16; and

the second agent comprises

d. a heavy chain complementarity determining region (CDR)1 (HCDR1), HCDR2, and HCDR3 and/or a light chain CDR1 (LCDR1), LCDR2 and LCDR3, wherein the HCDR1, the HCDR2, and the HCDR3 comprise amino acid sequences set forth in SEQ ID NO: 20, SEQ ID NO: 21, and SEQ ID NO: 22, respectively, and the LCDR1, the LCDR2, and the LCDR3 comprise the amino acid sequences set forth in SEQ ID NO: 23, SEQ ID NO: 24, and SEQ ID NO: 25, respectively;

e. 1) a heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 18, or an amino acid sequence comprising at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence set forth in SEQ ID NO: 18 and/or 2) a light chain comprising the amino acid sequence set forth in SEQ ID NO: 19, or an amino acid sequence comprising at least 80%, 85%,

90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence set forth in SEQ ID NO: 19; or

f. 1) a heavy chain variable region (VH) comprising the amino acid sequence set forth in SEQ ID NO: 26, or an amino acid sequence comprising at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence set forth in SEQ ID NO: 26 and/or 2) a light chain variable region (VL) comprising the amino acid sequence set forth in SEQ ID NO: 28, or an amino acid sequence comprising at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence set forth in SEQ ID NO: 28.

69. The method of any one of claims 40-44 or 62-66, wherein an agent of the two or more agents comprises an antibody, or antigen-binding fragment thereof, comprising

a. a heavy chain complementarity determining region (CDR)1 (HCDR1), HCDR2, and HCDR3 and/or a light chain CDR1 (LCDR1), LCDR2 and LCDR3, wherein the HCDR1, the HCDR2, and the HCDR3 comprise amino acid sequences set forth in SEQ ID NO: 6, SEQ ID NO: 7, and SEQ ID NO: 8, respectively, and the LCDR1, the LCDR2, and the LCDR3 comprise the amino acid sequences set forth in SEQ ID NO: 9, SEQ ID NO: 10, and SEQ ID NO: 11, respectively;

b. a heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 12, or an amino acid sequence comprising at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence set forth in SEQ ID NO: 12 and/or 2) a light chain comprising the amino acid sequence set forth in SEQ ID NO: 15, or an amino acid sequence comprising at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence set forth in SEQ ID NO: 15; or

c. a heavy chain variable region (VH) comprising the amino acid sequence set forth in SEQ ID NO: 13, or an amino acid sequence comprising at least 80%, 85%,

90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence set forth in SEQ ID NO: 13 and/or 2) a light chain variable region (VL) comprising the amino acid sequence set forth in SEQ ID NO: 16, or an amino acid sequence comprising at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence set forth in SEQ ID NO: 16.

70. A composition comprising a i) first antibody or antigen-binding fragment thereof and ii) a second antibody or antigen-binding fragment thereof, wherein the composition is capable of a combination index (CI) of less than 1, 0.9, 0.8, 0.7, 0.6, or 0.5 for neutralizing an infection with a pseudotyped virus with a SARS-CoV-2 spike protein at a percent neutralization level of at least 20%, at least 40%, at least 60%, or at least 80%.

71. The composition of claim 70, wherein the first antibody or antigen-binding fragment thereof comprises

a. a heavy chain complementarity determining region (CDR)1 (HCDR1), HCDR2, and HCDR3 and/or a light chain CDR1 (LCDR1), LCDR2 and LCDR3, wherein the HCDR1, the HCDR2, and the HCDR3 comprise amino acid sequences set forth in SEQ ID NO: 6, SEQ ID NO: 7, and SEQ ID NO: 8, respectively, and the LCDR1, the LCDR2, and the LCDR3 comprise the amino acid sequences set forth in SEQ ID NO: 9, SEQ ID NO: 10, and SEQ ID NO: 11, respectively;

b. a heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 12, or an amino acid sequence comprising at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence set forth in SEQ ID NO: 12 and/or 2) a light chain comprising the amino acid sequence set forth in SEQ ID NO: 15, or an amino acid sequence comprising at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence set forth in SEQ ID NO: 15; or

c. a heavy chain variable region (VH) comprising the amino acid sequence set forth in SEQ ID NO: 13, or an amino acid sequence comprising at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence set forth in SEQ ID NO: 13 and/or 2) a light chain variable region (VL) comprising the amino acid sequence set forth in SEQ ID NO: 16, or an amino acid sequence comprising at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence set forth in SEQ ID NO: 16.

