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(54) Title: EPITOPES OF SARS-COV-2 NEUTRALIZING ANTIBODIES

(57) Abstract: The invention provides novel anti-SARS-CoV-2-Spike antibodies, pharmaceutical compositions comprising such antibodies, and therapeutic methods of using such antibodies and pharmaceutical compositions.

EPITOPES OF SARS-COV-2 NEUTRALIZING ANTIBODIES

STATEMENT AS TO RIGHTS TO INVENTIONS MADE UNDER FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

[0001] This invention was made with government support under grant number P50 AI150476 awarded by The National Institutes of Health. The government has certain rights in the invention. This research was also supported by the Singapore Ministry of Health's National Medical Research Council under its COVID-19 Research Fund Grant Call Gap Funding Category (MOH-000468-00) and A*STAR A*CCLERATE GAP fund (ACCL/20-GAP001-C20H-F).

FIELD OF THE INVENTION

[0002] The present invention relates to anti-SARS-CoV-2-Spike antibodies and the use of anti-SARS-CoV-2-Spike antibodies in the treatment of COVID-19.

BACKGROUND OF THE INVENTION

[0003] In 2020, the spread of COVID-19 became a worldwide issue due to its high transmissibility and deadly effects. Infection by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is initiated by binding of viral Spike protein to host receptor angiotensin-converting enzyme 2 (ACE2), followed by fusion of viral and host membranes. While antibodies that block this interaction are in emergency use as early COVID-19 therapies, precise determinants of neutralization potency remain unknown.

[0004] There is a present need to develop new anti-SARS-CoV-2-Spike antibodies and better understand their mechanism of action in order to stop the spread of COVID-19.

BRIEF SUMMARY OF THE INVENTION

[0005] The present disclosure provides anti-SARS-CoV-2-Spike antibodies.The present disclosure provides anti-SARS-CoV-2-Spike antibodies.

[0006] In one aspect, the present disclosure provides a method of preventing formation of syncytia comprising a fusion between a SARS-CoV-2 infected cell displaying a SARS-CoV-2 Spike protein on its surface, and a second cell displaying an ACE-2 receptor on its surface, the syncytia formation mediated by the SARS-CoV-2 Spike protein binding to the ACE-2

receptor, the method comprising contacting a cell infected with SARS-CoV-2, or at risk of being infected with SARS-CoV-2 with an isolated anti-SARS-CoV-2-Spike antibody or an antigen binding fragment thereof specifically binding to the Spike protein, trapping the Spike protein in a pre-fusion state, thereby preventing the formation of the syncytia.

[0007] In some embodiments, the isolated anti-SARS-CoV-2-Spike antibody or antigen binding fragment is an IgG, IgM, IgA, Fab, single domain antibody.

[0008] In some embodiments, the isolated anti-SARS-CoV-2-Spike antibody or antigen binding fragment binds to a quaternary epitope of the Spike protein.

[0009] In some embodiments, the isolated anti-SARS-CoV-2-Spike antibody binds to the quaternary epitope through residues in the CDR.

[0010] In some embodiments, the isolated anti-SARS-CoV-2-Spike antibody or antigen binding fragment comprises a heavy chain variable domain sequence that is at least 90% identical to SEQ ID NO. 7.

[0011] In some embodiments, the isolated anti-SARS-CoV-2-Spike antibody or antigen binding fragment comprises a light chain variable domain sequence that is at least 90% identical to SEQ ID NO. 8.

[0012] In some embodiments, the isolated anti-SARS-CoV-2-Spike antibody or antigen binding fragment comprises a heavy chain variable region comprising complementarity determining regions (CDRs), wherein: a. the heavy chain CDR1 is SEQ ID NO. 1; b. the heavy chain CDR2 is SEQ ID NO. 2; and c. the heavy chain CDR3 is SEQ ID NO. 3; and a light chain variable region comprising CDRs, wherein: d. the light chain CDR1 is SEQ ID NO. 4; e. the light chain CDR2 is SEQ ID NO. 5; and f. the light chain CDR3 is SEQ ID NO. 6.

[0013] In some embodiments, the heavy chain variable region, SEQ ID NO. 7, comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 mutations at E38, S57, Y58, D59, G62, S63, N64, and/or R106.

[0014] In some embodiments, the mutation at position D59 is selected from D59G, D59L, D59K, D59I, D59M, D59W, D59T, D59F, or D59Y.

[0015] In some embodiments, the mutation at position N64 is selected from N64R or N64I.

[0016] In some embodiments, the mutation at position R106 is selected from R106E, R106D, R106N, R106Q, R106A, R106V, or R106L.

[0017] In some embodiments, the light chain variable region, SEQ ID NO. 8, comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 mutations at S69, L114, and/or R116.

[0018] In some embodiments, the isolated anti-SARS-CoV-2-Spike antibody is a human antibody.

[0019] In some embodiments, the isolated anti-SARS-CoV-2-Spike antibody is a humanized antibody.

[0020] In some embodiments, the isolated anti-SARS-CoV-2-Spike antibody is a monoclonal antibody.

[0021] In another aspect, the present disclosure provides method of treating a SARS-CoV-2 infection in a subject in need of such treatment, the method comprising administering to the subject an antibody described herein.

[0022] In some embodiments, the antibody is in a pharmaceutical formulation comprising a pharmaceutically acceptable carrier.

[0023] In another aspect, the present disclosure provides an isolated anti-SARS-CoV-2-Spike antibody, wherein the isolated antibody or antigen binding fragment comprises a heavy chain variable domain sequence that is at least 90% identical to SEQ ID NO. 7.

[0024] In some embodiments, the isolated anti-SARS-CoV-2-Spike antibody or antigen binding fragment comprises a light chain variable domain sequence that is at least 90% identical to SEQ ID NO. 8.

[0025] In some embodiments, the isolated anti-SARS-CoV-2-Spike antibody or antigen binding fragment comprises a heavy chain variable region comprising complementarity determining regions (CDRs), wherein: a. the heavy chain CDR1 is SEQ ID NO. 1; binds through T29, S36, Y37, E38); b. the heavy chain CDR2 is SEQ ID NO 2 (ISYDGSNK); binds through V55, I56, S57, Y58, D59, N64, Y66; and c. the heavy chain CDR3 is SEQ ID NO. 3 (ARLITMVRGEDY; binds through R106, L107, T109, M110, V112, R113, G114, E115), and a light chain variable region comprising CDRs, wherein: d. the light chain CDR1

is SEQ ID NO. 4 (QSISSY; binds through S36, Y38); e. the light chain CDR2 is SEQ ID NO. 5 (AAS; binds through S69, G70); and f. the light chain CDR3 is SEQ ID NO. 6 (QQSYNLPRT; binds through S107, Y108, N109, L114, R116).

[0026] In some embodiments, the heavy chain variable region, SEQ ID NO. 7, comprises at least one mutation at E38, S57, Y58, D59, G62, S63, N64, and/or R106.

[0027] In some embodiments, the mutation at position D59 is selected from D59G, D59L, D59K, D59I, D59M, D59W, D59T, D59F, or D59Y.

[0028] In some embodiments, the isolated anti-SARS-CoV-2-Spike antibody comprises a mutation at position N64 is selected from N64R or N64I.

[0029] In some embodiments, the isolated anti-SARS-CoV-2-Spike antibody mutation at position R106 is selected from R106E, R106D, R106N, R106Q, R106A, R106V, or R106L.

[0030] In some embodiments, the light chain variable region, SEQ ID NO. 8, comprises a mutation at S69, L114 and/or R116.

[0031] In some embodiments, the isolated anti-SARS-CoV-2-Spike antibody is a human antibody.

[0032] In some embodiments, the isolated anti-SARS-CoV-2-Spike antibody is a humanized antibody.

[0033] In some embodiments, the isolated anti-SARS-CoV-2-Spike antibody is a monoclonal antibody.

[0034] In some embodiments, isolated polynucleotide composition comprising a first nucleic acid encoding the VH region of any of the amino acid sequences described herein, and a second nucleic acid encoding the VL region of any of the amino acid sequences described herein.

[0035] In some embodiments, the present disclosure provides a plasmid comprising at least one polynucleotide sequence of any of the polynucleotide compositions described herein.

[0036] In some embodiments, the present disclosure provides a host cell comprising a polynucleotide sequence described herein.

[0037] In some embodiments, the present disclosure provides a method of producing antibodies comprising culturing the host cell under conditions that promote the production of the antibodies described herein.

[0038] In some embodiments, the present disclosure provides pharmaceutical compositions comprising as an active ingredient, at least one isolated antibody or antigen binding fragment thereof described herein and a pharmaceutically acceptable carrier.

[0039] In some embodiments, the present disclosure provides pharmaceutical composition described herein for use in preventing or retarding formation of SARs-CoV-2 mediated syncytia formation by binding to RBD and stabilizing a SARs-CoV-2 Spike protein conformation retarding or preventing S1 shedding and trapping a pre-fusion state of the SARs-CoV-2.

BRIEF DESCRIPTION OF THE DRAWINGS

[0040] The invention may be better understood from the following detailed description when read in conjunction with the accompanying drawings. Included in the drawings are the following figures:

[0041] Figure 1 shows isolation of SARS-CoV-2 receptor-blocking antibodies from a naïve human library (A) Blocking of ACE2/RBD (SARS-CoV-2) interactions by 27 Fab clones, tested by competition ELISA. The samples used in the assays were unpurified Fab from bacterial supernatant, hence the percentages of blocking were not indicative of their true potency. Red arrows indicate the 6 clones in subsequent studies. (B) KD of Fab based on 1:1 Langmuir fitting and apparent KD of IgG based on 1:2 bivalent analyte fitting of BLI sensorgrams for immobilized Fc-RBD. Values are the mean and standard deviation of two independent experiments. (C) Binding and dissociation of Fabs and IgGs to and from immobilized Fc-RBD by BLI. The concentration of Fabs and IgGs shown is 12.5 nM. (D) Epitope binning of 5A6 by BLI analysis. 5A6 is immobilized as the ligand. Tagless RBD is introduced as the first analyte. The second antibody is introduced as the second analyte. As controls, buffer alone, an isotype IgG and 5A6 IgG were included as the second analyte. See also Figures 7-10.

[0042] Figure 2 shows SARS-CoV-2 neutralization by receptor blocking antibodies. (A) Infection of CHO-ACE2 cells by SARS-CoV-2 pseudovirus were determined in the presence of receptor blocking IgGs (left panel) or Fabs (right panel). Luciferase activities in the CHO-ACE2 cells were measured, and the percent neutralization was calculated. Data are presented as means ± SEM in triplicates and are representative of two independent experiments. The IC50 was calculated by a variable slope four parameter non-linear regression model using either Graphpad PRISM 7 Software, or ^Quest Graph™ IC50 Calculator from AAT Bioquest Inc. (http://www.aatbio.com/tools/ic50calculator) with top and bottom constraints set at 100% and 0% respectively. (B) Infection of Vero E6 C1008 cells by SARS-CoV-2 live virus (hCoV-19/Singapore/3/2020) were determined in the presence of receptor blocking IgGs (left panel) or Fabs (right panel). Infection induced cytopathic effect was determined by detecting the amount of ATP present in the uninfected live cells from which the percent neutralization was calculated. Data are presented as means ± SEM in triplicates and are representative of two independent experiments. The IC50 was calculated by a variable slope four parameter non-linear regression model in Graphpad PRISM 7 Software. Pseudo- and live virus neutralization assays were not performed for 6F8 Fab due to 6F8 IgG's low and similar potency to other clones. (C) Evaluation of antiviral activity of 5A6 in a model of reconstituted human airway epithelia (HAE). Viral genome quantification was performed using RT-qPCR, and results presenting relative viral production (intracellular or apical) are expressed compared to control. Bars represent the means ± SD in duplicates. ***P <0.001, **P<0.01 and *P <0.05 compared to the control (no Ab) by one-way ANOVA. The trans-epithelial resistance (TEER in Ω/cm2) was measures at 48hpi. (D) Correlation curve of affinity/avidity for RBD and live virus neutralization potency (IC50) of receptor blocking IgG antibodies (circles), Fab antibodies (triangles) and ACE2-Fc (black diamond). The IC50 values were calculated using a four parameter logistic regression model in the Quest Graph™ IC50 Calculator from AAT Bioquest, Inc. (E) Binding of the IgG (solid lines, circles) and 5A6 Fab (dashed line, red triangle) to the purified SARS-CoV-2 pseudovirus. See also Figure 11 and Figure 15.

[0043] Figure 3 shows Anti-SARS-CoV-2 Spike RBD IgG antibodies affect trypsin induced cell syncytia formation. Vero E6 cells were transfected with furin recognition mutation of SARS-CoV-2 S-protein (R682RAR to A682AAR)-GFP. After 48 hours, the cell culture

medium was changed to DMEM (no serum) and treated WT/WO antibodies and incubated for 1 hour at 37°C. The cells were then treated WT/WO trypsin 15 μg/ml for 2 hours at 37°C. Cells were fixed with 4%PFA and stained with DAPI. (A) 5A6 IgG (20 μg/ml), 5A6 Fab (20 μg/ml), 3D11 IgG (20 μg/ml) and 2H4 IgG (20 μg/ml) treated S-protein expressing Vero E6 cell images in 10x, 20x and 40x objective view. Images were taken by Olympus confocal microscope. (B) Dosage response of 5A6 IgG, 5A6 Fab, 3D11 IgG and 2H4 IgG. S-protein expressing Vero E6 were treated with 0, 0.1, 0.5, 2, 10 μg/ml of each antibody. $2x10^5$ cells/sample were used for transfection of 5A6 IgG dosage response. 1.6x105 cells/sample were used for tranfection of 5A6 Fab and 3D11 IgG. Data quantification was calculated on syncytia numbers and nuclei number presented in each syncytium.

[0044] Figure 4 shows Structures of Spike-Fab complexes. (A) Schematic representation of three Fabs, 5A6 (goldenrod), 2H4 (purple), and 3D11 (sky blue), bound to the SARS-CoV-2 Spike protein. All Fabs are shown in relation to the complex formed by an open RBD (red) and the extracellular domain of ACE2 (rose brown). (B) Spike:2H4 complexes depicted as surface models, with 2H4 in purple, RBDs in coral, NTDs in plum, and the S2 core in rose brown. A triad of small circles to the lower left of each complex figure represent the three RBDs, with an inset arrow indicating the open (up) or closed (down) conformation, and purple fill indicated a bound Fab. The ensemble of Spike:2H4 complexes is reminescent of several intermediates in the conformational cycle triggered by serial binding of ACE2. (C) A cut-away of Spike:2H4 complex II highlighting the steric effect of 2H4 bound to a closed RBD on the counter-clockwise adjacent RBD and NTD. The 2H4-bound RBD clashes with both RBDs from either the fully closed trimer conformation (PDB: 6zgi; dark green) and the fully opened conformation with three ACE2 molecules (PDB: 7a98; cadet blue). (D) The single major Spike:3D11 complex, colors as in B (3D11 in sky blue). All RBDs are open, resembling the open trimer bound to three copies of ACE2. At right, the extracelluar view along the Spike trimer axis reveals its S2 core essentially unsheathed. (E) A cut-away of the Spike:3D11 complex showing its effect on the neigboring RBD is similar to that of 2H4, but less pronounced. Colors as in C., 3D11 in sky blue. (F) Spike:5A6 complexes, colors as in B. with 5A6 in goldenrod. Each complex exhibits the same quaternary state across two RBDs, with 5A6 bound between one closed RBD and a counter-clockwise adjacent open RBD, also bearing a copy of 5A6. The third RBD is usually open and may also bind 5A6. (G) The quaternary epitope seen in all Spike:5A6 complexes involves two distinct interfaces, and

appears to trap the pre-fusion Spike by locking closed one RBD. Binding to either interface results in steric occlusion of ACE2 (PDB: 7a94; cadet blue) from the RBD. Notably, both Fabs synergistically block ACE2 binding to the open RBD, while the Fab at the quaternary epitope blocks ACE2 binding to two RBDs simultaneously. See also Figures 12-14.

[0045] Figure 5 shows binding mode and epitope of 5A6. (A) A tour through the primary interface between Spike RBD and 5A6, using three immediately adjacent cross-sections along the viewing axis. Spike residues and labels are colored in coral or by heteroatom, and 5A6 residues are colored goldenrod, with labels for VH residues in black and VL residues in gray. Fab residue labels use the IMGT numbering system (Lefranc et al., 2003). Predicted hydrogen bonds are shown as dashed gray lines. The interface features extensive hydrogen bonding, numerous hydrophobic contacts, and multiple salt bridges. A aromatic cluster formed by 5A6 VL Y38 and Y108, and RBD F486, a salt bridge between 5A6 VH R106 and RBD E484, and a cation-pi interaction between Fab VH R112 and RBD Y449 are particularly notable. (B) The secondary interface between 5A6 and the neighboring open RBD comprises mostly hydrogen bonds, many of which involve main-chain atoms. Atom and label colors are as in (A). An interesting feature is stabilization of an alternate conformation of RBD R408 by 5A6 VL T20 and T88. (C) Two views of the Spike:5A6 IgG complex cryo-EM map (translucent gray) overlaid on the surface model of Spike:5A6 Fab complex I (colors as in Figure 4). The docked Fab complex model and the IgG complex cryo-EM density reveal a congruent epitope binding geometry in both formats, with two RBDs in the characteristic open/closed trapped conformation. Fc domains are visible as unmodeled blobs to the back of each Fab, and are like a superposition of multiple possible stoichiometries. The third RBD seems to be a superposition of open and closed RBDs with IgG bound. The surface model of a full-length human IgG x-ray crystal structure (PDB: 1hzh) is shown for scale (comparison is facilitated by use of orthographic projection).

[0046] Figure 6 shows spike functional modulation by receptor-blocking antibodies
A schematic model representing the possible effects of receptor-blocking antibodies, and ACE2 itself, on the conformational cycle of the SARS-CoV-2 Spike trimer. On the viral surface, the Spike is found predominantly in either the closed conformation, or a "receptor seeking" conformation with one RBD open. When serially bound by ACE2 or an orthosteric mimetic antibody like 2H4, the Spike trimer passes through a series of conformations that

eventually permit S1 shedding and the S2 post-fusion transition that mediates membrane fusion. Alternatively, allosteric antibodies such as 3D11 can advance the trimer directly to the end of the opening process, potentiating formation of syncytia through fusion of neighboring cells. Allosteric opening most likely contributes to lower potency in a high-affinity receptor-blocking antibody, and might even suggest the possibility antibody-dependent enhancement of infection. Finally, the Spike might instead be recognized by 5A6, which inhibits membrane fusion and syncytia formation by preventing S1 shedding and trapping the pre-fusion trimer. By enjoining the exposure and conformational transition of the S2 subunit, the 5A6 8 complex represents an unproductive dead-end for the Spike trimer. See also Figure 16.

[0047] Figure 7 shows blocking of ACE2/SARS-CoV-2 RBD interaction by 1F4, 2H4, 3D11, 3F11, 5A6 and 6F8 IgGs tested by competition ELISA, Related to Figure 1. Data are presented as means ± SD in triplicates and are representative of two independent experiments.

[0048] Figure 8 shows binding avidity of 1F4, 2H4, 3D11, 3F11, 5A6 and 6F8 IgG antibodies to SARS-CoV-2 Spike RBD proteins tested by ELISA, Related to Figure 1. Data are presented as means ± SD in triplicates and are representative of two independent experiments.

[0049] Figure 9 shows binding affinity of five Fab clones to SARS-CoV-2 Spike RBD protein measured by biolayer interferometry, Related to Figure 1 Fab binding to immobilized Fc-RBD was tested using a range of Fab concentrations from 100 nM to 3.125 nM (in 2-fold dilution). A representative set of measurements is shown with sensorgrams in black and curve fittings in red.

[0050] Figure 10 shows binding avidity of six IgGs to the RBD by biolayer interferometry, Related to Figure 1 IgG Binding to immobilized Fc-RBD was tested using a range of IgG concentrations from 12.5 nM to 0.39 nM (in 2-fold dilutions). The anti-Fc sensor chip was quenched with excess irrelevant, same-isotype IgG to prevent confounding from antibody binding directly to the chip. Representative sensorgrams are shown in black, with curve fittings in red.