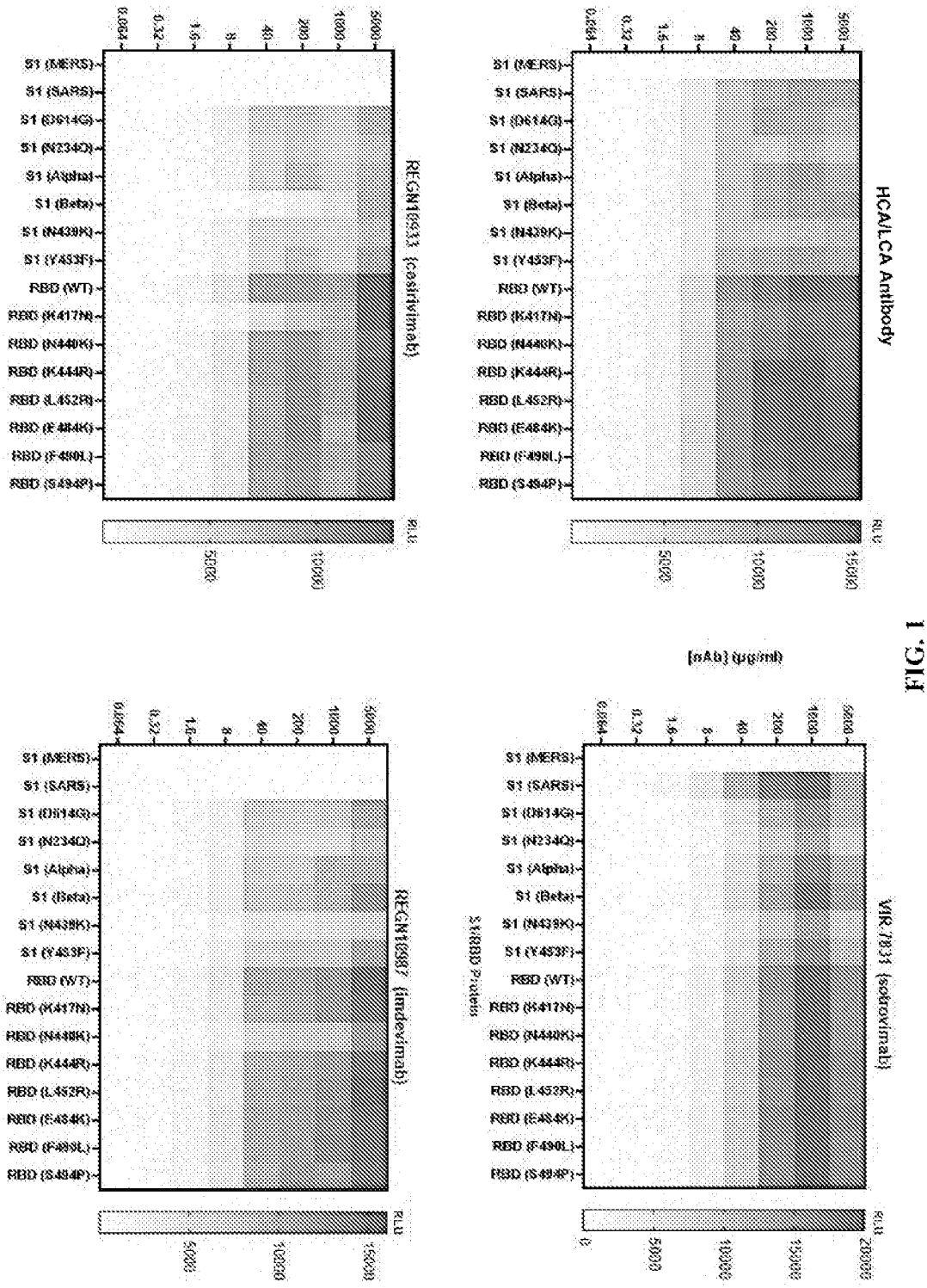

HCA/LCA Antibody
REGN10933 (casirivimab)
REGN10987 (imdevimab)
VIR-7831 (sotrovimab)
S1 (MERS)
S1 (SARS)
S1 (D614G)
S1 (N234Q)
S1 (Alpha)
S1 (Beta)
S1 (N439K)
S1 (Y453F)
RBD (WT)
RBD (K417N)
RBD (N440K)