[0051] Figure 11 shows the potency of 2H4, 3D11 and 5A6 IgG antibodies in neutralizing live SARS-CoV-2 virus assays determined by measuring the viral genome copy number

(GCN), Related to Figure 2. Infection of Vero E6 C1008 cells by SARS-CoV-2 live virus (hCoV-19/Singapore/3/2020) were determined in the presence of receptor blocking IgGs 2H4, 3D11 and 5A6. 48 hours post infection, culture supernatant was harvested and viral GCN was determined by RT-qPCR targeting the E gene and GCN values were determined by comparing Ct values against a logGCN standard curve. The GCN values were then converted to percent neutralization and plotted with a non-linear regression curve fit using PRISM. IC50 was calculated by a variable slope four parameter non-linear regression model in Graphpad PRISM 7 without or ^with top and bottom constraints set at 100% and 0% respectively. Data are presented as means ± SEM from 6 replicates.

[0052] Figure 12 shows Cryo-EM densities and resolution estimation, related to Figure 4. Density maps colored by local resolution, Fourier shell correlation curves, and particle orientation distributions for the structures reported in this work. All maps use the same local resolution scale, shown at the top right of the figure. (A) The apo Spike, with all RBDs closed. (B) The apo Spike, with one RBD open. (C) The Spike:3D11 complex. (D) Refinement of Spike:3D11, focused on the Fab variable domains and RBD 16 epitope. (E) Spike:2H4 complexes with one, two, or three Fabs bound. (F) Spike:5A6 complexes. (G) Refinment of Spike:5A6 complex I, focused on the Fab variable domains and quatenary epitope involving two RBDs (one open, with the clockwise adjacent RBD trapped closed).

[0053] Figure 13 shows additional structural details, related to Figure 4. (A) Eight subclasses of the Spike:3D11 complex, determined using symmetry relaxation in Relion 3.1. At left, top views show that these classes vary in the occupancy of Fab at each RBD. Only Fabs are colored, with missing or weak Fab densities are indicated by black ellipses. At right, two extremum classes and one intermediate show relative motion of the RBDs and NTDs, relaxations which likely contribute to the S2 unsheathing that eventually permits Spike-mediated membrane fusion. Fabs, RBDs, and NTDs are colored, and a dashed line delineates Fab and RBD. The general direction of S2-opening movements, as observed in the classes, are indicated by black arrows. (B) The quaternary epitope bound by 5A6 is cryptic because the Fab stabilizes unique conformations of RBDs, observed only the the complex, that contribute to the epitope. RBDs from Spike:5A6 complex I (goldenrod) are shown relative to the fully closed Spike (PDB: 6zgi, forest green) and to the Spike with one RBD open and bound to ACE2 (PDB: 7a94, cadet blue). Interestingly, the open RBD bound to 5A6 is more

open than that bound to ACE2, yet the neighboring RBD trapped closed by 5A6 is more closed than in the singular ACE2 complex or the fully closed Spike. (C) The hinge regions connecting the Fc domain of an IgG antibody to each of its two Fabs are 23 residues long, approximately 10 of which are flexible due to disulfide bonds. Assuming a standard polypeptide length of about 3.5 Å per residue, each hinge might extend as far as 35 Å, allowing for some 70 Å separation between the two Fabs. As shown, the shortest gaps between Fabs in the Spike:2H4 and Spike:5A6 complexes are ~90 Å, however variation of the elbow angles between Fab V and C domains could reduce the effective separation. Different Fab clones have elbow angles across just over 90° (Stanfield et al., 2006), and changes as great as 37° have been observed between multiple structures of the same clone (Wilson and Stanfield, 1994). For example, a 15° elbow bend might reduce separation by 10 Å at each Fab (20 Å total), to about the maximum length of the hinge. Bivalent, IgG-bound states thus likely differ in Fab elbow angle and feature some relaxation of the RBDs, in order to support the avid binding of IgG antibodies to Spike trimer observed in our experiments. D) Comparison of 2H4, 3D11, and 5A6 to non-receptor binding motif antibodies reported in literature. The 2D representation of molecular surface models, with superposed RBDs, shows that C135 and S309 bind to the outward face of the RBD, which is exposed in the closed state, while our antibodies 5A6 and 2H4 bind to the tip of the RBD at epitopes that partially overlap the RBS. Finally, COVA1-16, CR3022, and our 3D11 clone all bind to the inward face of the RBD, which is hidden in the closed state. These last three have overlapping epitopes, but different binding geometries such that, unlike COVA1-16 and 3D11, CR3022 actually clashes severely with the NTD even when the bound RBD is open. E) Example cryo-EM images and selected 2D class averages for Spike incubated with 2H4 IgG (left), 3D11 IgG (center), or 5A6 IgG (right). Images were collected on a Talos Arctica at 200 keV and low-pass filtered to 20 Å. The Spike:2H4 IgG sample contains numerous, relatively small particles, and some of its 2D class averages resemble monomeric Spike (classes 4 and 6) or two Spike monomers crosslinked by antibody (class 3). In the Spike:3D11 IgG sample, much of the protein is contained within stereotypical aggregates approximately 150 nm in size. Notable 2D averages resemble a Fab bound to Spike RBD (classes 3-5), rare Spike trimers in the closed conformation (class 2), and a potential Spike dimer or pair of monomers crosslinked by antibody (class 6). In contrast to the others, Spike:5A6 IgG is a well-behaved

sample (despite the crowded micrograph). The 2D class averages are easily recognizable as intact Spike trimer, as is the unique binding mode of 5A6.

[0054] Figure 14 shows Cryo-EM processing, Related to Figure 4 (A) A micrograph drawn from the Spike:5A6 complex dataset, representative of those 11 obtained for the Fab complexes. (B) Selected 2D class averages of Spike:5A6 particles, evincing clear secondary structure and multiple Fabs bound to the RBDs. (C) Cryo-EM image processing workflow for Spike alone, leading to structures of the trimer with all RBDs closed, and with one RBD open or in an intermediate state. (D) Processing workflow for the Spike:2H4 complex, resulting in structures with one, two, or three Fabs bound, as presented in the text.
(E) Processing workflow for the Spike:3D11 complex, culminating in a high-resolution structure of the Fab and RBD epitope. (F) Processing workflow for the Spike:5A6 complex, resulting in the complexes presented in the text. Note the fourth class found during the second 3D classification step is a lower resolution duplicate of Spike:5A6 complex III. Processing culminates in a high-resolution of the Fab and its quaternary epitope involving two RBDs.

[0055] Figure 15 shows antibody binding to Spike trimer measured by surface plasmon resonance, Related to Figure 2. (A) Binding affinity of Fab clones 1F4, 2H4, 3D11, 3D11, and 5A6 for intact Spike trimer measured by SPR. A range of Fab concentrations from 100 nM to 3.125 nM (in 2-fold serial dilution) are shown, with sensorgrams in black and curve fits in red. (B) Binding avidity of IgG clones 2H4, 3D11, 3F11, 5A6, and 6F8 for intact Spike trimer measured by SPR. A range of IgG concentrations from 12.5 nM to 0.39 nM (in 2-fold serial dilution) are shown, with sensorgrams in black and curve fits in red. (C) Log-log scatter plot comparing antibody binding constants for Fc-RBD (X axis) to those for Spike trimer (Y axis). Affinity or avidity of antibodies or Fab fragments for the flexible Fc-RBD construct represent binding without geometric constraints, while measurements using immobilized Spike trimers represent binding with the specific geometries afforded by the Spike:antibody complexes. For most species, SPR and BLI measurements are similar, however 3D11 IgG and ACE2-Fc bind significantly more weakly to relatively unrestricted Fc-RBD than to Spike trimer (note that the 3D11 IgG binds >10x more tightly than 3D11 Fab in both sets of experiments, indicating avid binding). 5A6 IgG binds somewhat more tightly to Spike trimer than to Fc-RBD, perhaps indicating that RBDs within a Spike trimer have particularly favorable geometries for binding.

[0056] Figure 16 shows neutralization of the SARS-CoV-2 pseudovirus with Spike mutant D614G, Related to Figure 6. A) Neutralization by 5A6 of SARS-CoV-2 pseudovirus bearing either wild-type Spike protein (red), or Spike with the D614G mutation (black). The efficacy of 5A6 IgG is against D614G mutant Spike is improved over wild-type. B) Neutralization by 3D11 of SARS-CoV-2 pseudovirus bearing either wild-type Spike protein (red), or Spike with the D614G mutation (black). 3D11 IgG suffers a severe loss of efficacy against the mutant pseudovirus (more than 5-fold weaker IC50). Data are presented as means ± SEM in triplicates and are representative of two independent experiments. IC50 was calculated by variable slope four parameter non-linear regression model using Graphpad PRISM 7 Software or ^Quest Graph™ IC50 23 Calculator from AAT Bioquest, Inc (https://www.aatbio.com/tools/ic50-calculator) with 24 top and bottom constrains set at 100% and 0% respectively.

[0057] Figure 17 shows variable domain identity to the germline sequences.

[0058] Figure 18 shows binding kinetics of antibodies and Fabs measured against Fc-RBD by BLI or Spike trimer by SPR.

[0059] Figure 19 shows Cryo-EM data collection, refinement and validation statistics.

[0060] Figure 20 shows an overview of the 5A6 binding surface.

[0061] Figure 21 shows an overview of the 5A6 binding surface, the main contributor from this loop is Tyr32 according to the sequence numbering in Figure 46 and/or Figure 47 (or the corresponding position according to IMGT numbering). L1 should be seen in context with L3.

[0062] Figure 22 shows an overview of the 5A6 binding surface. L2 is not forming a proper interface at this point. Diversifying upstream of Gly57 according to the sequence numbering in Figure 46 and/or Figure 47 (or the corresponding position according to IMGT numbering)might give a chance for a second interaction. Ser56 according to the sequence numbering in Figure 46 and/or Figure 47 (or the corresponding position according to IMGT numbering) might be a good option for a point mutation to introduce pi-stacking (Tyr) or a hydrogen bond.

[0063] Figure 23 shows an overview of the 5A6 binding surface. Tyr92 according to the sequence numbering in Figure 46 and/or Figure 47 (or the corresponding position according

to IMGT numbering)provides the main interaction. Pro95 according to the sequence numbering in Figure 46 and/or Figure 47 (or the corresponding position according to IMGT numbering) might be involved in constraining the loop in the desired geometry. L94 according to the sequence numbering in Figure 46 and/or Figure 47 (or the corresponding position according to IMGT numbering) engages RBD V483 (red circle) as part of an apparently critical hydrophobic core. Arg96 according to the sequence numbering in Figure 46 and/or Figure 47 (or the corresponding position according to IMGT numbering) is too distant to interact with the RBD Glu residue to productively interact and could become (for example) A) hydrophobic (Ala > Ile > Leu) or B) part of an engineered hydrogen bonding network (as an e.g. Asp) with HC residue Val50 according to the sequence numbering in Figure 46 (or the corresponding position according to IMGT numbering). L3 (in blue) forms an extended interface with L1 (in yellow) around a hydrogen bonding network. Changes to either loop will affect the other, making this hard to improve upon.

[0064] Figure 24 shows an overview of the 5A6 binding surface. Glu33 (or E38 according to IMGT numbering) is a suboptimal amino acid at this position. Neutralizing the charge (Asn > Gln) is an obvious choice. Alternatively, a hydrophobic can be placed here (A > I > L) and even a Gly compares very favorably with Glu (there is actually not a single amino acid that could be worse at this position, anything is better than Glu). H1 forms an extended interface with H2. Interdependency is much lower compared to the L1-L3 interface and offering a better overall target for diversification.

[0065] Figure 25 shows an overview of the 5A6 binding surface. H2 (green) forms a contiguous interface with H1 and contains Val50 (or V55 according to IMGT numbering) which engages V483 (red circle). Residues besides the Ser52 and Tyr53 (or S57 and Y58 according to IMGT numbering) could be good targets for diversification. Val50 (or V55 according to IMGT numbering) might be mutated in context with L94 (or L114 according to IMGT numbering) (corresponding LC residue) to compensate for V483A (potential hydrogen bonding network if both become Tyr).

[0066] Figure 26 shows an overview of the 5A6 binding surface, in particular H3 (blue).

[0067] Figure 27 shows an overview of the 5A6 binding surface.

[0068] Figure 28 shows an overview of the 5A6 binding surface.

[0069] Figure 29 shows ddg predictions with rosetta with limited backbone flexibility (cartoon of the structure is magenta and the ddg model is green). The ddg prediction accommodated V483A (in spike) and attempted to reconfigure a network around E38 (VH, CDR1) interacting with R116 (also known as raw sequence R96) (VL, CDR3). E38 (orange) when mutated to Q (red) could bond with E484 and allow R116 (also known as raw sequence R96) (orange in the structure, blue in the ddg model) to interact with N40 (VH, FR2, yellow) to maintain the scaffold.Figure 30 shows V483 in green sticks with hydrogens and L114 (VL, CDR3, magenta) in the ddg model (green) to show favorable interactions in the WT.

[0070] Figure 31 shows single point mutants at heavy chain position S52 according to the sequence numbering in Figure 46 (or S57 according to IMGT numbering). Mutations that improve binding (at least 5x slower Koff compared to 5A6 WT) are highlighted in Green. Mutations that weaken binding (at least 5x faster Koff compared to 5A6 WT) are highlighted as Red.

[0071] Figure 32 shows single point mutants at heavy chain position Y53 according to the sequence numbering in Figure 46 (or Y58 according to IMGT numbering). Mutations that improve binding (at least 5x slower Koff compared to 5A6 WT) are highlighted in Green. Mutations that weaken binding (at least 5x faster Koff compared to 5A6 WT) are highlighted as Red.

[0072] Figure 33 shows single point mutants at heavy chain position D54 according to the sequence numbering in Figure 46 (or D59 according to IMGT numbering). Mutations that improve binding (at least 5x slower Koff compared to 5A6 WT) are highlighted in Green. Mutations that weaken binding (at least 5x faster Koff compared to 5A6 WT) are highlighted as Red.

[0073] Figure 34 shows single point mutants at heavy chain position G55 according to the sequence numbering in Figure 46 (or G62 according to IMGT numbering). Mutations that improve binding (at least 5x slower Koff compared to 5A6 WT) are highlighted in Green. Mutations that weaken binding (at least 5x faster Koff compared to 5A6 WT) are highlighted as Red.

[0074] Figure 35 shows single point mutants at light chain position S56 according to the sequence numbering in Figure 46 (or S69 according to IMGT numbering). Mutations that

improve binding (at least 5x slower K_{off} compared to 5A6 WT) are highlighted in Green. Mutations that weaken binding (at least 5x faster Koff compared to 5A6 WT) are highlighted as Red.

[0075] Figure 36 shows single point mutants at heavy chain position N57 according to the sequence numbering in Figure 46 (or N64 according to IMGT numbering). Mutations that improve binding (at least 5x slower K_{off} compared to 5A6 WT) are highlighted in Green. Mutations that weaken binding (at least 5x faster K_{off} compared to 5A6 WT) are highlighted as Red.

[0076] Figure 37 shows single point mutants at light chain position L94 according to the sequence numbering in Figure 47 (or L114 according to IMGT numbering). Mutations that improve binding (at least 5x slower K_{off} compared to 5A6 WT) are highlighted in Green. Mutations that weaken binding (at least 5x faster K_{off} compared to 5A6 WT) are highlighted as Red.

[0077] Figure 38 shows single or double point mutants at light chain R96 and S56 according to the sequence numbering in Figure 46 and Figure 47 (or light chain R116 and S69 according to IMGT numbering). Mutations that improve binding (at least 5x slower K_{off} compared to 5A6 WT) are highlighted in Green. Mutations that weaken binding (at least 5x faster K_{off} compared to 5A6 WT) are highlighted as Red.

[0078] Figure 39 shows single point mutants at heavy chain E33 according to the sequence numbering in Figure 47 (or Y58 according to IMGT numbering) with single or double mutants at light chain R96 and S56 according to the sequence numbering in Figure 46 and Figure 47 (or R116 and S69 according to IMGT numbering).. Mutations that improve binding (at least 5x slower K_{off} compared to 5A6 WT) are highlighted in Green. Mutations that weaken binding (at least 5x faster K_{off} compared to 5A6 WT) are highlighted as Red.

[0079] Figure 40 shows binding ELISA of supernatants of 27 Fab clones to the antigen protein of biotinylated RBD-mFc. The 27 Fab clones were tested in a binding ELISA assay to assess their antigen binding to biotinylated RBD with a mouse Fc tag, and detected by goat-anti-human Fab-HRP.

[0080] Figure 41 shows blocking of spike RBD protein binding to ACE2-His by supernatants of 27 Fab clones. The 27 Fab clones were tested in an ELISA assay to assess their potency in

blocking spike protein binding to the recombinant ACE2 protein (ACE2 with His tag), with an irrelevant Fab clone used as a negative control. Out of 27 unique clones, 19 clones were selected and cloned into IgG1 format for further characterisation: 1A8, 1B11, 1C2, 1C3, 1E5, 1F4, 2C12, 2H4, 3A11, 3C5, 3D2, 3D11, 3E9, 3F1, 3F11, 3H7, 3H11, 5A6, and 6F8.

[0081] Figure 42 shows a binding ELISA of 19 IgGs to the antigen protein of biotinylated RBD-mFc. The 19 antibody clones were tested in a binding ELISA assay to assess their antigen binding to biotinylated RBD with a mouse Fc tag, and detected by anti-human Fc-HRP, with an irrelevant IgG1 used as a negative control antibody.

[0082] Figure 43 shows blocking of spike RBD protein binding to ACE2-Fc by 19 IgGs. The 19 antibody clones were tested in an ELISA assay to assess their potency in blocking spike protein binding to the recombinant ACE2 protein (ACE2 with human Fc tag), with an irrelevant IgG1 used as a negative control antibody.

[0083] Figure 44 shows pseudotyped virus neutralization assay by 19 IgGs. The 19 antibody clones were tested in a pseudotyped virus neutralization assay to assess their potency in neutralizing pseudotyped virus entry to ACE2 expression cells, with an irrelevant IgG1 used as a negative control antibody.

[0084] Figure 45 shows 5A6 IMGT numbering.

[0085] Figure 46 shows the variable heavy chain of 5A6 with corresponding raw sequence numbers, IMGT numbering, and Kabat numbering. The figure also shows prospective mutation essential and prospective mutation desired positions. Red shows primary interface residues, purple shows secondary interface residues. T29, S36, Y37, E38 interface with T470, I472, G482, V483, E484, F490 to form a buried surface. E38 receives electrophilic polarization by the side-chain of E484 and forms a hydrogen bond with the backbone amide nitrogen of E484. Y37 forms a parallel-displaced π-π interaction with F490. V55, I56, S57, Y58, D59, N64, Y66 form a buried interface with T470, E471, I472, N481, G482, V483. The positively charged ring edge of Y58 forms an anion-π interaction with E471. Y66 forms a hydrogen bond with N481. R106, L107, T109, M110, V112, R113, G114, E115 form a buried interface with E484, G485, Y489, F490, L492, Q493, S494. R106 forms a salt bridge with E484. R113 forms a cation-π interaction with Y449.

[0086] Figure 47 the variable light chain of 5A6 with corresponding raw sequence numbers, IMGT numbering, and Kabat numbering. Red shows primary interface residues, purple shows secondary interface residues. The figure also shows prospective mutation essential and prospective mutation desired positions. R18, T20, T22, S28, S36, S65, S77, S79, G80, S83, G84, T85, D86, T88, T90 form a buried interface with Y369, A372, F374, S375, T376, F377, K378, G404, D405, R408, Q414, K417, V503, G504, Y508. The backbone carbonyl oxygen of S83 forms a hydrogen bond with the backbone amide nitrogens of F377, K378. The backbone amide nitrogen of T85 forms a hydrogen bond with the backbone carbonyl oxygen of S375. D86, R24 form a hydrogen-bonding-network with Y508. S36 interfaces with F486 to form a buried surface. Y38 forms a hydrogen bonding network with N487, Y489 and a T-shaped π-π interaction with F486. S69 and G70 interface with Y449 to form a buried surface. S107, Y108, N109, L114, R116 interface with V483, E484, G485, F186 to form a buried surface. Y108 forms a face-to-face π-π interaction with F486. R116 forms a hydrogen bond with the backbone carbonyl oxygen of E484.

DETAILED DESCRIPTION OF THE INVENTION

I. Introduction

[0087] Infection by SARS-CoV-2 is initiated by binding of viral Spike protein to host receptor angiotensin-converting enzyme 2 (ACE2), followed by fusion of viral and host membranes. The virus enters cells by fusion of the viral envelop with cellular plasma membranes and alternatively by endocytosis and subsequent fusion of the viral envelope with endosomal membranes. The SARS-CoV-2 Spike protein comprises two subunits, S1 and S2, and is responsible for target recognition and mediating viral entry. Upon binding to the host cell receptor through the receptor binding domain (RBD) at the tip of the S1 subunit, the Spike protein undergoes dramatic conformational changes and proteolytic processing. Further shedding of the S1 subunit exposes the S2 subunit fusion peptide, which inserts into the host cell membrane and induces viral fusion. Both SARS-CoV-2 and SARS-CoV use ACE2 as the entry receptor to infect host cells. The RBD binds to ACE2 via the receptor binding motif (RBM), a small patch made up of about 20 amino acids.

[0088] In addition to mediating viral entry, excess Spike protein in the membranes of coronavirus-infected cells drives neighboring cells expressing ACE2 to fuse and form

syncytia (multinucleated giant cells) through a pH-independent mechanism. Synctia are associated with lung tissue damage in SARS-CoV and MERS-CoV infections, and have been widely observed in autopsies of patients afflicted with severe COVID-19. Synctia are also implicated in chronic cardiovascular injury due to COVID-19. Blocking the RBD/ACE2 interaction is useful in the treatment of coronaviruses, for example COVID-19.

[0089] Receptor engagement to a Spike RBD locks it in the open conformation and triggers a cooperative process in which the Spike conformational ensemble is driven towards further opening by successive rounds of receptor binding. This process culminates in unsheathing of the S1-ACE2 subcomplex. S1 shedding in turn facilitates the post-fusion state transition, leading to membrane fusion and viral entry. Spike protein on the surface of infected cells can also mediate ACE2-dependent fusion of neighboring cells to form multinucleated giant cells, presumably through the same cycle of proteolysis and conformational transitions. Genetic variation in Spike, inside and outside the RBM, can influence function by altering the conformational equilibrium of the trimer.

[0090] Infection by SARS-CoV-2 is initiated by binding of viral Spike protein to host receptor angiotensin-converting enzyme 2 (ACE2), followed by fusion of viral and host membranes. While antibodies that block this interaction are in emergency use as early COVID-19 therapies, precise determinants of neutralization potency remain unknown. A series of antibodies was discovered that all potently block ACE2 binding, yet exhibit divergent neutralization efficacy against live virus. Strikingly, these neutralizing antibodies can either inhibit or enhance Spike-mediated membrane fusion and formation of syncytia, which are associated with chronic tissue damage in COVID-19 patients. Cryo-EM structures are used to reveal the conformational landscapes of Spike-Fab complexes and provide 3D mapping of antibody-Spike epitopes, which are used to draw mechanistic insights that explain distinct bioactivities in the known intermediates in Spike opening (see Figure 6). Multiple cryogenic electron microscopy structures of Spike-antibody complexes reveal distinct binding modes that not only block ACE2 binding, but also alter the Spike protein conformational cycle triggered by ACE2 binding. The data in the present disclosure shows that stabilization of different Spike conformations leads to modulation of Spike-mediated membrane fusion, with profound implications in COVID-19 pathology and immunity. Before

the invention is described in greater detail, it is to be understood that the invention is not limited to particular embodiments described herein.

II. Definitions

[0091] Before the invention is described in greater detail, it is to be understood that the invention is not limited to particular embodiments described herein as such embodiments may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and the terminology is not intended to be limiting. The scope of the invention will be limited only by the appended claims. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Where a range of values is provided, it is understood that each intervening value, to the tenth of the unit of the lower limit unless the context clearly dictates otherwise, between the upper and lower limit of that range and any other stated or intervening value in that stated range, is encompassed within the invention. The upper and lower limits of these smaller ranges may independently be included in the smaller ranges and are also encompassed within the invention, subject to any specifically excluded limit in the stated range. Where the stated range includes one or both of the limits, ranges excluding either or both of those included limits are also included in the invention. Certain ranges are presented herein with numerical values being preceded by the term "about." The term "about" is used herein to provide literal support for the exact number that it precedes, as well as a number that is near to or approximately the number that the term precedes. In determining whether a number is near to or approximately a specifically recited number, the near or approximating unrecited number may be a number, which, in the context presented, provides the substantial equivalent of the specifically recited number. All publications, patents, and patent applications cited in this specification are incorporated herein by reference to the same extent as if each individual publication, patent, or patent application were specifically and individually indicated to be incorporated by reference. Furthermore, each cited publication, patent, or patent application is incorporated herein by reference to disclose and describe the subject matter in connection with which the publications are cited. The citation of any publication is for its disclosure prior to the filing date and should not be construed as an admission that the invention described

herein is not entitled to antedate such publication by virtue of prior invention. Further, the dates of publication provided might be different from the actual publication dates, which may need to be independently confirmed.

[0092] It is noted that the claims may be drafted to exclude any optional element. As such, this statement is intended to serve as antecedent basis for use of such exclusive terminology as "solely," "only," and the like in connection with the recitation of claim elements, or use of a "negative" limitation. As will be apparent to those of skill in the art upon reading this disclosure, each of the individual embodiments described and illustrated herein has discrete components and features readily separated from or combined with the features of any of the other several embodiments without departing from the scope or spirit of the invention. Any recited method may be carried out in the order of events recited or in any other order that is logically possible. Although any methods and materials similar or equivalent to those described herein may also be used in the practice or testing of the invention, representative illustrative methods and materials are now described.

[0093] As described in the present invention, the following terms will be employed, and are defined as indicated below.

[0094] The articles "a" and "an" are used herein to refer to one or to more than one (*i.e.,* to at least one) of the grammatical object of the article. By way of example, "an element" means one element or more than one element.

[0095] "About" as used herein when referring to a measurable value such as an amount, a temporal duration, and the like, is meant to encompass variations of ±20% or ±10%, more preferably ±5%, even more preferably ±1%, and still more preferably ±0.1% from the specified value, as such variations are appropriate to perform the disclosed methods.

[0096] By "antigen binding domain" or "ABD" herein is meant a set of six Complementary Determining Regions (CDRs) that, when present as part of a polypeptide sequence, specifically binds a target antigen as discussed herein. Thus, an "antigen binding domain" binds a target antigen as outlined herein. As is known in the art, these CDRs are generally present as a first set of variable heavy CDRs (vhCDRs or VHCDRs or CDR-HC or CDRH) and a second set of variable light CDRs (vlCDRs or VLCDRs or CDR-LC or CDRL), each comprising three CDRs: vhCDR1, vhCDR2, vhCDR3 (also referred to herein as CDRH1,

CDRH2, CDRH3) for the heavy chain and vlCDR1, vlCDR2 and vlCDR3 (also referred to herein as CDRL1, CDRL2, CDRL3) for the light chain. The CDRs are present in the variable heavy and variable light domains, respectively, and together form an Fv region. Thus, in some cases, the six CDRs of the antigen binding domain are contributed by a variable heavy and variable light chain. In a "Fab" format, the set of 6 CDRs are contributed by two different polypeptide sequences, the variable heavy domain (vh or VH; containing the vhCDR1, vhCDR2 and vhCDR3) and the variable light domain (vl or VL; containing the vlCDR1, vlCDR2 and vlCDR3), with the C-terminus of the vh domain being attached to the N-terminus of the CH1 domain of the heavy chain and the C-terminus of the vl domain being attached to the N-terminus of the constant light domain (and thus forming the light chain). In a scFv format, the VH and VL domains are covalently attached, generally through the use of a linker as outlined herein, into a single polypeptide sequence, which can be either (starting from the N-terminus) vh-linker-vl or vl-linker-vh, with the former being generally preferred (including optional domain linkers on each side, depending on the format used. As is understood in the art, the CDRs are separated by framework regions in each of the variable heavy and variable light domains: for the light variable region, these are FR1-vlCDR1-FR2-vlCDR2-FR3-vlCDR3-FR4, and for the heavy variable region, these are FR1-vhCDR1-FR2-vhCDR2-FR3-vhCDR3-FR4, with the framework regions showing high identity to human germline sequences. Antigen binding domains of the invention include, Fab, Fv and scFv.

[0097] By "linker" herein is meant a linker used in scFv and/or other antibody structures. Generally, there are a number of suitable scFv linkers that can be used, including traditional peptide bonds, generated by recombinant techniques. The linker peptide may predominantly include the following amino acid residues: Gly, Ser, Ala, or Thr. The linker peptide should have a length that is adequate to link two molecules in such a way that they assume the correct conformation relative to one another so that they retain the desired activity. In one embodiment, the linker is from about 1 to 50 amino acids in length, preferably about 1 to 30 amino acids in length. In one embodiment, linkers of 1 to 20 amino acids in length may be used, with from about 5 to about 10 amino acids finding use in some embodiments. Useful linkers include glycine-serine polymers, including for example (GS)n, (GSGGS)n, (GGGGS)n, and (GGGS)n, where n is an integer of at least one (and generally from 3 to 4), glycine-alanine polymers, alanine-serine polymers, and other flexible linkers. Alternatively, a variety of non-proteinaceous polymers, including but not limited to polyethylene glycol

(PEG), polypropylene glycol, polyoxyalkylenes, or copolymers of polyethylene glycol and polypropylene glycol, may find use as linkers, that is may find use as linkers. Other linker sequences may include any sequence of any length of CL/CH1 domain but not all residues of CL/CH1 domain; for example the first 5-12 amino acid residues of the CL/CH1 domains. Linkers can be derived from immunoglobulin light chain, for example Cκ or Cλ. Linkers can be derived from immunoglobulin heavy chains of any isotype, including for example Cγ1, Cγ2, Cγ3, Cγ4, Cα1, Cα2, Cδ, Cε, and Cμ. Linker sequences may also be derived from other proteins such as Ig-like proteins (*e.g.,* TCR, FcR, KIR), hinge region-derived sequences, and other natural sequences from other proteins. In some embodiments, the linker is a "domain linker", used to link any two domains as outlined herein together. While any suitable linker can be used, many embodiments utilize a glycine-serine polymer, including for example (GS)n, (GSGGS)n, (GGGGS)n, and (GGGS)n, where n is an integer of at least one (and generally from 3 to 4 to 5) as well as any peptide sequence that allows for recombinant attachment of the two domains with sufficient length and flexibility to allow each domain to retain its biological function.

[0098] The term "antibody" is used in the broadest sense and includes, for example, an intact immunoglobulin or an antigen binding portion. Antigen binding portions may be produced by recombinant DNA techniques or by enzymatic or chemical cleavage of intact antibodies. Thus the term antibody includes traditional tetrameric antibodies of two heavy chains and two light chains, as well as antigen binding fragments such as Fv, Fab and scFvs. In some cases, the invention provides bispecific antibodies that include at least one antigen binding domain as outlined herein.

[0099] By "modification" herein is meant an amino acid substitution, insertion, and/or deletion in a polypeptide sequence or an alteration to a moiety chemically linked to a protein. For example, a modification may be an altered carbohydrate or PEG structure attached to a protein. By "amino acid modification" herein is meant an amino acid substitution, insertion, and/or deletion in a polypeptide sequence. For clarity, unless otherwise noted, the amino acid modification is always to an amino acid coded for by DNA, *e.g.,* the 20 amino acids that have codons in DNA and RNA.

[00100] By "amino acid substitution" or "substitution" herein is meant the replacement of an amino acid at a particular position in a parent polypeptide sequence with a different

amino acid. In particular, in some embodiments, the substitution is to an amino acid that is not naturally occurring at the particular position, either not naturally occurring within the organism or in any organism. For example, the substitution M252Y refers to a variant polypeptide, in this case an Fc variant, in which the methionine at position 252 is replaced with tyrosine. For clarity, a protein which has been engineered to change the nucleic acid coding sequence but not change the starting amino acid (for example exchanging CGG (encoding arginine) to CGA (still encoding arginine) to increase host organism expression levels) is not an "amino acid substitution"; that is, despite the creation of a new gene encoding the same protein, if the protein has the same amino acid at the particular position that it started with, it is not an amino acid substitution.

[00101] By "variant protein" or "protein variant", or "variant" as used herein is meant a protein that differs from that of a parent protein by virtue of at least one amino acid modification. Protein variant may refer to the protein itself, a composition comprising the protein, or the amino sequence that encodes it. Preferably, the protein variant has at least one amino acid modification compared to the parent protein, *e.g.,* from about one to about seventy amino acid modifications, and preferably from about one to about five amino acid modifications compared to the parent. As described below, in some embodiments the parent polypeptide, for example an Fc parent polypeptide, is a human wild type sequence, such as the Fc region from IgG1, IgG2, IgG3 or IgG4. The protein variant sequence herein will preferably possess at least about 80% identity with a parent protein sequence, and most preferably at least about 90% identity, more preferably at least about 95%-98%-99% identity. Variant protein can refer to the variant protein itself, compositions comprising the protein variant, or the DNA sequence that encodes it.

[00102] Accordingly, by "antibody variant" or "variant antibody" as used herein is meant an antibody that differs from a parent antibody by virtue of at least one amino acid modification, "IgG variant" or "variant IgG" as used herein is meant an antibody that differs from a parent IgG (again, in many cases, from a human IgG sequence) by virtue of at least one amino acid modification, and "immunoglobulin variant" or "variant immunoglobulin" as used herein is meant an immunoglobulin sequence that differs from that of a parent immunoglobulin sequence by virtue of at least one amino acid modification. "Fc variant" or "variant Fc" as used herein is meant a protein comprising an amino acid modification in an Fc

domain. The Fc variants of the present invention are defined according to the amino acid modifications that compose them. Thus, for example M252Y or 252Y is an Fc variant with the substitution tyrosine at position 252 relative to the parent Fc polypeptide. Likewise, M252Y/S254T/T256E defines an Fc variant with the substitutions M252Y, S254T and T256E relative to the parent Fc polypeptide. The identity of the wild type amino acid may be unspecified, in which case the aforementioned variant is referred to as 252Y/254T/256E. It is noted that the order in which substitutions are provided is arbitrary, that is to say that, for example, 252Y/254T/256E is the same Fc variant as 254T/252Y/256E, and so on. For all positions discussed in the present disclosure that relate to antibodies, unless otherwise noted, amino acid position numbering is according to IMGT numbering. All IMGT numbering was done using ANARCI. (See Lefranc, M.-P. et al., Dev. Comp. Immunol., 27, 55-77 (2003) PMID: 12477501; hereby entirely incorporated by reference). Other types of numbering that may be used or equated to the IMGT numbering disclosed herein include Kabat for the variable region numbering and according to the EU index for the constant regions, including the Fc region. The EU index or EU index as in Kabat or EU numbering scheme refers to the numbering of the EU antibody (Edelman et al., 1969, Proc Natl Acad Sci USA 63:78-85, hereby entirely incorporated by reference.) The modification can be an addition, deletion, or substitution. Substitutions can include naturally occurring amino acids and, in some cases, synthetic amino acids. See Figure 46 and Figure 47 for examples of the numbering system used herein.

[00103] As used herein, "protein" herein is meant at least two covalently attached amino acids, which includes proteins, polypeptides, oligopeptides and peptides. The peptidyl group may comprise naturally occurring amino acids and peptide bonds.

[00104] By "Fab" or "Fab region" as used herein is meant the polypeptide that comprises the VH, CH1, VL, and CL immunoglobulin domains. Fab may refer to this region in isolation, or this region in the context of a full-length antibody, antibody fragment or Fab fusion protein.

By "Fv" or "Fv fragment" or "Fv region" as used herein is meant a polypeptide that comprises the VL and VH domains of a single antigen binding domain (ABD). As will be appreciated by those in the art, these generally are made up of two chains, or can be combined (generally with a linker as discussed herein) to form a scFv.

[00105] By "amino acid" and "amino acid identity" as used herein is meant one of the 20 naturally occurring amino acids that are coded for by DNA and RNA.

[00106] By "parent polypeptide" as used herein is meant a starting polypeptide that is subsequently modified to generate a variant. The parent polypeptide may be a naturally occurring polypeptide, or a variant or engineered version of a naturally occurring polypeptide. Parent polypeptide may refer to the polypeptide itself, compositions that comprise the parent polypeptide, or the amino acid sequence that encodes it. Accordingly, by "parent immunoglobulin" as used herein is meant an unmodified immunoglobulin polypeptide that is modified to generate a variant, and by "parent antibody" as used herein is meant an unmodified antibody that is modified to generate a variant antibody. It should be noted that "parent antibody" includes known commercial, recombinantly produced antibodies as outlined below.

[00107] By "heavy constant region" herein is meant the CH1-hinge-CH2-CH3 portion of an antibody, generally from human IgG1, IgG2 or IgG4.

[00108] By "target antigen" as used herein is meant the molecule that is bound specifically by the variable region of a given antibody.

[00109] By "target cell" as used herein is meant a cell that expresses a target antigen.

[00110] By "variable region" as used herein is meant the region of an immunoglobulin that comprises one or more Ig domains substantially encoded by any of the V.kappa., V.lamda., and/or VH genes that make up the kappa, lambda, and heavy chain immunoglobulin genetic loci respectively.

[00111] By "wild type or WT" herein is meant an amino acid sequence or a nucleotide sequence that is found in nature, including allelic variations. A WT protein has an amino acid sequence or a nucleotide sequence that has not been intentionally modified.

[00112] By "position" as used herein is meant a location in the sequence of a protein. Positions may be numbered sequentially, or according to an established format, for example the EU index for antibody numbering.

[00113] By "residue" as used herein is meant a position in a protein and its associated amino acid identity. For example, Asparagine 297 (also referred to as Asn297 or N297) is a residue at position 297 in the human antibody IgG1.

[00114] The antibodies of the present invention are generally recombinant. "Recombinant" means the antibodies are generated using recombinant nucleic acid techniques in exogenous host cells.

[00115] "Percent (%) amino acid sequence identity" with respect to a protein sequence is defined as the percentage of amino acid residues in a candidate sequence that are identical with the amino acid residues in the specific (parental) sequence, 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. Alignment for purposes of determining percent amino acid sequence identity can be achieved in various ways that are within the skill in the art, for instance, using publicly available computer software such as BLAST, BLAST-2, ALIGN or Megalign (DNASTAR) software. Those skilled in the art can determine appropriate parameters for measuring alignment, including any algorithms needed to achieve maximal alignment over the full length of the sequences being compared. One particular program is the ALIGN-2 program outlined at paragraphs [0279] to [0280] of US Pub. No. 20160244525, hereby incorporated by reference. Another approximate alignment for nucleic acid sequences is provided by the local homology algorithm of Smith and Waterman, Advances in Applied Mathematics, 2:482-489 (1981). This algorithm can be applied to amino acid sequences by using the scoring matrix developed by Dayhoff, Atlas of Protein Sequences and Structure, M.O. Dayhoff ed., 5 suppl. 3:353-358, National Biomedical Research Foundation, Washington, D.C., USA, and normalized by Gribskov, Nucl. Acids Res. 14(6):6745-6763 (1986).

[00116] An example of an implementation of this algorithm to determine percent identity of a sequence is provided by the Genetics Computer Group (Madison, WI) in the "BestFit" utility application. The default parameters for this method are described in the Wisconsin Sequence Analysis Package Program Manual, Version 8 (1995) (available from Genetics Computer Group, Madison, WI). Another method of establishing percent identity in the context of the present invention is to use the MPSRCH package of programs copyrighted by the University of Edinburgh, developed by John F. Collins and Shane S. Sturrok, and

distributed by IntelliGenetics, Inc. (Mountain View, CA). From this suite of packages, the Smith-Waterman algorithm can be employed where default parameters are used for the scoring table (for example, gap open penalty of 12, gap extension penalty of one, and a gap of six). From the data generated the "Match" value reflects "sequence identity." Other suitable programs for calculating the percent identity or similarity between sequences are generally known in the art, for example, another alignment program is BLAST, used with default parameters. For example, BLASTN and BLASTP can be used using the following default parameters: genetic code = standard; filter = none; strand = both; cutoff = 60; expect = 10; Matrix = BLOSUM62; Descriptions = 50 sequences; sort by = HIGH SCORE; Databases = non-redundant, GenBank + EMBL + DDBJ + PDB + GenBank CDS translations + Swiss protein + Spupdate + PIR. Details of these programs can be found at the internet address located by placing http:// in front of blast.ncbi.nlm.nih.gov/Blast.cgi.