RBD (K444R)
RBD (L452R)
RBD (E484K)
RBD (F490L)
RBD (S494P)
S1/RBD Protein
[mAb] (µg/ml)
RLU

FIG. 1

FIG. 2

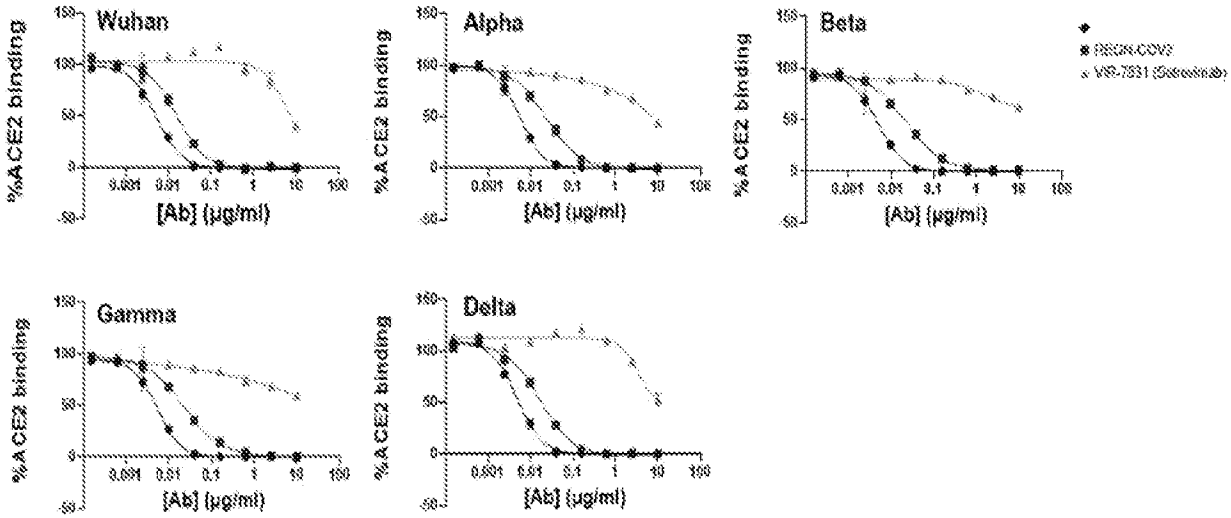

Wuhan
Alpha
Beta
Gamma
Delta
%ACE2 binding
[Ab] (µg/ml)
REGN-COV2
VIR-7831 (Sotrovimab)