[00117] The degree of identity between an amino acid sequence of the present invention ("invention sequence") and the parental amino acid sequence is calculated as the number of exact matches in an alignment of the two sequences, divided by the length of the "invention sequence," or the length of the parental sequence, whichever is the shortest. The result is expressed in percent identity.

[00118] In some embodiments, two or more amino acid sequences are at least 50%, 60%, 70%, 80%, or 90% identical. In some embodiments, two or more amino acid sequences are at least 95%, 97%, 98%, 99%, or even 100% identical.

[00119] "Specific binding" or "specifically binds to" or is "specific for" a particular antigen or an epitope means binding that is measurably different from a non-specific interaction. Specific binding can be measured, for example, by determining binding of a molecule compared to binding of a control molecule, which generally is a molecule of similar structure that does not have binding activity. For example, specific binding can be determined by competition with a control molecule that is similar to the target.

[00120] The term "Kassoc" or "Ka", as used herein, is intended to refer to the association rate of a particular antibody-antigen interaction, whereas the term "Kdis" or "Kd," as used herein, is intended to refer to the dissociation rate of a particular antibody-antigen interaction. The term "K_D", as used herein, is intended to refer to the dissociation constant, which is obtained from the ratio of Kd to Ka (*i.e.*, Kd/Ka) and is expressed as a

molar concentration (M). K_D values for antibodies can be determined using methods well established in the art. In some embodiments, the method for determining the K_D of an antibody is by using surface plasmon resonance, for example, by using a biosensor system such as a BIACORE® system. In some embodiments, the K_D of an antibody is determined by Bio-Layer Interferometry. In some embodiments, the K_D value is measured with the immobilized. In other embodiments, the K_D value is measured with the antibody (*e.g.,* parent mouse antibody, chimeric antibody, or humanized antibody variants) immobilized. In certain embodiments, the K_D value is measured in a bivalent binding mode. In other embodiments, the K_D value is measured in a monovalent binding mode.

[00121] A "disease" includes a state of health of an animal, including a human, wherein the animal cannot maintain homeostasis, and wherein if the disease is not ameliorated then the animal's health continues to deteriorate.

[00122] In contrast, a "disorder" in an animal, including a human, includes a state of health in which the animal is able to maintain homeostasis, but in which the animal's state of health is less favorable than it would be in the absence of the disorder. Left untreated, a disorder does not necessarily cause a further decrease in the animal's state of health.

[00123] The terms "treatment", "treating", "treat", and the like, refer to obtaining a desired pharmacologic and/or physiologic effect. The effect may be prophylactic in terms of completely or partially preventing a disease or symptom thereof or reducing the likelihood of a disease or symptom thereof and/or may be therapeutic in terms of a partial or complete cure for a disease and/or adverse effect attributable to the disease. "Treatment", as used herein, covers any treatment of a disease in a mammal, particularly in a human, and includes: (a) preventing the disease from occurring in a subject which may be predisposed to the disease but has not yet been diagnosed as having it; (b) inhibiting the disease, *i.e.,* arresting its development or progression; and (c) relieving the disease, *i.e.,* causing regression of the disease and/or relieving one or more disease symptoms. "Treatment" is also meant to encompass delivery of an agent in order to provide for a pharmacologic effect, even in the absence of a disease or condition. For example, "treatment" encompasses delivery of a composition that can elicit an immune response or confer immunity in the absence of a disease condition, *e.g.,* in the case of a vaccine.

[00124] As used herein, the term "mammal" refers to any mammal, including, but not limited to, mammals of the order Rodentia, such as mice and hamsters, and mammals of the order Logomorpha, such as rabbits. In some embodiments, the mammals are from the order Carnivora, including felines (cats) and canines (dogs). In some embodiments, the mammals are from the order Artiodactyla, including bovines (cows) and swines (pigs) or of the order Perssodactyla, including Equines (horses). It is most preferred that the mammals are of the order Primates, Ceboids, or Simoids (monkeys) or of the order Anthropoids (humans and apes). In some embodiments, the mammal is a human. In some embodiments, the mammal is cynomolgus monkey.

[00125] An "effective amount" or "therapeutically effective amount" of a composition includes that amount of the composition which is sufficient to provide a beneficial effect to the subject to which the composition is administered. An "effective amount" of a delivery vehicle includes that amount sufficient to effectively bind or deliver a composition.

[00126] By "individual" or "host" or "subject" or "patient" is meant any mammalian subject for whom diagnosis, treatment, or therapy is desired, particularly humans. Other subjects may include cynomolgus monkey, cattle, dogs, cats, guinea pigs, rabbits, rats, mice, horses, and so on.

[00127] The term "in combination with" as used herein refers to uses where, for example, a first therapy is administered during the entire course of administration of a second therapy; where the first therapy is administered for a period of time that is overlapping with the administration of the second therapy, *e.g.*, where administration of the first therapy begins before the administration of the second therapy and the administration of the first therapy ends before the administration of the second therapy ends; where the administration of the second therapy begins before the administration of the first therapy and the administration of the second therapy ends before the administration of the first therapy ends; where the administration of the first therapy begins before administration of the second therapy begins and the administration of the second therapy ends before the administration of the first therapy ends; where the administration of the second therapy begins before administration of the first therapy begins and the administration of the first therapy ends before the administration of the second therapy ends. As such, "in combination" can also refer to regimen involving administration of two or more therapies. "In combination with" as used

herein also refers to administration of two or more therapies which may be administered in the same or different formulations, by the same or different routes, and in the same or different dosage form type.

[00128] "Encoding" includes the inherent property of specific sequences of nucleotides in a polynucleotide, such as a gene, a cDNA, or an mRNA, to serve as templates for synthesis of other polymers and macromolecules in biological processes having either a defined sequence of nucleotides (*i.e.,* rRNA, tRNA and mRNA) or a defined sequence of amino acids and the biological properties resulting therefrom. Thus, a gene encodes a protein if, for example, transcription and translation of mRNA corresponding to that gene produces the protein in a cell or other biological system. Both the coding strand, the nucleotide sequence of which is identical to the mRNA sequence and is usually provided in sequence listings, and the non-coding strand, used as the template for transcription of a gene or cDNA, can be referred to as encoding the protein or other product of that gene or cDNA.

[00129] The term "nucleic acid" includes RNA or DNA molecules having more than one nucleotide in any form including single-stranded, double-stranded, oligonucleotide or polynucleotide. The term "nucleotide sequence" includes the ordering of nucleotides in an oligonucleotide or polynucleotide in a single-stranded form of nucleic acid.

[00130] By "nucleic acid construct" it is meant a nucleic acid sequence that has been constructed to comprise one or more functional units not found together in nature. Examples include circular, linear, double-stranded, extrachromosomal DNA molecules (plasmids), cosmids (plasmids containing COS sequences from lambda phage), viral genomes including non-native nucleic acid sequences, and the like.

[00131] The term "operably linked" as used herein includes a polynucleotide in functional relationship with a second polynucleotide, *e.g.,* a single-stranded or double-stranded nucleic acid moiety comprising the two polynucleotides arranged within the nucleic acid moiety in such a manner that at least one of the two polynucleotides is able to exert a physiological effect by which it is characterized, upon the other. By way of example, a promoter operably linked to the coding region of a gene is able to promote transcription of the coding region. The order specified when indicating operably linkage is not important. For example, the phrases: "the promoter is operably linked to the nucleotide sequence" and "the nucleotide sequence is operably linked to the promoter" are used interchangeably herein and

are considered equivalent. In some cases, when the nucleic acid encoding the desired protein further comprises a promoter/regulatory sequence, the promoter/regulatory sequence is positioned at the 5' end of the desired protein coding sequence such that it drives expression of the desired protein in a cell.

[00132] The terms "oligonucleotide," "polynucleotide," and "nucleic acid molecule", used interchangeably herein, refer to polymeric forms of nucleotides of any length, either ribonucleotides or deoxyribonucleotides. Thus, this term includes, but is not limited to, single-, double-, or multi-stranded DNA or RNA, genomic DNA, cDNA, DNA-RNA hybrids, or a polymer comprising purine and pyrimidine bases or other natural, chemically or biochemically modified, non-natural, or derivatized nucleotide bases. The backbone of the polynucleotide can comprise sugars and phosphate groups (as may typically be found in RNA or DNA), or modified or substituted sugar or phosphate groups.

[00133] The term "recombinant," as applied to a polynucleotide means the polynucleotide is the product of various combinations of cloning, restriction or ligation steps, and other procedures resulting in a construct distinct and/or different from a polynucleotide found in nature. The terms respectively include replicates of the original polynucleotide construct and progeny of the original virus construct.

[00134] The term "promoter" as used herein includes a DNA sequence operably linked to a nucleic acid sequence to be transcribed such as a nucleic acid sequence encoding a desired molecule. A promoter is generally positioned upstream of a nucleic acid sequence to be transcribed and provides a site for specific binding by RNA polymerase and other transcription factors.

[00135] A "vector" is capable of transferring gene sequences to target-cells. Typically, "vector construct," "expression vector," and "gene transfer vector," mean any nucleic acid construct capable of directing the expression of a gene of interest and which can transfer gene sequences to target-cells, which can be accomplished by genomic integration of all or a portion of the vector, or transient or inheritable maintenance of the vector as an extrachromosomal element. Thus, the term includes cloning, and expression vehicles, as well as integrating vectors.

[00136] The term "regulatory element" as used herein includes a nucleotide sequence which controls some aspect of the expression of nucleic acid sequences. Examples of regulatory elements illustratively include an enhancer, an internal ribosome entry site (IRES), an intron, an origin of replication, a polyadenylation signal (pA), a promoter, an enhancer, a transcription termination sequence, and an upstream regulatory domain, which contribute to the replication, transcription, and/or post-transcriptional processing of a nucleic acid sequence. In cases, regulatory elements can also include cis-regulatory DNA elements as well as transposable elements (TEs). Those of ordinary skill in the art are capable of selecting and using these and other regulatory elements in an expression construct with no more than routine experimentation. Expression constructs can be generated using a genetic recombinant approach or synthetically using well-known methodology.

[00137] A "control element" or "control sequence" is a nucleotide sequence involved in an interaction of molecules contributing to the functional regulation of a polynucleotide, including replication, duplication, transcription, splicing, translation, or degradation of the polynucleotide. The regulation may affect the frequency, speed, or specificity of the process, and may be enhancing or inhibitory in nature. Control elements known in the art include, for example, transcriptional regulatory sequences such as promoters and enhancers. A promoter is a DNA region capable under certain conditions of binding RNA polymerase and initiating transcription of a coding region usually located downstream (in the 3' direction) from the promoter.

[00138] The statement that an amino acid residue is "phosphorylated" used herein means that a phosphate group is ester-linked to the side chain of the amino acid residue. Typical amino acid residues that may be phosphorylated include serine (Ser), threonine (Thr), and tyrosine (Tyr).

[00139] As used herein, the term "pharmaceutical composition" refers to the combination of an active agent with a carrier, inert or active, making the composition especially suitable for diagnostic or therapeutic use in vivo or ex vivo.

[00140] As used herein, the term "pharmaceutically acceptable carrier" refers to any of the standard pharmaceutical carriers, such as a phosphate buffered saline solution, water, emulsions (*e.g.,* such as an oil/water or water/oil emulsions), and various types of wetting agents. The compositions also can include stabilizers and preservatives. For examples of

carriers, stabilizers and adjuvants, see *e.g.*, Martin, Remington's Pharmaceutical Sciences, 15th Ed., Mack Publ. Co., Easton, PA [1975].

[00141] Throughout the description, where compositions are described as having, including, or comprising specific components, or where processes and methods are described as having, including, or comprising specific steps, it is contemplated that, additionally, there are compositions of the present invention that consist essentially of, or consist of, the recited components, and that there are processes and methods according to the present invention that consist essentially of, or consist of, the recited processing steps.

[00142] As a general matter, compositions specifying a percentage are by weight unless otherwise specified. Further, if a variable is not accompanied by a definition, then the previous definition of the variable controls.

[00143] Various aspects of the invention are set forth below in sections; however, aspects of the invention described in one particular section are not to be limited to any particular section.

III. Detailed Description of the Embodiments

A. Antibodies

[00144] The present disclosure provides novel anti-SARS-CoV-2-Spike antibodies. Such antibodies bind human SARS-CoV-2.

[00145] Table 1 lists exemplary peptide sequences of heavy chain variable regions and light chain variable regions that, in combination as designated in Table 1, are exemplary antibodies to SARS-CoV-2. In some embodiments, the heavy chain variable region and the light chain variable region are arranged in a Fab format.

Table 1		
Clone	Heavy chain variable region amino acid sequence	Light chain variable region amino acid sequence
5A6	QVQLQESGGGLVQPGGSLRLSCAASGFTFSSYEMNWVRQAPGKGLEWVAVISYDGSNKYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARLITMVRGEDYWGQGTL (SEQ ID NO: 7)	DIQLTQSPSSLSASVGHRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYNLPRTFGGGTK (SEQ ID NO: 8)

	CDRH1: GFTFSSYE (SEQ ID NO: 1) CDRH2: ISYDGSNK (SEQ ID NO: 2) CDRH3: ARLITMVRGEDY (SEQ ID NO: 3)	CDRL1: QSISSY (SEQ ID NO: 4) CDRL2: AAS (SEQ ID NO: 5) CDRL3: QQSYNLPRT (SEQ ID NO: 6)
1A5	QVQLQESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKDYFRWLWGQGTL (SEQ ID NO: 15) CDRH1: GFTFSSYA (SEQ ID NO: 9) CDRH2: ISGSGGST(SEQ ID NO: 10) CDRH3: AKDYFRWL (SEQ ID NO: 11)	NFMLTQPHSVSESPGKTVAISCTGNSGSIASHYVQWFQQRPGSAPTTVIYEDNQRPSGVPDRFSGSIDRSSNSASLTISGLKSEDEADYYCQSYGSGFVVFGGGTK (SEQ ID NO: 16) CDRL1: SGSIASHY (SEQ ID NO: 12) CDRL2: EDN (SEQ ID NO: 13) CDRL3: QSYGSGFVV (SEQ ID NO: 14)
1A8	QVQLQESGPGLVKPSETLSLTCTVSGVSISSRSDHWGWVRQPPGKGLEWIGSISYSGSTYYNPSLKSRVTISVDTSKNQLSLKLSSVTAADTAVYYCARLASLYSTFDIWGHGTL(SEQ ID NO: 23) CDRH1: GVSISSRSDH (SEQ ID NO: 17) CDRH2: ISYSGST (SEQ ID NO: 18) CDRH3: ARLASLYSTFDI (SEQ ID NO: 19)	EIVLTQSPDSLAVSLGERATINCKSSQSVLYSSNNKNYLAWYQQKPGQPPKLLIYWASTRESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQQYYGTPYTFGQGTK (SEQ ID NO: 24) CDRL1: QSVLYSSNNKNY (SEQ ID NO: 20) CDRL2: WAS (SEQ ID NO: 21) CDRL3: QQYYGTPYT (SEQ ID NO: 22)
1B2	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYYMHWVRQAPGQGLEWMGIINPSGGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCATGEMAGDFDYWGQGTL (SEQ ID NO: 31) CDRH1: GYTFTSYY (SEQ ID NO: 25)	NFMLTQPHSVSESPGKTVTISCTGSGGRIATNYVQWYQQRPGSAPTTVIYEDNKRPSGVPHRFSGSIDASSNSASLTISGLETEDEADYYCQSHDTSRQAVFGGGTK (SEQ ID NO: 32) CDRL1: GGRIATNY (SEQ ID NO: 28)

	CDRH2: INPSGGST (SEQ ID NO: 26) CDRH3: ATGEMAGDFDY (SEQ ID NO: 27)	CDRL2: EDN (SEQ ID NO: 29) CDRL3: QSHDTSRQAV (SEQ ID NO: 30)
1B11	EVQLVQSGAEVKKPGSSVKVSC KASGGTFSSYAISWVRQAPGQG LEWMGGIIPIFGTANYAQKFQG RVTITADESTSTAYMELSSLRSE DTAVYYCARDNPGYSSSWSPN WFDPWGQGTL (SEQ ID NO: 39) CDRH1: GGTFSSYA (SEQ ID NO: 33) CDRH2: IIPIFGTA (SEQ ID NO: 34) CDRH3:ARDNPGYSSSWSPNWF DP (SEQ ID NO: 35)	DVVMTQSPLSLPVTPGEPASIS CRSSQSLLYSNGYNYLDWYL QKPGQSPQLLIYLGSNRASGV PDRFSGSGSGTDFTLKISRVEA EDVGVYYCMQALQTPYTFGQ GTK (SEQ ID NO: 40) CDRL1: QSLLYSNGYNY (SEQ ID NO: 36) CDRL2: LGS (SEQ ID NO: 37) CDRL3: MQALQTPYT (SEQ ID NO: 38)
1C2	EVQLVQSGAEVKKPGASVKVSC KASGYTFTSYYMHWVRQAPGQ GLEWMGIINPSGGSTSYAQKFQ GRVTMTRDTSTSTVYMELSSLR SEDTAVYYCASSSAGTFYFDYW GQGTL (SEQ ID NO: 47) CDRH1: GYTFTSYY (SEQ ID NO: 41) CDRH2: INPSGGST (SEQ ID NO: 42) CDRH3: ASSSAGTFYFDY (SEQ ID NO: 43)	DVVMTQSPLSLPVTPGEPASIS CRSSQSLLHSNGFTYLDWYL QKPGLSPQLLIYLGSNRAPGV PDRFSGSGSGTDFTLKISRVEA EDVGVYYCMQGIQTPLTFGG GTK (SEQ ID NO: 48) CDRL1: QSLLHSNGFTY (SEQ ID NO: 44) CDRL2: LGS (SEQ ID NO: 45) CDRL3: MQGIQTPLT (SEQ ID NO: 46)
1C3	EVQLVQSGAEVKKPGASVKVSC KASGYPFSTYYIHWVRQAPGQG LEWMGIIDPSGGSTSYAQKFQG RVTMTRDTSTSTVYMELRSLRS	NFMLTQPHSVSESPGKTVTIS CTRSSGSIASYYVQWYQQRP GSSPTTVIYEDDQRPSGVPDR FSGSIDSASNSASLTISGLQTE

	DDTAVFYCARVAEQHLDYYFDYWGQGTL (SEQ ID NO: 55) CDRH1: GYPFSTYY (SEQ ID NO: 49) CDRH2: IDPSGGST (SEQ ID NO: 50) CDRH3: ARVAEQHLDYYFDY (SEQ ID NO: 51)	DEADYYCQSFDSSIQHVVFGGGTQ (SEQ ID NO: 56) CDRL1: SGSIASYY (SEQ ID NO: 52) CDRL2: EDD (SEQ ID NO: 53) CDRL3: QSFDSSIQHVV (SEQ ID NO: 54)
1D12	EVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMGWISAYNGNTNYAQKLQGRVTMTTDTSTSTAYMELRSLRSEDTAVYYCARLEWLRGAFDIWGQGTT (SEQ ID NO: 63) CDRH1: GGTFSSYA (SEQ ID NO: 57) CDRH2: ISAYNGNT (SEQ ID NO: 58) CDRH3: ARLEWLRGAFDI (SEQ ID NO: 59)	NFMLTQPHSVSESPGKTVTISCTGSSGSIASNYVHWYQQRPGSAPTTVIYEDNQRPSGVPDRFSGSIDSSSNSASLTISGLKTEDEADYYCQSYDGSAWVFGGGTK (SEQ ID NO: 64) CDRL1: SGSIASNY (SEQ ID NO: 60) CDRL2: EDN (SEQ ID NO: 61) CDRL3: QSYDGSAWV (SEQ ID NO: 62)
1E5	EVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMGGIIPIFGTANYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARALVGKWLLLRGFDYWGQGTL (SEQ ID NO: 71) CDRH1: GGTFSSYA (SEQ ID NO: 65) CDRH2: IIPIFGTA (SEQ ID NO: 66) CDRH3: ARALVGKWLLLRGFDY (SEQ ID NO: 67)	NFMLTQPHSVSESPGKTLTISCTRSSGRIASNYVQWYQQRPGSAPTTVIYEDTQRPSGVPDRFSGSIDSSSNSASLTISGLKTEDEADYYCQSFDSGNQRVVFGGGTK (SEQ ID NO: 72) CDRL1: SGRIASNY (SEQ ID NO: 68) CDRL2: EDT (SEQ ID NO: 69) CDRL3: QSFDSGNQRVV (SEQ ID NO: 70)

1F4	QVQLQQSGPGLVKPSQTLSLTC AISGDSVSSNSAAWNWIRQSPSR GLEWLGRTYYRSKWYNDYAVS VKSRITINPDTSKNQFSLQLNSV TPEDTAVYYCAREKGIEGPAFDP WGQGTL (SEQ ID NO: 79) CDRH1: GDSVSSNSAA (SEQ ID NO: 73) CDRH2: TYYRSKWYN (SEQ ID NO: 74) CDRH3: AREKGIEGPAFDP (SEQ ID NO: 75)	QSVLTQPPSVSGTPGQRVTISC SGSSSNIGRNFVSWYQQLPGA APRLLMYRNNQRPSGVPDRF SGSESATSASLAITGLQPEDEA DYYCQSYDNSLFVVFGGGTK (SEQ ID NO: 80) CDRL1: SSNIGRNF (SEQ ID NO: 76) CDRL2: RNN (SEQ ID NO: 77) CDRL3: QSYDNSLFVV (SEQ ID NO: 78)
1H7	QVQLQQWGAGLLKPSETLPLTC AVYGGSFSGYYWSWIRQPPGKG LEWIGEINHSGSTNYNPSLKSRV TISVDTSKNQFSLKLSSVTAADT AVYYCARGRWLRGAFDIWGQG TM (SEQ ID NO: 87) CDRH1: GGSFSGYY (SEQ ID NO: 81) CDRH2: INHSGST (SEQ ID NO: 82) CDRH3: ARGRWLRGAFDI (SEQ ID NO: 83)	NFMLTQPHSVSESPGKTVTIS CTRSSGSIASNYVQWYQQRP GSSPTTVIYEDNQRPSGVPDR FSGSVDSSSNSASLTISGLKTE DEADYYCQSYDENIRVFGGG TK (SEQ ID NO: 88) CDRL1: SGSIASNY (SEQ ID NO: 84) CDRL2: EDN(SEQ ID NO: 85) CDRL3: QSYDENIRV (SEQ ID NO: 86)
2C9	QVQLVQSGAEVKKPGSSVKVSC KASGGTFSSYAISWVRQAPGQG LEWMGRIIPILGIANYAQKFQGR VTITADKSTSTAYMELSSLRSED TAVYYCARHGGVGATTGYYYM DVWGKGTT (SEQ ID NO: 95) CDRH1: GGTFSSYA (SEQ ID NO: 89) CDRH2: IIPILGIA (SEQ ID NO: 90)	EIVLTQSPGTLSSSPGERATLS CTASQTVGGSYLAWYQQKR GQPPRLLIYGASTRAPGIPERF SGSGSGTDFTLTISTLEPEDFA VYFCQQYASSRTFGQGTR (SEQ ID NO: 96) CDRL1: QTVGGSY (SEQ ID NO: 92) CDRL2: GAS (SEQ ID NO: 93)

	CDRH3: ARHGGVGATTGYYYMDV (SEQ ID NO: 91)	CDRL3: QQYASSRT (SEQ ID NO: 94)
2C10	QVQLQQWGAGLLKPSETLSLTC GVYGGSFSGYYWSWIRQSPGKG LEWIGEINYRGNTNYNPSLKSRV TISVDTSKNQFSLNVNSVTAADT AVYYCARWDGGNSVDHWGQG TL (SEQ ID NO: 103) CDRH1: GGSFSGYY (SEQ ID NO: 97) CDRH2: INYRGNT (SEQ ID NO: 98) CDRH3: ARWDGGNSVDH (SEQ ID NO: 99)	QSVVTQPPSASGSPGQSVTISC SGSSSTIGTNYVAWYQQLPGT APKLLIYDNYKRPSGIPDRFSG WRSGTSATLVISGLQTGDEAD YYCGTWDSRLSVGVFGGGTK (SEQ ID NO: 104) CDRL1: SSTIGTNY (SEQ ID NO: 100) CDRL2: DNY (SEQ ID NO: 101) CDRL3: GTWDSRLSVGV (SEQ ID NO: 102)
2C12	QVQLVESGGGVVQPGRSLRLSC AASGFTFSSYAMHWVRQAPGK GLEWVAVISYDGSNKYYADSV KGRFTISRDNSKNTLYLQMNSL RAEDTAVYYCARGGRFHYYYY AMDVWGQGTT (SEQ ID NO: 111) CDRH1: GFTFSSYA (SEQ ID NO: 105) CDRH2: ISYDGSNK (SEQ ID NO: 106) CDRH3: ARGGRFHYYYYAMDV (SEQ ID NO: 107)	DIQMTQSPSSLSASIGDRVTIT CRASQSINIYLNWYQQKPGK APKLLIYAASSLQSGVPSRFSG SGSATDFTLTISSLQPEDFATY YCQQSYITPQTFGQGTK (SEQ ID NO: 112) CDRL1: QSINIY (SEQ ID NO: 108) CDRL2: AAS (SEQ ID NO: 109) CDRL3: QQSYITPQT (SEQ ID NO: 110)
2D3	EVQLVQSGAEVKKPGSSVKVSC KASGGTFSSYAISWVRQAPGQG LEWMGGIIPIFGTANYAQKFQG RVTITADESTSTAYMELSSLRSE DTAVYYCASSGWLRGAFDIWG QGTM (SEQ ID NO: 119)	NFMLTQPHSVSESPGKTVTIS CTGSSGSIASNYVQWYQQRP GSAPTTIIYEDNQRPSGVPDRF SGSVDSSSNSASLTISGLKTED EADYYCQSYDSSNWVFGGGT K (SEQ ID NO: 120)

	CDRH1: GGTFSSYA (SEQ ID NO: 113) CDRH2: IIPIFGTA (SEQ ID NO: 114) CDRH3: ASSGWLRGAFDI (SEQ ID NO: 115)	CDRL1: SGSIASNY (SEQ ID NO: 116) CDRL2: EDN (SEQ ID NO: 117) CDRL3: QSYDSSNWV (SEQ ID NO: 118)
2G7	QVQLQQWGAGLLKPSETLSLTC AVYGGSFSGYYWSWIRQPPGKG LEWIGEINHSGSTNYNPSLKSRV TISVDTSKNQFSLKLSSVTAADT AVYYCARGKWLRGAFDIWGQG TM (SEQ ID NO: 127) CDRH1: GGSFSGYY (SEQ ID NO: 121) CDRH2: INHSGST (SEQ ID NO: 122) CDRH3: ARGKWLRGAFDI (SEQ ID NO: 123)	NFMLTQPHSVSESPGKTITISC TRSGGTIGSNYVQWYQQRPG SSPTTVIYEDNQRPSGVPDRFS GSIDSSSNSASLTISGLKTEDE ADYYCQSYDSSNRVFGGGTK (SEQ ID NO: 128) CDRL1: GGTIGSNY (SEQ ID NO: 124) CDRL2: EDN (SEQ ID NO: 125) CDRL3: QSYDSSNRV (SEQ ID NO: 126)
2H4	QVQLVQSGAEVTKPGASVKVSC KASGYTFSGYYIHWVRQAPGQG LEWMGRVNPNSGGTKYAQKFQ DRVTLTRDTSISTAYMELTSLRS DDTAMYFCARGGRPGLPAAGYI DYWGQGTL (SEQ ID NO: 135) CDRH1: GYTFSGYY (SEQ ID NO: 129) CDRH2: VNPNSGGT (SEQ ID NO: 130) CDRH3: ARGGRPGLPAAGYIDY (SEQ ID NO: 131)	ETTLTQSPAFVSAAPGDKVSIS CKASEFIGDDVNWYQQKPGE APVFIIQEARVPVRGIPPRFSG SGYGTDFTLTIDDIQSEDSAFY FCLQYDSFPLTFGQGTK (SEQ ID NO: 136) CDRL1: EFIGDD (SEQ ID NO: 132) CDRL2: EAR (SEQ ID NO: 133) CDRL3: LQYDSFPLT (SEQ ID NO: 134)
3A11	EVQLVQSGAEVKKPGASVKVSC KASGYTFSTYDISWVRQAPGQG LEWMGWISTYNGDTNYAQKFQ	QSALTQPASVSGSPGQAITMP CTGTSSDVGTYNYVSWYQHF PGKAPKLLIYDVSHRPAGISD

	GRVTMTTDTSTSTIYMELRSLRSDDTAVYYCARGDSSVGYEYFQHWGQGTL (SEQ ID NO: 143) CDRH1: GYTFSTYD (SEQ ID NO: 137) CDRH2: ISTYNGDT (SEQ ID NO: 138) CDRH3: ARGDSSVGYEYFQH (SEQ ID NO: 139)	RFSGSKSGNTASLTISGLQAEDEADYYCASFSSSSTLLVFGGGTK (SEQ ID NO: 144) CDRL1: SSDVGTYNY (SEQ ID NO: 140) CDRL2: DVS (SEQ ID NO: 141) CDRL3: ASFSSSSTLLV (SEQ ID NO: 142)
3C5	QVQLQQWGAGLLKPSETLSLTCGVYGGSLSGYYWSWIRQPPGKGLEWIGEINHSGSTNYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARRWWLRGAFDIWGQGTT (SEQ ID NO: 151) CDRH1: GGSLSGYY (SEQ ID NO: 145) CDRH2: INHSGST (SEQ ID NO: 146) CDRH3: ARRWWLRGAFDI (SEQ ID NO: 147)	NFMLTQPHSVSESPGKTVTISCTGSSGSIASNYVQWYQQRPGSAPTTVIYEDNQRPSGVPDRFSGSIDSSSNSASLTISGLKTEDEADYYCQSYDSSNWVFGGGTK (SEQ ID NO: 152) CDRL1: SGSIASNY (SEQ ID NO: 148) CDRL2: EDN (SEQ ID NO: 149) CDRL3: QSYDSSNWV (SEQ ID NO: 150)
3D2	QVQLQQWGAGLLKPSETLSLTCAVYGGSFSGYYWSWIRQPPGKGLEWIGEINHSGSTNYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARRWWLRGAFDIWGQGTT (SEQ ID NO: 159) CDRH1: GGSFSGYY (SEQ ID NO: 153) CDRH2: INHSGST (SEQ ID NO: 154) CDRH3: ARRWWLRGAFDI (SEQ ID NO: 155)	NFMLTQPHSVSESPGKTVTISCTGSSGSIARNYVHWYQQRPGSAPTTVIYEDNQRPSGVPDRFSGSIDSSSNSASLTISGLKTEDEADYYCQSYDRTNKRVFGGGTR (SEQ ID NO: 160) CDRL1: SGSIARNY (SEQ ID NO: 156) CDRL2: EDN (SEQ ID NO: 157) CDRL3: QSYDRTNKRV (SEQ ID NO: 158)

3D11	QVQLQQWGAGLLKPSETLSLTC AVYGGSFSGYYWSWIRQPPGKG LEWIGEINHSGSTNYNPSLKSRV TISVDTSKNQFSLKLSSVTAADT AVYYCARRWWLRGAFDIWGQ GTT (SEQ ID NO: 167) CDRH1: GGSFSGYY (SEQ ID NO: 161) CDRH2: INHSGST (SEQ ID NO: 162) CDRH3: ARRWWLRGAFDI (SEQ ID NO: 163)	NFMLTQPHSVSASPGKTVTIP CTGSSGNIASNYVQWYQQRP GSAPTTVIYEDNQRPSGVPDR FSGSIDSSSNSASLTISGLKTED EADYYCQSYDNNIQVFGGGT K (SEQ ID NO: 168) CDRL1: SGNIASNY (SEQ ID NO: 164) CDRL2: EDN (SEQ ID NO: 165) CDRL3: QSYDNNIQV (SEQ ID NO: 166)
3E9	EVQLVQSGAEVKKPGASVKVSC KASGYTFTSYGISWVRQAPGQG LEWMGWISAYNGNTNYAQKLQ GRVTMTTDTSTSTAYMELRSLR SDDTAVYYCARGIITMISDYWG QGTL (SEQ ID NO: 175) CDRH1: GYTFTSYG (SEQ ID NO: 169) CDRH2: ISAYNGNT (SEQ ID NO: 170) CDRH3: ARGIITMISDY (SEQ ID NO: 171)	NFMLTQPHSVSESPGKTVTIS CTGSSGSIASNYVQWYQQRP GSAPTTVIYEDNQRPSGVPDR FSGSIDSSSNSASLTISGLKTED EADYYCQSYDSSNLQWVFGG GTK (SEQ ID NO: 176) CDRL1: SGSIASNY (SEQ ID NO: 172) CDRL2: EDN (SEQ ID NO: 173) CDRL3: QSYDSSNLQWV (SEQ ID NO: 174)
3F1	QVQLVQSGGGVVQPGRSLRLSC AASGFTFSSYGMHWVRQAPGK GLEWVAVISYDGSNKYYADSV KGRFTISRDNSKNTLYLQMNSL RAEDTAVYYCARDGGGGMDV WGQGTT (SEQ ID NO: 183) CDRH1: GFTFSSYG (SEQ ID NO: 177) CDRH2: ISYDGSNK (SEQ ID NO: 178)	NFMLTQPHSVSESPGKTVTIS CTASGGSIADNFVQWYQQRP GSAPTTLIYDYSRRPYGVPDR FSGSIDRSSNSASLTVSGLMTE DEADYYCQSYDISNPVFGGG TK (SEQ ID NO: 184) CDRL1: GGSIADNF (SEQ ID NO: 180) CDRL2: DYS (SEQ ID NO: 181)

	CDRH3: ARDGGGGMDV (SEQ ID NO: 179)	CDRL3: QSYDISNPV (SEQ ID NO: 182)
3F11	EVQLVQSGAEVKKPGASVKVSCKASGYTFSSSGISWVRQAPGQGLEWMGWISTYNGNTNYAQNFQGRVTMTTDTSTSTVYMELRGLTSDDTAVYYCATSIAVAGIDYWGQGTL (SEQ ID NO: 191) CDRH1: GYTFSSSG (SEQ ID NO: 185) CDRH2: ISTYNGNT (SEQ ID NO: 186) CDRH3: ATSIAVAGIDY (SEQ ID NO: 187)	ETTLTQSPGTLSLSPGESATLSCRASHSDGRNYIAWYQQTPGQAPRLLVYDTSNRAAGVPDRFR GSGSGTDFTLTISRLEPEDFAVYFCHQFRRSVSTFGQGTK (SEQ ID NO: 192) CDRL1: HSDGRNY (SEQ ID NO: 188) CDRL2: DTS (SEQ ID NO: 189) CDRL3: HQFRRSVST (SEQ ID NO: 190)
3H7	QVQLVQSGGGVVQPGRSLRLSCAASGFTFSNYGMHWVRQAPGKGLEWVAVIWHDGTNKYYADSVKGRFTVSRDNSKNTLYLQMDTLRAEDTAVYYCVRDQGAGVWNGYSYWGQGTL (SEQ ID NO: 199) CDRH1: GFTFSNYG (SEQ ID NO: 193) CDRH2: IWHDGTNK (SEQ ID NO: 194) CDRH3: VRDQGAGVWNGYSY (SEQ ID NO: 195)	NFMLTQPHSVSESPGKTVTISCTRSTDSIASNYVQWYQQRPGSAPTTVIYEDNQRPSGVPDRFSGSIDSSSNSASLTISGLKTEDEADYYCQSYDGVNRGVIFGGGTK (SEQ ID NO: 200) CDRL1: TDSIASNY (SEQ ID NO: 196) CDRL2: EDN (SEQ ID NO: 197) CDRL3: QSYDGVNRGVI (SEQ ID NO: 198)
3H11	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYYMHWVRQAPGQGLEWMGIINPSGGSTSYAQKFQGRVTMTRDTSTNTVYMELSSLRSEDTAVYYCASSVVPAAIYDYYYGMDVWGQGTT (SEQ ID NO: 207)	NFMLTQPHSVSESPGKTVTISCTRSSGNIASYYVQWYQQRPGSSPTTVIYEDNQRPSGVPDRFSGSIDSSSNSASLTISGLQTEDEADYYCQSYDRPNHVVFGGGTR (SEQ ID NO: 208)

	CDRH1: GYTFTSYY (SEQ ID NO: 201) CDRH2: INPSGGST (SEQ ID NO: 202) CDRH3: ASSVVPAAIYDYYYGMDV (SEQ ID NO: 203)	CDRL1: SGNIASYY (SEQ ID NO: 204) CDRL2: EDN (SEQ ID NO: 205) CDRL3: QSYDRPNHVV (SEQ ID NO: 206)
6F8	QVQLVESGGGLVQPGGSLRLSCAASGFTVSSNYMSWVRQAPGKGLEWVSVIYSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDYGDYYFDYWGQGTL (SEQ ID NO: 215) CDRH1: GFTVSSNY (SEQ ID NO: 209) CDRH2: IYSGGST (SEQ ID NO: 210) CDRH3: ARDYGDYYFDY (SEQ ID NO: 211)	EIVLTQSPGTLSLSPGERATLSCTASQTINNNYLAWYQQKPGQGPSLLIYDASSRATGVPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYGSSPRTFGQGTK (SEQ ID NO: 216) CDRL1: QTINNNY (SEQ ID NO: 212) CDRL2: DAS (SEQ ID NO: 213) CDRL3: QQYGSSPRT (SEQ ID NO: 214)

[00146] In some embodiments, the anti-SARS-CoV-2-Spike antibodies in the present disclosure include a heavy chain variable region having an amino acid sequence at least 80% (e.g., 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:7 and a light chain variable region having an amino acid sequence at least 80% (e.g., 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:8.

[00147] In some embodiments, the anti-SARS-CoV-2-Spike antibodies include a vhCDR1 comprising SEQ ID NO:1, a vhCDR2 comprising SEQ ID NO:2, a vhCDR3 comprising SEQ ID NO:3, a vlCDR1 comprising SEQ ID NO:4, a vlCDR2 comprising SEQ ID NO:5, and a vlCDR3 comprising SEQ ID NO:6. In some embodiments, one or more of such 6 CDRs have from 1, 2, 3, 4 or 5 amino acid modifications. In further embodiments, a

single CDR contains 1 or 2 amino acid substitutions, and the modified anti-SARS-CoV-2-Spike antibodies retain binding to human SARS-CoV-2.

[00148] In some embodiments, the anti-SARS-CoV-2-Spike antibodies include a heavy chain variable region having an amino acid sequence identical to any of the clones listed in Table 1. In some embodiments, the anti-SARS-CoV-2-Spike antibodies include a light chain variable region having an amino acid sequence identical to any of the clones listed in Table 1. In some embodiments, the anti-SARS-CoV-2-Spike antibodies include a heavy chain variable region and a light chain variable region having an amino acid sequence identical to any of the clones listed in Table 1.

[00149] In addition to the sequence variants described herein in the heavy chain and light chain variable regions and/or CDRs, changes in the framework region(s) of the heavy and/or light variable region(s) can be made. In some embodiment, variants in the framework regions (*e.g.*, excluding the CDRs) retain at least about 80, 85, 90 or 95% identity to a germline sequence.

[00150] In some embodiments, variations are made in the framework regions that retain at least 80, 85, 90 or 95% identity to the germline gene sequences, while keeping 6 CDRs unchanged.

[00151] In some embodiments, variations are made in both the framework regions that retain at least 80, 85, 90 or 95% identity to the germline gene sequences, and the 6 CDRs. The CDRs can have amino acid modifications (*e.g.*, from 1, 2, 3, 4 or 5 amino acid modifications in the set of CDRs (that is, the CDRs can be modified as long as the total number of changes in the set of 6 CDRs is less than 6 amino acid modifications, with any combination of CDRs being changed; *e.g.*, there may be one change in vlCDR1, two in vhCDR2, none in vhCDR3, etc.).

[00152] By selecting amino acid sequences of CDRs and/or variable regions of a heavy chain and a light chain from those described herein and combining them with amino acid sequences of framework regions and/or constant regions of a heavy chain and a light chain of an antibody as appropriate, a person skilled in the art will be able to design an anti-SARS-CoV-2 antibody according to the present invention. The antibody framework regions and/or

constant region (Fc domain) described in the current invention can derive from an antibody of any species, such as from human, rabbit, dog, cat, mouse, horse or monkey.