FIG. 3

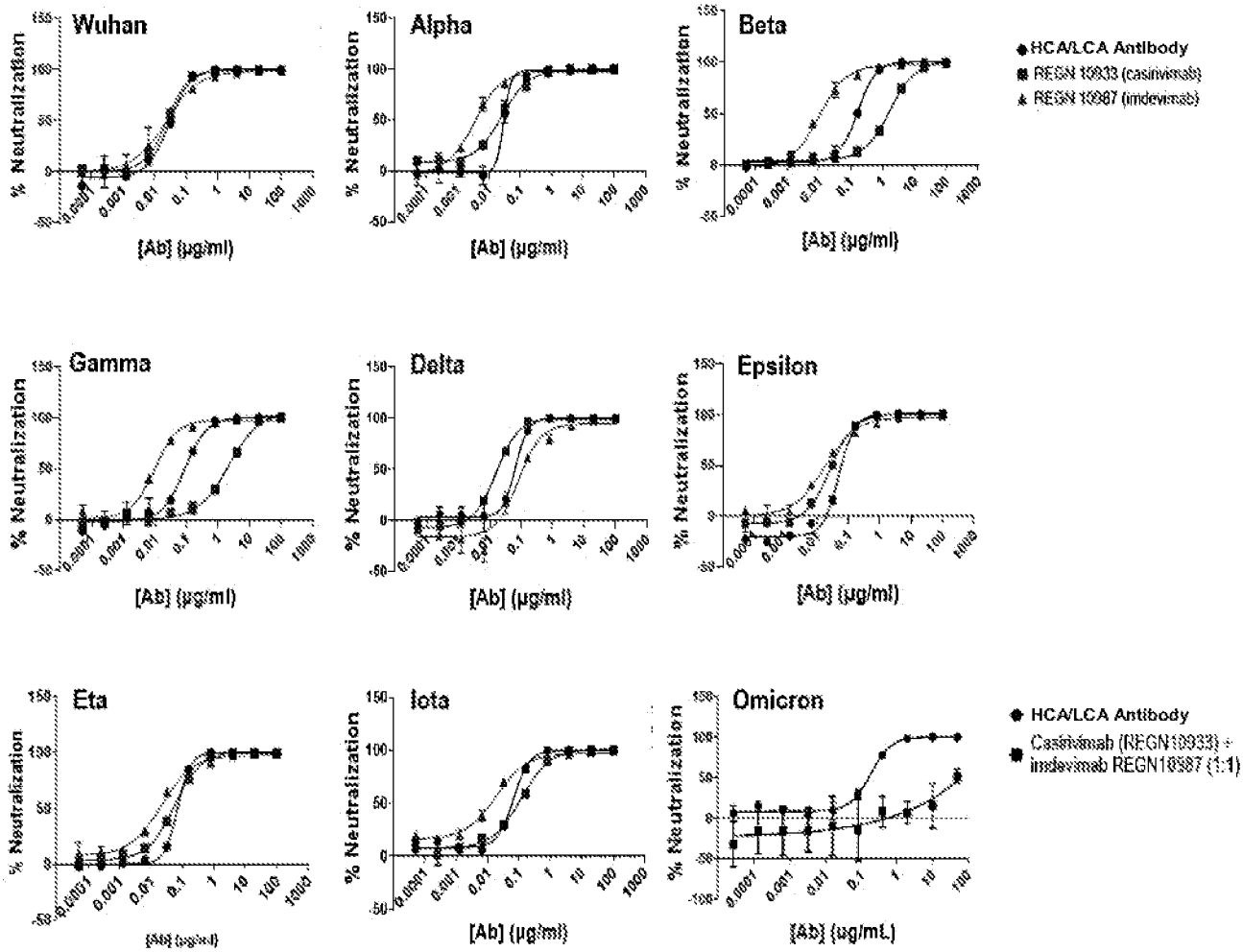

Wuhan
Alpha
Beta
Gamma
Delta
Epsilon
Eta
Iota
Omicron
% Neutralization
[Ab] (µg/ml)
[Ab] (ug/mL)
HCA/LCA Antibody
REGN10933 (casirivimab)
REGN10987 (imdevimab)
Casirivimab (REGN10933) + imdevimab REGN10987 (1:1)