[00153] In some embodiments, the constant region is derived from human, and includes a heavy chain constant region derived from those of IgG, IgA, IgM, IgE, and IgD subtypes or variants thereof, and a light chain constant region derived from kappa or lambda subtypes or variants thereof. In some embodiments, the heavy chain constant region is derived from a human IgG, including IgG1, IgG2, IgG3, and IgG4. In some embodiments, the amino acid sequence of the heavy chain constant region is at least 80%, 85%, 90%, or 95% identical to a human IgG1, IgG2, IgG3, or IgG4 constant region. In some other embodiments, the amino acid sequence of the constant region is at least 80%, 85%, 90%, or 95% identical to an antibody constant region from another mammal, such as rabbit, dog, cat, mouse, horse or monkey. In some embodiments, the antibody constant region includes a hinge, a CH2 domain, a CH3 domain and optionally a CH1 domain.

[00154] In some embodiments, the antibodies described herein can be derived from a mixture from different species, *e.g.,* forming a chimeric antibody and/or a humanized antibody. In general, both "chimeric antibodies" and "humanized antibodies" refer to antibodies that combine regions from more than one species. For example, "chimeric antibodies" traditionally comprise variable region(s) from a mouse (or rat, in some cases) and the constant region(s) from a human. "Humanized antibodies" generally refer to non-human antibodies that have had the variable-domain framework regions swapped for sequences found in human antibodies. Generally, in a humanized antibody, the entire antibody, except the CDRs, is encoded by a polynucleotide of human origin or is identical to such an antibody except within its CDRs. The CDRs, some or all of which are encoded by nucleic acids originating in a non-human organism, are grafted into the beta-sheet framework of a human antibody variable region to create an antibody, the specificity of which is determined by the engrafted CDRs. The creation of such antibodies is described in, *e.g.,* WO 92/11018, Jones, 1986, Nature 321:522-525, Verhoeyen et al., 1988, Science 239:1534-1536, all entirely incorporated by reference. "Backmutation" of selected acceptor framework residues to the corresponding donor residues is often required to regain affinity that is lost in the initial grafted construct (US 5530101; US 5585089; US 5693761; US 5693762; US 6180370; US 5859205; US 5821337; US 6054297; US 6407213, all entirely incorporated by reference).

The humanized antibody optimally also will comprise at least a portion of an immunoglobulin constant region, typically that of a human immunoglobulin, and thus will typically comprise a human Fc region. Humanized antibodies can also be generated using mice with a genetically engineered immune system, as described for example in Roque et al., 2004, Biotechnol. Prog. 20:639-654, entirely incorporated by reference. A variety of techniques and methods for humanizing and reshaping non-human antibodies are well known in the art (See Tsurushita & Vasquez, 2004, Humanization of Monoclonal Antibodies, Molecular Biology of B Cells, 533-545, Elsevier Science (USA), and references cited therein, all entirely incorporated by reference). Humanization methods include but are not limited to methods described in Jones et al., 1986, Nature 321:522-525; Riechmann et al.,1988; Nature 332:323-329; Verhoeyen et al., 1988, Science, 239:1534-1536; Queen et al., 1989, Proc Natl Acad Sci, USA 86:10029-33; He et al., 1998, J. Immunol. 160: 1029-1035; Carter et al., 1992, Proc Natl Acad Sci, USA 89:4285-9, Presta et al., 1997, Cancer Res. 57(20):4593-9; Gorman et al., 1991, Proc. Natl. Acad. Sci. USA 88:4181-4185; O'Connor et al., 1998, Protein Eng 11:321-8, all entirely incorporated by reference. Humanization or other methods of reducing the immunogenicity of nonhuman antibody variable regions may include resurfacing methods, as described for example in Roguska et al., 1994, Proc. Natl. Acad. Sci. USA 91:969-973, entirely incorporated by reference. Other humanization methods may involve the grafting of only parts of the CDRs, including but not limited to methods described in Tan et al., 2002, J. Immunol. 169:1119-1125; De Pascalis et al., 2002, J. Immunol. 169:3076-3084, all entirely incorporated by reference.

[00155] In some embodiments, the antibodies of the current invention comprise a heavy chain variable region derived from a particular human germline heavy chain immunoglobulin gene and/or a light chain variable region derived from a particular human germline light chain immunoglobulin gene. Such antibodies may contain amino acid differences as compared to the human germline sequences, due to, for example, naturally-occuring somatic mutations or intentional introduction of site-directed mutation. However, a humanized antibody typically is at least 80% identical in amino acids sequence to an amino acid sequence encoded by a human germline immunoglobulin gene and contains amino acid residues that identify the antibody as being derived from human sequences when compared to the germline immunoglobulin amino acid sequences of other species (*e.g.,* murine germline sequences). In certain cases, a humanized antibody may be at least 95, 96, 97, 98 or 99%, or

even at least 96%, 97%, 98%, or 99% identical in amino acid sequence to the amino acid sequence encoded by the human germline immunoglobulin gene. Typically, a humanized antibody derived from a particular human germline sequence will display no more than 10-20 amino acid differences from the amino acid sequence encoded by the human germline immunoglobulin gene. In certain cases, the humanized antibody may display no more than 5, or even no more than 4, 3, 2, or 1 amino acid difference from the amino acid sequence encoded by the germline immunoglobulin gene.

[00156] In some embodiments, the antibodies of the current disclosure are humanized and affinity matured, as is known in the art. Structure-based methods may be employed for humanization and affinity maturation, for example as described in US Patent No 7,657,380. Selection based methods may be employed to humanize and/or affinity mature antibody variable regions, including but not limited to methods described in Wu et al., 1999, J. Mol. Biol. 294:151-162; Baca et al., 1997, J. Biol. Chem. 272(16):10678-10684; Rosok et al., 1996, J. Biol. Chem. 271(37): 22611-22618; Rader et al., 1998, Proc. Natl. Acad. Sci. USA 95: 8910-8915; Krauss et al., 2003, Protein Engineering 16(10):753-759, all entirely incorporated by reference.

B. Characteristics of exemplary antibodies

[00157] The present disclosure provides novel SARS-CoV-2 antibodies. The anti-SARS-CoV-2-Spike antibodies described herein block the interaction between viral Spike protein and host receptor angiotensin-converting enzyme 2 (ACE2). In some embodiments, the anti-SARS-CoV-2-Spike antibodies bind human SARS-CoV-2 with high affinities. In some embodiments, the antibodies have neutralizing activity against SARS-CoV-2. In some embodiments, the SARS-CoV-2 antibodies block Spike mediated cell-cell fusion. In some embodiments, the SARS-CoV-2 antibodies block Spike mediated cell-cell fusion as an IgG but not as an antibody fragment, Fab. In some embodiments, the SARS-CoV-2 antibodies inhibit syncytia formation. The cell-cell fusion process induces formation of syncytia, a component of tissue damage in patients with severe COVID-19, In addition, nucleic acids encoding these antibodies, as well as host cells that include such nucleic acids are described in the present disclosure. Also provided in the present disclosure are methods of using such antibodies to treat COVID-19 and pharmaceutical compositions and administration of pharmaceutical compositions comprising anti-SARS-CoV-2-Spike antibodies.

[00158] In some embodiments, the anti-SARS-CoV-2-Spike antibodies described herein block the interaction between Spike protein to ACE2. In some embodiments, the anti-SARS-CoV-2-Spike antibodies described herein block the interaction between Spike protein to ACE2 and also alter the Spike protein conformational cycle triggered by ACE2 binding. In some embodiments, the anti-SARS-CoV-2-Spike antibodies described herein block the interaction between Spike protein to ACE2 and also alter the Spike protein conformational cycle triggered by ACE2 binding. In some embodiments, the anti-SARS-CoV-2-Spike antibodies described herein block the interaction between SARS-CoV-2 Spike protein to ACE2 and also alter the SARS-CoV-2 Spike protein conformational cycle triggered by ACE2 binding. Stabilization of different Spike conformations leads to modulation of Spike-mediated membrane fusion. In some embodiments, the anti-SARS-CoV-2-Spike antibodies block Spike mediated cell-cell fusion. Modulation of Spike-mediated membrane fusion affects COVID-19 pathology and immunity. Inhibition of Spike-mediated cell-cell fusion can inhibit the formation of syncytia, a component of tissue damage in patients with severe COVID-19.

[00159] In some embodiments, the anti-SARS-CoV-2-Spike antibodies described herein block the interaction between Spike protein to ACE2 and also inhibit syncytia. In some embodiments, the anti-SARS-CoV-2-Spike antibodies described herein block the interaction between Spike protein to ACE2 and also inhibit cell-cell fusion and syncytia formation in addition to blocking receptor binding. In some embodiments, the anti-SARS-CoV-2-Spike antibodies described herein block the interaction between Spike protein to ACE2 and also inhibit syncytia by trapping the pre-fusion state.

[00160] In some embodiments, the anti-SARS-CoV-2-Spike antibodies function as orthosteric receptor mimetics. In some embodiments, the anti-SARS-CoV-2-Spike antibodies function as orthosteric receptor mimetics conducive to the same cooperative processes as receptor binding. An example of an antibody that functions as an orthosteric receptor mimetic is 2H4. In some embodiments, anti-SARS-CoV-2-Spike antibodies that function in the manner of 2 H4 neither inhibit or promote syncytia formation.

[00161] In some embodiments, the anti-SARS-CoV-2-Spike antibodies function as allosteric effectors. In some embodiments, the anti-SARS-CoV-2-Spike antibodies function as allosteric effectors that advance Spike directly to the final stages of S2 unsheathing. An

example of an antibody that functions as an allosteric effector is 3D11. In some embodiments, anti-SARS-CoV-2-Spike antibodies that function in the manner of 3D11 promote syncytia formation.

[00162] In some embodiments, the anti-SARS-CoV-2-Spike antibodies function by stabilizing a Spike conformation that prohibits S1 shedding and traps the pre-fusion state. In some embodiments, stabilizing a Spike conformation that prohibits S1 shedding and traps the pre-fusion state prevents both targeted viral fusion and Spike-mediated cell-cell fusion. In some embodiments, synergy between receptor blockade and pre-fusion trapping allows for prevention of targeted viral fusion and Spike-mediated cell-cell fusion. An example of an antibody that acts by stabilizing a Spike conformation that prohibits S1 shedding and traps the pre-fusion state is 5A6. In some embodiments, anti-SARS-CoV-2-Spike antibodies that function by stabilizing a Spike conformation that prohibits S1 shedding and traps the pre-fusion state inhibit syncytia formation. In some embodiments, anti-SARS-CoV-2-Spike antibodies that function in the manner of 5A6 inhibit syncytia formation.

[00163] The magnitude of binding and neutralization enhancement in the IgG format of the anti-SARS-CoV-2-Spike antibodies described herein supports bivalent binding. Modelling studies suggest the hinge linking IgG Fc and Fab domains may have difficulty bridging the gaps seen in structures of Spike:Fab complexes (See Figure 13C). The 5A6 IgG complex structure confirms that 5A6 Fab and IgG forms do bind with congruent geometries and a morph between 5A6 Fab bound to closed and open RBDs shows that shorter distances between Fabs do obtain for intermediate RBD confirmations. This result implies that high-affinity, bivalent binding to intermediate RBD conformation is replaced by high-density, monovalent binding as the concentration of 5A6 IgG increases. 3D11 and 2H4 Spike Ig complexes were not tractable for single-particle cryo-EM and qualitative image analysis suggests that 3D11 and 2H4 do not trap defined conformational states of the Spike trimer (Figure 13E).

[00164] The 3D11 antibody has greatly reduced potency against pseudovirus bearing D614G Spike while that of 5A6 is slightly improved, though position 614 is outside the RBD and far from the epitope of either antibody in the RBD (Figure 16). The D614G mutant is known to occupy states with multiple open RBDs, and has been found to shed the S1 subunit less readily than the original SARS-CoV-2 Spike protein. The effects of 3D11 and 5A6 are

mediated by open RBD conformations that represent immediately available binding sites for 3D11 and present the full quaternary epitope of 5A6. The reduced shedding of the more stable D614G Spike may also assist the pre-fusion trapping activity of 5A6, while conveying resistance against trimer denaturation by 3D11. The quaternary epitope recognized by 5A6 conveys cooperative binding as well as avidity, and both aspects may hinder viral escape via mutations in Spike protein.

[00165] In some embodiments, binding of the anti-SARS-CoV-2-Spike antibodies to human is measured by ELISA. In some embodiments, binding of the anti-SARS-CoV-2-Spike antibodies to human SARS-CoV-2 is measured by FACS. In such embodiments, antibodies described herein display an EC50 that can range from 0.05nM to 2.5nM as measured by either ELISA or FACS. In such embodiments, antibodies described herein display an EC50 that can range from 0.1nM to 2.2nM as measured by either ELISA or FACS.

[00166] In some embodiments, the anti-SARS-CoV-2-Spike antibodies described herein bind human SARS-CoV-2 with high affinities. The K_D value can be measured with the antigen immobilized or with the antibody immobilized. The K_D value can also be measured in a monovalent or a bivalent binding mode. For example, when measured by Bio-Layer interferometry, the K_D values between the antibodies and human SARS-CoV-2 can be about 5×10^{-2}M or less, 2.5×10^{-2}M or less, 1×10^{-2}M or less, 5×10^{-3}M or less, 2.5×10^{-3}M or less, 1×10^{-3}M or less, 5×10^{-4}M or less, 2.5×10^{-4}M or less, 1×10^{-4}M or less, 5×10^{-5}M or less, 2.5×10^{-5}M or less, 5×10^{-6}M or less, 2.5×10^{-6}M or less, 1×10^{-6}M or less, 5×10^{-7}M or less, 2.5×10^{-7}M or less, 1×10^{-7}M or less, 5×10^{-8}M or less, 1×10^{-8}M or less, 1×10^{-9}M or less, or 1×10^{-10}M or less. The K_D value can be 1×10^{-6}M or less, 5×10^{-7}M or less, 2.5×10^{-7}M or less, 1×10^{-7}M or less, 5×10^{-8}M or less, 2.5×10^{-8}M or less, 1×10^{-8}M or less, 5×10^{-9}M or less, 1×10^{-9}M or less, 5×10^{-10}M or less, 1×10^{-10}M or less, 5×10^{-11}M or less, 1×10^{-11}M or less, 5×10^{-12}M or less, or 1×10^{-12}M or less. In some embodiments, the K_D values range from about 0.1 nM to about 1 μM, about 0.25 nM to about 500 nM, 0.5 nM to about 250 nM, 1 nM to about 100 nM M, or about 2 nM to about 50 nM.

[00167] The binding affinities of the anti-SARS-CoV-2-Spike antibodies described herein are compared with other anti-SARS-CoV-2-Spike antibodies. In some embodiments, the anti-SARS-CoV-2-Spike antibodies described herein have higher binding affinity than other antibodies. One advantage of having a higher binding affinity than 4C7 is that the

antibodies described herein can be more efficacious in modulating immune response to SARS-CoV-2.

[00168] In some embodiments, the anti-SARS-CoV-2 antibodies display low immunogenicity when administered into human subjects. These antibodies can contain an Fc domain derived from human IgG1, human IgG2 or human IgG3. In some embodiments, these antibodies are humanized using the framework regions derived from human immunoglobulins.

[00169] Effects of the anti-SARS-CoV-2 antibodies on cell function can be assayed using a variety of methods known in the art and described herein, including for example, by the method described in Example 1. Accordingly, the anti-SARS-CoV-2 antibodies can serve as SARS-CoV-2 antagonists.

[00170] The anti-SARS-CoV-2-Spike antibodies described herein bind human SARS-CoV-2. In some embodiments, the anti- SARS-CoV-2 antibodies bind human SARS-CoV-2 with high affinities. In some embodiments, the antibodies have neutralizing activity against SARS-CoV-2. In some embodiments, the SARS-CoV-2 antibodies block Spike mediated cell-cell fusion as an IgG but not as an antibody fragment Fab. In some embodiments, the SARS-CoV-2 antibodies inhibit syncytia formation. The cell-cell fusion process induces formation of syncytia, a component of tissue damage in patients with severe COVID-19.

[00171] In some embodiments, anti- SARS-CoV-2 antibodies described act as SARS-CoV-2 antagonists, and block interaction of SARS-COV-2 with Spike protein. As a result, such anti- SARS-CoV-2 antibodies prevent syncytia formation. Examples of such anti-SARS-CoV-2 antibodies include antibodies that contain a heavy chain variable region comprising an amino acid sequence at least about 80% (*e.g.*, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:7, and a light chain variable region comprising amino acid sequence at least about 80% (*e.g.*, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:8; and/or a vhCDR1 comprising SEQ ID NO:1, a vhCDR2 comprising SEQ ID NO:2, a vhCDR3 comprising SEQ ID NO:3, a vlCDR1 comprising SEQ ID NO:4, a vlCDR2 comprising SEQ ID NO:5, and a vlCDR3 comprising SEQ ID NO:6.

[00172] In some embodiments, the anti-SARS-CoV-2-Spike antibodies described herein provide a method of preventing formation of syncytia comprising a fusion between a SARS-CoV-2 infected cell displaying a SARS-CoV-2 Spike protein on its surface, and a second cell displaying an ACE-2 receptor on its surface, the syncytia formation mediated by the SARS-CoV-2 Spike protein binding to the ACE-2 receptor, the method comprising contacting a cell infected with SARS-CoV-2, or at risk of being infected with SARS-CoV-2 with an isolated anti-SARS-CoV-2-Spike antibody or an antigen binding fragment thereof specifically binding to the Spike protein, trapping the Spike protein in a pre-fusion state, thereby preventing the formation of the syncytia. In some embodiments, the isolated anti-SARS-CoV-2-Spike antibody or antigen binding fragment is an IgG, IgM, IgA, Fab, single domain antibody. In some embodiments, the isolated anti-SARS-CoV-2-Spike antibody or antigen binding fragment binds to a quaternary epitope of the Spike protein. Examples of binding to a quaternary epitope of the Spike protein can be found in Figures 21-30. In some embodiments, the quaternary epitope of the binder is composed of both the ACE2 interacting amino acid residues in one RBD as well as amino acids in an adjacent RBD. In some embodiments, the isolated anti-SARS-CoV-2-Spike antibody binds to the quaternary epitope through residues in the CDR. Examples of binding to a quaternary epitope of the Spike protein can be found in Figures 21-30. The quaternary epitope of the binder is composed of both the ACE2 interacting amino acid residues in one RBD as well as amino acids in an adjacent RBD addition to framework amino acid residues binding to an adjacent RBD where the secondary binding is achieved through framework residues of the antibody. In some embodiments, the binding is within 4 angstroms.

[00173] In some embodiments, the isolated antibody or antigen binding fragment comprises a light chain variable domain sequence that is at least 90% identical to SEQ ID NO. 7. In some embodiments, the isolated antibody or antigen binding fragment comprises a heavy chain variable domain sequence that is at least 90% identical to SEQ ID NO. 8. In some embodiments, the isolated anti-SARS-CoV-2-Spike antibody or antigen binding fragment comprises a heavy chain variable region comprising complementarity determining regions (CDRs), wherein: a. the heavy chain CDR1 is SEQ ID NO. 1 (GFTFSSYE) b. the heavy chain CDR2 is SEQ ID NO 2 (ISYDGSNK); and c. the heavy chain CDR3 is SEQ ID NO. 3 (QQSYNLPRT), and a light chain variable region comprising CDRs, wherein: d. the

light chain CDR1 is SEQ ID NO. 4 (QSISSY) e. the light chain CDR2 is SEQ ID NO. 5 (AAS); and f. the light chain CDR3 is SEQ ID NO. 6 (QQSYNLPRT).

[00174] In some embodiments, the heavy chain variable region, SEQ ID NO. 7, comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 mutations. Exemplary positions for the mutations include, without limitation, any of the positions E33, S52, Y53, D54, G55, S56, N57, L94, and/or R96 according to the sequence numbering in Figure 46, alone or in combination (or the corresponding position according to IMGT numbering). Exemplary positions for the mutations include, without limitation, any of the positions E38, S57, Y58, D59, G62, S63, N64, R106 according to IMGT numbering, alone or in combination.

[00175] In some embodiments, the heavy chain variable region, SEQ ID NO. 7, comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 mutations at E38, S57, Y58, D59, G62, S63, N64, and/or R106. In some embodiments, the mutation at position D59 is selected from D59G, D59L, D59K, D59I, D59M, D59W, D59T, D59F, or D59Y. In some embodiments, the mutation at position N64 is selected from N64R or N64I. In some embodiments, the mutation at position R106 is selected from R106E, R106D, R106N, R106Q, R106A, R106V, or R106L.

[00176] In some embodiments, the heavy chain variable region, SEQ ID NO. 7, comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 mutations. Exemplary positions for the mutations include, without limitation any of the positions listed in Figures 31 to 39 which are numbered according to the sequence numbering in Figure 46, alone or in combination (or the corresponding position according to IMGT numbering).

[00177] In some embodiments, the isolated antibody or antigen binding fragment comprises a heavy chain variable domain sequence that is at least 90% identical to SEQ ID NO. 7.

[00178] In some embodiments, the light chain variable region, SEQ ID NO. 8, comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 mutations. An exemplary position for the mutations include, without limitation position S69, L114 and/or R116 according to IMGT numbering.

[00179] In some embodiments, the light chain variable region, SEQ ID NO. 8, comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 mutations at any of the positions listed in Figures 31 to 39, alone or in combination.

[00180] In some embodiments, the isolated antibody or antigen binding fragment comprises a light chain variable domain sequence that is at least 90% identical to SEQ ID NO. 8.

[00181] In some embodiments, the isolated antibody is a human antibody. In some embodiments, the isolated antibody is a humanized antibody.

[00182] In some embodiments, the isolated antibody is a monoclonal antibody.

[00183] In some embodiments, the isolated antibody is effective in treating a SARS-CoV-2 infection. In some embodiments, the isolated antibody is useful in preventing or retarding formation of SARs-CoV-2 mediated syncytia formation by binding to RBD and stabilizing a SARs-CoV-2 Spike protein conformation retarding or preventing S1 shedding and trapping a pre-fusion state of the SARs-CoV-2.
In some embodiments, the isolated anti-SARS-CoV-2-S1 antibody or antigen binding fragment comprises a heavy chain variable region comprising complementarity determining regions (CDRs), wherein: a. the heavy chain CDR1 is SEQ ID NO. 1 (GFTFSSYE; binds through T28, S31, Y32, E33 according to the sequence numbering in Figure 46 (or the corresponding position according to IMGT numbering)) b. the heavy chain CDR2 is SEQ ID NO 2 (ISYDGSNK; binds through V50, I51, S52, Y53, D54, N57, Y59 according to the sequence numbering in Figure 46 (or the corresponding position according to IMGT numbering)) ; and c. the heavy chain CDR3 is SEQ ID NO. 3 (ARLITMVRGEDY; binds through R98, L99, T101, M102, V103, R104, G105, E106 according to the sequence numbering in Figure 46 (or the corresponding position according to IMGT numbering)), and a light chain variable region comprising CDRs, wherein: d. the light chain CDR1 is SEQ ID NO. 4 (QSISSY; binds through S30, Y31 according to the sequence numbering in Figure 47 (or the corresponding position according to IMGT numbering)) e. the light chain CDR2 is SEQ ID NO. 5 (AAS; binds through S56, G57 according to the sequence numbering in Figure 47 (or the corresponding position according to IMGT numbering) ; the binding residues are not identified in the application as CDR2, but slide 2 ids them as **the** CDR2 - off the CDR); and f. the light chain CDR3 is SEQ ID NO. 6 (QQSYNLPRT; binds through S91,

Y92, N93, L94, R96 according to the numbering in Figure 47 (or the corresponding position according to IMGT numbering)). In some embodiments, the isolated anti-SARS-CoV-2-S1 antibody or antigen binding fragment comprises a heavy chain variable region comprising complementarity determining regions (CDRs), wherein: a. the heavy chain CDR1 is SEQ ID NO. 1; binds through T29, S36, Y37, E38) b. the heavy chain CDR2 is SEQ ID NO 2 (ISYDGSNK); binds through V55, I56, S57, Y58, D59, N64, Y66; and c. the heavy chain CDR3 is SEQ ID NO. 3 (ARLITMVRGEDY; binds through R106, L107, T109, M110, V112, R113, G114, E115), and a light chain variable region comprising CDRs, wherein: d. the light chain CDR1 is SEQ ID NO. 4 (QSISSY; binds through S36, Y38) e. the light chain CDR2 is SEQ ID NO. 5 (AAS; binds through S69, G70); and f. the light chain CDR3 is SEQ ID NO. 6 (QQSYNLPRT; binds through S107, Y108, N109, L114, R116), wherein the positions are according to IMGT numbering.

[00184] In some embodiments, the heavy chain variable region, SEQ ID NO. 7, comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 mutations at any of the positions E33, S52, Y53, D54, G55, S56, N57, L94, and/or R96 (or the corresponding position according to IMGT numbering). In some embodiments, the heavy chain variable region, SEQ ID NO. 7, comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 mutations at any of the positions E38, S57, Y58, D59, G62, S63, N64, R106 according to IMGT numbering, alone or in combination.. In some embodiments, the light chain variable region, SEQ ID NO. 7, comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 mutations at any of the positions listed in Figures 31 to 39. In some embodiments, the isolated antibody or antigen binding fragment comprises a heavy chain variable domain sequence that is at least 90% identical to SEQ ID NO. 7. In some embodiments, the light chain variable region, SEQ ID NO. 8, comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 mutations at position S56 and R96 according to the sequence numbering in Figure 47. In some embodiments, the light chain variable region, SEQ ID NO. 8, comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 mutations at position S69, L114, and/or R116 according to IMGT numbering. In some embodiments, the light chain variable region, SEQ ID NO. 8, comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 mutations at position L114 and/or R116 according to IMGT numbering. In some embodiments, the light chain variable region, SEQ ID NO. 8, comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 mutations at any of the positions listed in

Figures 31 to 39. In some embodiments, the isolated antibody or antigen binding fragment comprises a light chain variable domain sequence that is at least 90% identical to SEQ ID NO. 8. In some embodiments, the isolated antibody is a human antibody. In some embodiments, the isolated antibody is a humanized antibody. In some embodiments, the isolated antibody is a monoclonal antibody. In some embodiments, the isolated antibody is effective in treating a SARS-CoV-2 infection. In some embodiments, the isolated antibody is useful in preventing or retarding formation of SARs-CoV-2 mediated syncytia formation by binding to RBD and stabilizing a SARs-CoV-2 Spike protein conformation retarding or preventing S1 shedding and trapping a pre-fusion state of the SARs-CoV-2.

[00185] In some embodiments, mutations to the heavy chain variable region of 5A6 may be made according to the positions suggested in Figure 46. In some embodiments, mutations to the light chain variable region of 5A6 may be made according to Figure 47. In some embodiments, mutations to the heavy chain variable region of SEQ ID NO: 7 may be made according to the positions suggested in Figure 46. In some embodiments, mutations to the light chain variable region of SEQ ID NO: 8 may be made according to Figure 47. In some embodiments, mutations to the CDRs of 5A6 may be made according to the positions suggested in Figure 46 and/or Figure 47.

[00186] In some embodiments, a SARS-Cov-2-Spike antibody is effective in preventing syncytia formation if it has a k_{off} < 7.14E-3/sec. In some embodiments, a SARS-Cov-2-Spike antibody may be effective in preventing syncytia formation if the k_{off} is in the range of 5X < k_{off} < 10X as compared to 5A6 WT. In some embodiments, it is uncertain if a SARS-Cov-2-Spike antibody is effective in preventing syncytia formation if it has a k_{off} > 10X as compared to 5A6 WT.

[00187] In some embodiments, a SARS-Cov-2-Spike antibody is effective in preventing syncytia formation if it has a k_{off} < 5X as compared to 5A6 WT. In some embodiments, a SARS-Cov-2-Spike antibody may be effective in preventing syncytia formation if the koff is in the range of 5X < k_{off} < 10X as compared to 5A6 WT. In some embodiments, it is uncertain if a SARS-Cov-2-Spike antibody is effective in preventing syncytia formation if it has a k_{off} > 10X as compared to 5A6 WT.

[00188] In some embodiments, a SARS-Cov-2-Spike antibody has a k_{off} < 7.14E-3/sec. In some embodiments, a SARS-Cov-2-Spike antibody has a k_{off} in the range of 5X <

k_{off} < 10X as compared to 5A6 WT. In some embodiments, a SARS-Cov-2-Spike antibody has a k_{off} > 10X as compared to 5A6 WT.

[00189] In some embodiments, a SARS-Cov-2-Spike antibody has a k_{off} < 7.14E-3/sec. In some embodiments, a SARS-Cov-2-Spike antibody does not have a k_{off} in the range of 5X < k_{off} < 10X as compared to 5A6 WT. In some embodiments, a SARS-Cov-2-Spike antibody does not have a k_{off} > 10X as compared to 5A6 WT.

[00190] In some embodiments, a SARS-Cov-2-Spike antibody has a k_{off} < 5X as compared to 5A6 WT. In some embodiments, a SARS-Cov-2-Spike antibody does not have a k_{off} in the range of 5X < k_{off} < 10X as compared to 5A6 WT. In some embodiments, a SARS-Cov-2-Spike antibody does not have a k_{off} > 10X as compared to 5A6 WT.

[00191] Exemplary mutations that may be made in order to improve k_{off} are disclosed in Figures 31-39 and 46-47. In Figures 31-39, mutations that improve binding (at least 5x slower K_{off} compared to 5A6 WT) are highlighted in Green. Mutations that weaken binding (at least 5x faster Koff compared to 5A6 WT) are highlighted as Red. In some embodiments, mutations with improved K_{off} are selected from D59G, D59L, D59K, D59I, D59M, D59W, D59T, D59F, or D59Y. In some embodiments, mutations with improved K_{off} are selected from N64R or N64I.

[00192] In some embodiments, a preferred mutation to the variable heavy region of 5A6 is to R98 according to the raw sequence numbering in Figure 47 (R106 according to IMGT numbering). The mutations VH R98 according to the raw sequence numbering in Figure 46 (R106 according to IMGT numbering) interacts directly with Spike E484 via a charge-charge interaction. In B.1.351 and P.1-like variants (aka South Africa and Brazil), Spike residue 484 is mutated from a negatively charged E to positive charged K. This E484K mutation strongly affects the affinity of 5A6 due to abrogating the salt bridge with 5A6 R98 according to the raw sequence numbering in Figure 46 (R106 according to IMGT numbering). Compensatory charge swaps in 5A6 including R98E, R98D according to the raw sequence numbering in Figure 46 (R106E, R106D according to IMGT numbering) will likely restore affinity. Other options are polar residues including R98N, R98Q, and small hydrophobic residues like R98A, R98V, R98L according to the raw sequence numbering in Figure 46 (R106N, R106Q and R106A, R106V according to IMGT numbering).

[00193] As those of skill in the art will appreciate the exemplary mutations set forth herein can be incorporated into a single antibody of the invention in the light chain variable region, heavy chain variable region and a combination thereof. The mutations can be thus incorporated in any number and combination.

[00194] Exemplary antibodies of the invention form, one or more primary interactions with the epitope through one or more CDR of one or more of the light and heavy chains. In some embodiments, the antibodies form one or more secondary interactions with the epitope.

[00195] With respect to the formation of primary interfaces, in various embodiments, the invention provides an antibody, and methods of using the antibody as described herein. An exemplary antibody of the invention includes particular amino acid residues interfacing with amino acids on the epitope. For example, in the light chain CDR1, an amino acid residue at position 36 interacts with F486 of the epitope. An exemplary interaction is formation of a buried surface. In an exemplary embodiment, the amino acid residue is S36. In various embodiments, an amino acid residue at position 38 interacts with one or both of N487, Y489, and F486. An exemplary interaction is a hydrogen bonding network between the amino acid at position 38 and N487 and Y489, and a T-shaped π-π interaction with F486. An exemplary amino acid residue is Y38.

[00196] In various embodiments, in the light chain CDR2, amino acid residues at positions 69 and 70 interface with Y449 of the epitope. An exemplary interaction is the formation of a buried surface. Exemplary residues at positions 69 and 70 include S69 and G70.

[00197] In various embodiments, in the light chain CDR3, one, two, three, four and/or five of the amino acids at positions 107, 108, 109, 114 and 116 interact with V483, E484, G485 and F186. An exemplary interaction is the formation of a buried surface. In various embodiments, the amino acid residues at positions 107, 108, 109, 114 and 116 are S107, Y108, N109, L114, and R116.

[00198] In an exemplary embodiment, in the heavy chain CDR1, amino acid residues at positions 29, 36, 37, and 38 interact with amino acid residues in the epitope, T470, I472, G482, V483, E484, F490. An exemplary interaction is formation of a buried surface. In various embodiments, the amino acid residue at 38 receives electrophilic polarization by the

side-chain of E484 and forms a hydrogen bond with the backbone amide nitrogen of E484. In an exemplary embodiment, the residue at 37 forms a parallel-displaced π-π interaction with F490. In various embodiments, the amino acid residues at 29, 36, 37, and 38 are T29, S36, Y37, and E38.

[00199] In an exemplary embodiment, in the heavy chain CDR2, one, two, three, four, five, six or seven amino acids at 55, 56, 57, 58, 59, 64 and/or 66 interact with T470, E471, I472, N481, G482, V483. An exemplary interaction is formation of a buried interface. In various embodiments, the amino acid residues are V55, I56, S57, Y58, D59, N64, and Y66. In an exemplary embodiment, the amino acid residue at position 58 forms an anion-π interaction with E471. In an exemplary embodiment, the amino acid residue at position 66 forms a hydrogen bone with N481.

[00200] In various embodiments, in heavy chain CDR3, the antibody interacts with the epitope via amino acid residues at positions 106, 107, 109, 110, 112, 113, 114, and/or 115. The amino acids at these positions interact with amino acid residues E484, G485, Y489, F490, L492, Q493, S494 of the epitope. An exemplary interaction is formation of a buried interface. In one embodiment, the amino acid residue at 106 forms a salt bridge with E484. In an exemplary embodiment, the amino acid residue at 113 forms a cation-π interaction with Y449. In various embodiments, the amino acid residues of heavy chain CDR3 are R106, L107, T109, M110, V112, R113, G114, and E115.

[00201] With respect to the formation of secondary interactions, light chain residues at one or more of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, and 15 of the amino acid residues at 18, 20, 22, 28, 36, 65, 77, 79, 80, 83, 84, 85, 86, 88, and/or 90 interacts with Y369, A372, F374, S375, T376, F377, K378, G404, D405, R408, Q414, K417, V503, G504, and/or Y508 of the epitope. An exemplary interaction is formation of a buried interface. In an exemplary embodiment, the backbone carbonyl oxygen of the residue at 83 forms a hydrogen bond with the backbone amide nitrogens of F377, and/or K378. In various embodiments, the residue at one or more of 86 and/or 24 form a hydrogen-bonding-network with Y508. In an exemplary embodiment the amino acid residues of the antibody are R18, T20, T22, S28, S36, S65, S77, S79, G80, S83, G84, T85, D86, T88, and T90.

C. Nucleic acids of the invention

[00202] Nucleic acids encoding the anti-SARS-CoV-2-Spike antibodies described herein are also provided, as well as expression vectors containing such nucleic acids and host cells transformed with such nucleic acids and/or expression vectors. As will be appreciated by those in the art, the protein sequences depicted herein can be encoded by any number of possible nucleic acid sequences due to the degeneracy of the genetic code. Table 2 gives exemplary nucleic acids encoding the heavy chain variable region and light chain variable region of the antibodies described herein.

Table 2		
Clone	Heavy chain variable region nucleic acid sequence	Light chain variable region nucleic acid sequence
5A6	CAGGTGCAGCTGCAGGAGTCGG GGGGAGGCTTGGTACAGCCTGG AGGGTCCCTGAGACTCTCCTGTG CAGCCTCTGGATTCACCTTCAGT AGTTATGAAATGAACTGGGTCC GCCAGGCTCCAGGCAAGGGGCT GGAGTGGGTGGCAGTTATATCA TATGATGGAAGCAATAAATACT ACGCAGACTCCGTGAAGGGCCG ATTCACCATCTCCAGAGACAATG CCAAGAACTCACTGTATCTGCAA ATGAACAGCCTGAGAGCCGAGG ACACGGCTGTGTATTACTGTGCG AGACTGATTACTATGGTTCGGGG AGAGGACTACTGGGGCCAGGGC ACCCTG (SEQ ID NO: 223) CDRH1: GGATTCACCTTCAGTAGTTATGA A (SEQ ID NO: 217) CDRH2: ATATCATATGATGGAAGCAATA AA (SEQ ID NO: 218) CDRH3: GCGAGACTGATTACTATGGTTCG GGGAGAGGACTAC (SEQ ID NO: 219)	GACATCCAGTTGACCCAGTCT CCATCCTCCCTGTCTGCATCTG TGGGACACAGAGTCACCATCA CTTGCCGGGCAAGTCAGAGCA TTAGCAGCTATTTAAATTGGT ATCAGCAGAAACCAGGGAAA GCCCCTAAGCTCCTGATTTAT GCTGCATCCAGTTTGCAAAGT GGGGTCCCATCAAGGTTCAGC GGCAGTGGATCTGGGACAGAT TTCACTCTCACCATCAGCAGC CTGCAGCCTGAAGATTTTGCG ACTTACTACTGTCAACAGAGT TACAATCTTCCGCGCACTTTC GGCGGAGGGACCAAG (SEQ ID NO: 224) CDRL1: CAGAGCATTAGCAGCTAT (SEQ ID NO: 220) CDRL2: GCTGCATCC (SEQ ID NO: 221) CDRL3: CAACAGAGTTACAATCTTCC GCGCACT (SEQ ID NO: 222)

1A5	CAGGTGCAGCTGCAGGAGTCGG GGGGAGGCTTGGTACAGCCTGG GGGGTCCCTGAGACTCTCCTGTG CAGCCTCTGGATTCACCTTTAGC AGCTATGCCATGAGCTGGGTCC GCCAGGCTCCAGGGAAGGGGCT GGAGTGGGTCTCAGCTATTAGTG GTAGTGGTGGTAGCACATACTA CGCAGACTCCGTGAAGGGCCGG TTCACCATCTCCAGAGACAATTC CAAGAACACGCTGTATCTGCAA ATGAACAGCCTGAGAGCCGAGG ACACGGCCGTATATTACTGTGCG AAAGATTACTTCAGGTGGTTATG GGGCCAGGGAACCCTG (SEQ ID NO: 231) CDRH1: GGATTCACCTTTAGCAGCTATGC C (SEQ ID NO: 225) CDRH2: ATTAGTGGTAGTGGTGGTAGCA CA (SEQ ID NO: 226) CDRH3: GCGAAAGATTACTTCAGGTGGTT A (SEQ ID NO: 227)	AATTTTATGCTGACTCAGCCC CACTCTGTGTCGGAGTCTCCG GGGAAGACGGTAGCCATCTCC TGCACCGGCAACAGTGGCAGC ATTGCCAGCCACTATGTGCAG TGGTTCCAACAGCGCCCGGGC AGTGCCCCCACTACTGTGATC TATGAAGATAACCAAAGACCC TCTGGGGTCCCTGATCGGTTC TCTGGCTCCATCGACAGGTCG TCCAACTCTGCCTCCCTCACC ATCTCTGGACTTAAGAGTGAG GACGAGGCTGACTATTACTGT CAGTCTTATGGCAGCGGCTTT GTGGTCTTCGGCGGAGGGACC AAG (SEQ ID NO: 232) CDRL1: AGTGGCAGCATTGCCAGCCA CTAT (SEQ ID NO: 228) CDRL2: GAAGATAAC (SEQ ID NO: 229) CDRL3: CAGTCTTATGGCAGCGGCTTT GTGGTC (SEQ ID NO: 230)
1A8	CAGGTGCAGCTGCAGGAGTCGG GCCCAGGACTGGTGAAGCCTTC GGAGACCCTGTCCCTCACCTGCA CTGTCTCTGGTGTCTCCATCAGC AGTAGAAGTGACCACTGGGGCT GGGTCCGCCAGCCCCCAGGGAA GGGGCTGGAGTGGATTGGAAGT ATCTCTTATAGTGGGAGCACCTA CTACAACCCGTCCCTCAAGAGCC GAGTCACCATATCCGTAGACAC CTCCAAGAACCAACTCTCCCTGA AGCTGAGCTCTGTGACCGCCGC AGACACGGCTGTCTATTACTGTG CGAGACTCGCTTCCCTTTATTCT ACTTTTGATATCTGGGGCCACGG CACCCTG (SEQ ID NO: 239)	GAAATTGTGTTGACGCAGTCT CCAGACTCCCTGGCTGTGTCT CTGGGCGAGAGGGCCACCATC AACTGCAAGTCCAGCCAGAGT GTTTTATACAGCTCCAACAAT AAGAACTACTTAGCTTGGTAT CAACAGAAACCAGGACAGCC TCCTAAGTTGCTCATTTACTG GGCTTCTACCCGGGAATCCGG GGTCCCTGACCGATTCAGTGG CAGCGGGTCTGGGACAGATTT CACTCTCACCATCAGCAGCCT GCAGGCTGAAGATGTGGCAGT TTATTACTGTCAGCAATATTA TGGTACTCCGTACACTTTTGG CCAGGGGACCAAG (SEQ ID NO: 240)