FIG. 4

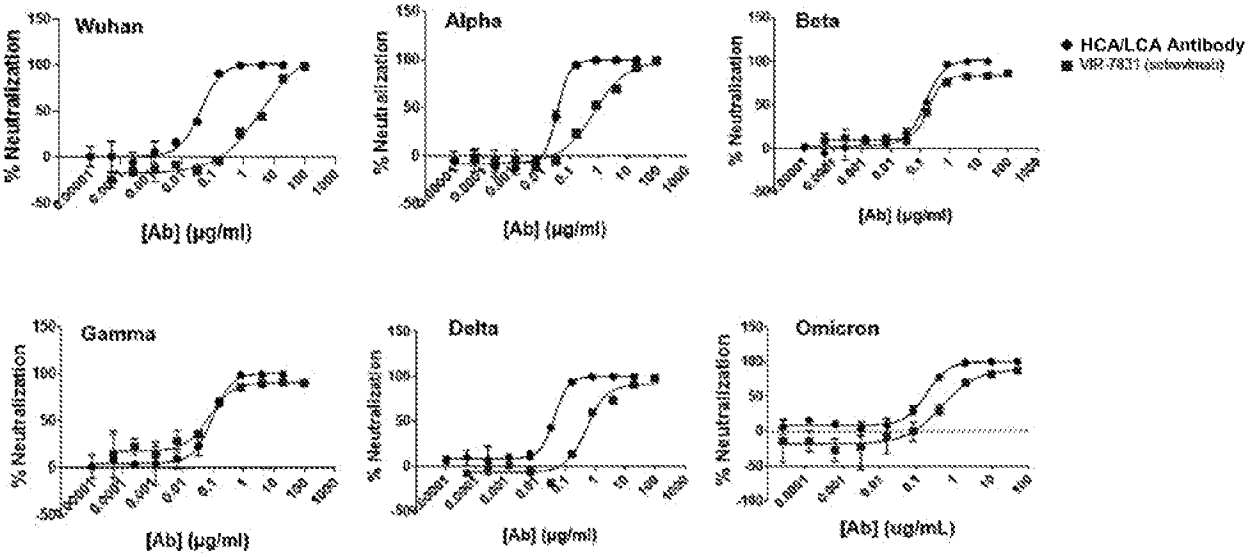
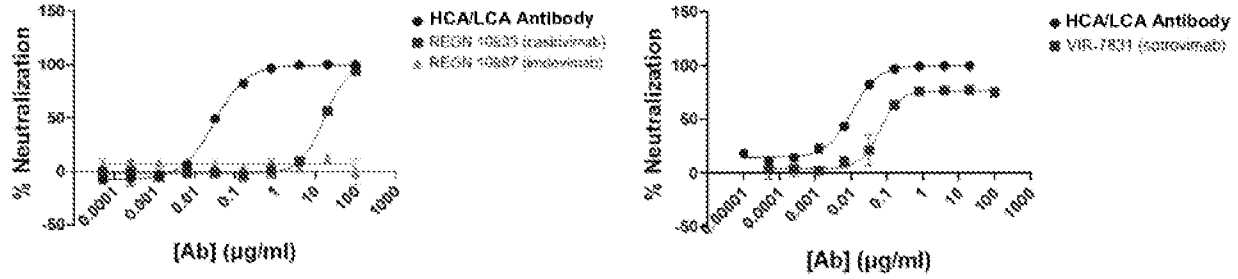

Wuhan
Alpha
Beta
Gamma
Delta
Omicron
% Neutralization
[Ab] (µg/ml)
[Ab] (ug/mL)
HCA/LCA Antibody
VIR-7831 (sotrovimab)

FIG. 5


% Neutralization
150
100
50
0
-50
0.0001
0.001
0.01
0.1
1
10
100
1000
[Ab] (µg/ml)
HCA/LCA Antibody
REGN 10933 (casirivimab)
REGN 10987 (imdevimab)
% Neutralization
150
100
50
0
-50
0.00001
0.0001
0.001
0.01
0.1
1
10
100
1000
[Ab] (µg/ml)
HCA/LCA Antibody
VIR-7831 (sotrovimab)