	CDRH1: GGTGTCTCCATCAGCAGTAGAA GTGACCAC (SEQ ID NO: 233) CDRH2: ATCTCTTATAGTGGGAGCACC (SEQ ID NO: 234) CDRH3: GCGAGACTCGCTTCCCTTTATTC TACTTTTGATATC (SEQ ID NO: 235)	CDRL1: CAGAGTGTTTTATACAGCTCC AACAATAAGAACTAC (SEQ ID NO: 236) CDRL2: TGGGCTTCT (SEQ ID NO: 237) CDRL3: CAGCAATATTATGGTACTCC GTACACT (SEQ ID NO: 238)
1B2	CAGGTCCAGCTGGTGCAGTCTG GGGCTGAGGTGAAGAAGCCTGG GGCCTCAGTGAAGGTTTCCTGCA AGGCATCTGGATACACCTTCACC AGCTACTATATGCACTGGGTGCG ACAGGCCCCTGGACAAGGGCTT GAGTGGATGGGAATAATCAACC CTAGTGGTGGTAGCACAAGCTA CGCACAGAAGTTCCAGGGCAGA GTCACCATGACCAGGGACACGT CCACGAGCACAGTCTACATGGA GCTGAGCAGCCTGAGATCTGAG GACACGGCCGTGTATTACTGTGC GACTGGGGAGATGGCAGGGGAT TTTGACTACTGGGGCCAGGGCA CCCTG (SEQ ID NO: 247) CDRH1: GGATACACCTTCACCAGCTACTA T (SEQ ID NO: 241) CDRH2: ATCAACCCTAGTGGTGGTAGCA CA (SEQ ID NO: 242) CDRH3: GCGACTGGGGAGATGGCAGGGG ATTTTGACTAC (SEQ ID NO: 243)	AATTTTATGCTGACTCAGCCC CACTCTGTGTCGGAGTCTCCG GGGAAGACCGTAACCATCTCC TGCACCGGCAGCGGTGGCAG GATTGCCACCAACTATGTGCA GTGGTACCAGCAGCGCCCGGG CAGTGCCCCCACCACTGTGAT CTATGAGGATAATAAAAGACC CTCTGGGGTCCCTCATCGGTT CTCTGGCTCCATCGACGCCTC CTCCAATTCTGCCTCCCTCACT ATCTCTGGACTGGAGACTGAG GACGAGGCTGACTACTACTGT CAGTCTCATGATACCAGCCGT CAGGCGGTTTTCGGCGGCGGG ACCAAG (SEQ ID NO: 248) CDRL1: GGTGGCAGGATTGCCACCAA CTAT (SEQ ID NO: 244) CDRL2: GAGGATAAT (SEQ ID NO: 245) CDRL3: CAGTCTCATGATACCAGCCG TCAGGCGGTT (SEQ ID NO: 246)
1B11	GAAGTGCAGCTGGTGCAGTCTG GGGCTGAGGTGAAGAAGCCTGG GTCCTCGGTGAAGGTCTCCTGCA AGGCTTCTGGAGGCACCTTCAGC	GATGTTGTGATGACTCAGTCT CCACTCTCCCTGCCCGTCACC CCTGGAGAGCCGGCCTCCATC TCCTGCAGGTCTAGTCAGAGC

	AGCTATGCTATCAGCTGGGTGCG ACAGGCCCCTGGACAAGGGCTT GAGTGGATGGGAGGGATCATCC CTATCTTTGGTACAGCAAACTAC GCACAGAAGTTCCAGGGCAGAG TCACGATTACCGCGGACGAATC CACGAGCACAGCCTACATGGAG CTGAGCAGCCTGAGATCTGAGG ACACGGCCGTGTATTACTGTGCG AGAGACAACCCCGGGTATAGCA GCAGCTGGTCCCCCAACTGGTTC GACCCCTGGGGCCAGGGAACCC TG (SEQ ID NO: 255) CDRH1: GGAGGCACCTTCAGCAGCTATG CT (SEQ ID NO: 249) CDRH2: ATCATCCCTATCTTTGGTACAGC A (SEQ ID NO: 250) CDRH3: GCGAGAGACAACCCCGGGTATA GCAGCAGCTGGTCCCCCAACTG GTTCGACCCC (SEQ ID NO: 251)	CTCCTGTATAGTAATGGATAC AACTATTTGGATTGGTACCTG CAGAAGCCAGGGCAGTCTCCA CAGCTCCTGATCTATTTGGGT TCTAATCGGGCCTCCGGGGTC CCTGACAGGTTCAGTGGCAGT GGATCAGGCACAGATTTTACA CTGAAAATCAGCAGAGTGGA GGCTGAGGATGTTGGGGTTTA TTACTGCATGCAAGCTCTACA AACCCCGTACACTTTTGGCCA GGGGACCAAG (SEQ ID NO: 256) CDRL1: CAGAGCCTCCTGTATAGTAA TGGATACAACTAT (SEQ ID NO: 252) CDRL2: TTGGGTTCT (SEQ ID NO: 253) CDRL3: ATGCAAGCTCTACAAACCCC GTACACT (SEQ ID NO: 254)
1C2	GAGGTCCAGCTGGTGCAGTCTG GGGCTGAGGTGAAGAAGCCTGG GGCCTCAGTGAAGGTCTCCTGCA AGGCATCTGGATACACCTTCACC AGCTACTATATGCACTGGGTGCG ACAGGCCCCTGGACAAGGGCTT GAGTGGATGGGAATAATCAACC CTAGTGGTGGTAGCACAAGCTA CGCACAGAAGTTCCAGGGCAGA GTCACCATGACCAGGGACACGT CCACGAGCACAGTCTACATGGA GCTGAGCAGCCTGAGATCTGAG GACACGGCCGTGTATTACTGTGC GAGCTCTTCGGCTGGTACGTTCT ACTTTGACTACTGGGGCCAGGG CACCCTG (SEQ ID NO: 263)	GATGTTGTGATGACTCAGTCT CCACTCTCCCTGCCCGTCACC CCTGGAGAGCCGGCCTCCATC TCCTGCAGGTCTAGTCAGAGC CTCCTGCATAGTAATGGATTC ACCTATTTGGATTGGTACCTG CAGAAGCCAGGGCTGTCTCCA CAGCTCCTGATCTACTTGGGT TCTAATCGGGCCCCCGGGGTC CCTGACAGGTTCAGTGGCAGT GGATCAGGCACAGATTTTACA CTGAAAATCAGCAGAGTGGA GGCTGAGGATGTTGGGGTTTA TTACTGCATGCAAGGTATACA AACCCCCCTCACTTTCGGCGG GGGGACCAAG (SEQ ID NO: 264)

	CDRH1: GGATACACCTTCACCAGCTACTAT (SEQ ID NO: 257) CDRH2: ATCAACCCTAGTGGTGGTAGCACA (SEQ ID NO: 258) CDRH3: GCGAGCTCTTCGGCTGGTACGTTCTACTTTGACTAC (SEQ ID NO: 259)	CDRL1: CAGAGCCTCCTGCATAGTAATGGATTCACCTAT (SEQ ID NO: 260) CDRL2: TTGGGTTCT (SEQ ID NO: 261) CDRL3: ATGCAAGGTATACAAACCCCCCTCACT (SEQ ID NO: 262)
1C3	GAGGTCCAGCTGGTACAGTCTGGGGCTGAGGTGAAGAAGCCTGGGGCCTCAGTGAAGGTTTCCTGCAAGGCATCTGGATACCCCTTCAGCACTTACTATATACACTGGGTGCGACAGGCCCCTGGACAAGGGCTTGAGTGGATGGGAATAATCGACCCTAGTGGTGGTAGCACAAGCTACGCACAGAAGTTCCAGGGCAGAGTCACCATGACCAGGGACACGTCCACGAGCACAGTCTACATGGAGCTGAGGAGCCTAAGATCTGACGACACGGCCGTGTTTTACTGTGCGAGAGTTGCCGAGCAACACCTGGACTACTACTTTGACTACTGGGGCCAGGGAACCCTG (SEQ ID NO: 271) CDRH1: GGATACCCCTTCAGCACTTACTAT (SEQ ID NO: 265) CDRH2: ATCGACCCTAGTGGTGGTAGCACA (SEQ ID NO: 266) CDRH3: GCGAGAGTTGCCGAGCAACACCTGGACTACTACTTTGACTAC (SEQ ID NO: 267)	AATTTTATGCTGACTCAGCCCCACTCTGTGTCGGAGTCTCCGGGGAAGACGGTAACCATCTCCTGCACCCGCAGCAGCGGCAGCATTGCCAGCTACTATGTGCAGTGGTACCAGCAGCGCCCGGGCAGTTCCCCCACCACTGTGATCTATGAAGATGACCAAAGACCCTCTGGGGTCCCTGATCGGTTCTCTGGCTCCATCGACAGTGCCTCCAACTCAGCCTCCCTCACCATCTCTGGCCTGCAGACTGAGGACGAGGCTGACTACTACTGTCAGTCTTTTGATAGCAGCATTCAACATGTGGTCTTCGGCGGAGGGACCCAG (SEQ ID NO: 272) CDRL1: AGCGGCAGCATTGCCAGCTACTAT (SEQ ID NO: 268) CDRL2: GAAGATGAC (SEQ ID NO: 269) CDRL3: CAGTCTTTTGATAGCAGCATTCAACATGTGGTC (SEQ ID NO: 270)

1D12	GAGGTCCAGCTGGTACAGTCTG GGGCTGAGGTGAAGAAGCCTGG GTCCTCGGTGAAGGTCTCCTGCA AGGCTTCTGGAGGCACCTTCAGC AGCTATGCTATCAGCTGGGTGCG ACAGGCCCCTGGACAAGGGCTT GAGTGGATGGGATGGATCAGCG CTTACAATGGTAACACAAACTAT GCACAGAAGCTCCAGGGCAGAG TCACCATGACCACAGACACATC CACGAGCACAGCCTACATGGAG CTGAGGAGCCTGAGATCTGAGG ACACGGCCGTGTATTACTGTGCG AGGCTTGAGTGGCTACGTGGTG CTTTTGATATCTGGGGCCAAGGG ACCACG (SEQ ID NO: 279) CDRH1: GGAGGCACCTTCAGCAGCTATG CT (SEQ ID NO: 273) CDRH2: ATCAGCGCTTACAATGGTAACA CA (SEQ ID NO: 274) CDRH3: GCGAGGCTTGAGTGGCTACGTG GTGCTTTTGATATC (SEQ ID NO: 275)	AATTTTATGCTGACTCAGCCC CACTCTGTGTCGGAGTCTCCG GGGAAGACGGTAACCATCTCC TGCACCGGCAGCAGTGGCAGC ATTGCCAGCAATTATGTGCAT TGGTACCAGCAGCGCCCGGGC AGTGCCCCCACCACTGTGATC TATGAGGATAACCAAAGACCC TCTGGGGTCCCTGATCGGTTC TCAGGCTCCATCGACAGCTCC TCCAACTCTGCCTCCCTCACC ATCTCTGGACTGAAGACTGAG GACGAGGCTGACTACTACTGT CAGTCTTATGATGGCAGCGCT TGGGTGTTCGGCGGAGGGACC AAG (SEQ ID NO: 280) CDRL1: AGTGGCAGCATTGCCAGCAA TTAT (SEQ ID NO: 276) CDRL2: GAGGATAAC (SEQ ID NO: 277) CDRL3: CAGTCTTATGATGGCAGCGC TTGGGTG (SEQ ID NO: 278)
1E5	GAGGTCCAGCTGGTGCAGTCTG GGGCTGAGGTGAAGAAGCCTGG GTCCTCGGTGAAGGTCTCCTGCA AGGCTTCTGGAGGCACCTTCAGC AGCTATGCTATCAGCTGGGTGCG ACAGGCCCCTGGACAAGGGCTT GAGTGGATGGGAGGGATCATCC CTATCTTTGGTACAGCAAACTAC GCACAGAAGTTCCAGGGCAGAG TCACGATTACCGCGGACGAATC CACGAGCACAGCCTACATGGAG CTGAGCAGCCTGAGATCTGAGG ACACGGCCGTGTATTACTGTGCG AGAGCGTTAGTCGGAAAGTGGT TATTACTACGGGGCTTTGACTAC	AATTTTATGCTGACTCAGCCC CACTCTGTGTCGGAGTCTCCG GGGAAGACGTTAACCATCTCC TGCACCCGCAGCAGTGGCAGG ATTGCCAGCAACTATGTGCAG TGGTACCAGCAGCGCCCGGGC AGTGCCCCCACCACTGTGATC TATGAGGATACCCAAAGACCC TCTGGGGTCCCTGATCGGTTC TCTGGCTCCATCGACAGCTCC TCCAACTCTGCCTCCCTCACC ATCTCTGGACTGAAGACTGAG GACGAGGCTGACTACTACTGT CAGTCTTTTGATAGCGGCAAT CAACGGGTGGTTTTCGGCGGA GGGACCAAA (SEQ ID NO: 288)

	TGGGGCCAGGGAACCCTG (SEQ ID NO: 287) CDRH1: GGAGGCACCTTCAGCAGCTATGCT (SEQ ID NO: 281) CDRH2: ATCATCCCTATCTTTGGTACAGCA (SEQ ID NO: 282) CDRH3: GCGAGAGCGTTAGTCGGAAAGTGGTTATTACTACGGGGCTTTGACTAC (SEQ ID NO: 283)	CDRL1: AGTGGCAGGATTGCCAGCAACTAT (SEQ ID NO: 284) CDRL2: GAGGATACC (SEQ ID NO: 285) CDRL3: CAGTCTTTTGATAGCGGCAATCAACGGGTGGTT (SEQ ID NO: 286)
1F4	CAGGTACAGCTGCAGCAGTCAGGTCCAGGACTGGTGAAGCCCTCGCAGACCCTCTCACTCACCTGTGCCATCTCCGGGGACAGTGTCTCTAGCAACAGTGCTGCTTGGAACTGGATCAGGCAGTCCCCATCGAGAGGCCTTGAGTGGCTGGGAAGGACATACTACAGGTCCAAGTGGTATAATGATTATGCAGTATCTGTGAAAAGTCGAATAACCATCAACCCAGACACATCCAAGAACCAGTTCTCCCTGCAGCTGAACTCTGTGACTCCCGAGGACACGGCTGTGTATTACTGTGCAAGAGAAAAGGGCATCGAAGGGCCTGCGTTCGACCCCTGGGGCCAGGGAACCCTG (SEQ ID NO: 295) CDRH1: GGGGACAGTGTCTCTAGCAACAGTGCTGCT (SEQ ID NO: 289) CDRH2: ACATACTACAGGTCCAAGTGGTATAAT (SEQ ID NO: 290) CDRH3: GCAAGAGAAAAGGGCATCGAAGGGCCTGCGTTCGACCCC (SEQ ID NO: 291)	CAGTCTGTGTTGACGCAGCCGCCCTCAGTGTCTGGGACCCCCGGGCAGAGGGTCACCATCTCTTGCTCTGGAAGCAGCTCCAACATCGGACGTAATTTTGTATCCTGGTACCAGCAGCTCCCAGGAGCGGCCCCCAGACTCCTCATGTATAGGAATAATCAGCGGCCCTCAGGGGTCCCTGACCGATTCTCTGGCTCCGAGTCTGCCACCTCAGCCTCCCTGGCCATCACTGGGCTCCAGCCTGAGGATGAAGCTGATTATTACTGCCAGTCCTATGACAACAGCCTGTTTGTGGTATTCGGCGGAGGGACCAAG (SEQ ID NO: 296) CDRL1: AGCTCCAACATCGGACGTAATTTT (SEQ ID NO: 292) CDRL2: AGGAATAAT (SEQ ID NO: 293) CDRL3: CAGTCCTATGACAACAGCCTGTTTGTGGTA (SEQ ID NO: 294)

1H7	CAGGTGCAGCTACAGCAGTGGG GCGCAGGACTGTTGAAGCCTTC GGAGACCCTGCCCCTCACCTGCG CTGTCTATGGTGGGTCCTTCAGT GGTTACTACTGGAGCTGGATCCG CCAGCCCCCAGGGAAGGGGCTG GAGTGGATTGGGGAAATCAATC ATAGTGGAAGCACCAACTACAA CCCGTCCCTCAAGAGTCGAGTCA CCATATCAGTAGACACGTCCAA GAACCAGTTCTCCCTGAAGCTGA GCTCTGTGACCGCCGCGGACAC GGCTGTGTATTACTGTGCGAGAG GGAGGTGGCTGCGGGGTGCTTTT GATATCTGGGGCCAAGGGACAA TG (SEQ ID NO: 303) CDRH1: GGTGGGTCCTTCAGTGGTTACTA C (SEQ ID NO: 297) CDRH2: ATCAATCATAGTGGAAGCACC (SEQ ID NO: 298) CDRH3: GCGAGAGGGAGGTGGCTGCGGG GTGCTTTTGATATC (SEQ ID NO: 299)	AATTTTATGCTGACTCAGCCC CACTCTGTGTCGGAGTCTCCG GGGAAGACGGTAACCATCTCC TGCACCCGCAGCAGTGGCAGC ATTGCCAGCAACTATGTGCAG TGGTACCAGCAGCGCCCGGGC AGTTCCCCCACCACTGTGATC TATGAGGATAACCAAAGACCC TCTGGGGTCCCTGATCGGTTC TCTGGCTCCGTCGACAGCTCC TCCAACTCTGCCTCCCTCACC ATCTCTGGACTGAAGACTGAG GACGAGGCTGACTACTACTGT CAGTCTTATGATGAAAACATT CGGGTGTTCGGCGGAGGGACC AAG (SEQ ID NO: 304) CDRL1: AGTGGCAGCATTGCCAGCAA CTAT (SEQ ID NO: 300) CDRL2: GAGGATAAC (SEQ ID NO: 301) CDRL3: CAGTCTTATGATGAAAACAT TCGGGTG (SEQ ID NO: 302)
2C9	CAGGTCCAGCTGGTGCAGTCTG GGGCTGAGGTGAAGAAGCCTGG GTCCTCGGTGAAGGTCTCCTGCA AGGCTTCTGGAGGCACCTTCAGC AGCTATGCTATCAGCTGGGTGCG ACAGGCCCCTGGACAAGGGCTT GAGTGGATGGGAAGGATCATCC CTATCCTTGGTATAGCAAACTAC GCACAGAAGTTCCAGGGCAGAG TCACGATTACCGCGGACAAATC CACGAGCACAGCCTACATGGAG CTGAGCAGCCTGAGATCTGAGG ACACGGCCGTGTATTACTGTGCG AGACATGGGGGGGTGGGAGCTA	GAAATTGTGTTGACGCAGTCT CCAGGCACCCTGTCTTCGTCT CCTGGGGAGAGAGCCACCCTC TCCTGCACGGCCAGCCAGACT GTCGGCGGCAGCTACTTAGCC TGGTACCAGCAAAAACGTGGC CAGCCTCCCAGGCTCCTCATC TATGGTGCGTCCACTAGGGCC CCTGGCATCCCAGAGAGATTT AGTGGCAGTGGGTCTGGGACA GACTTCACTCTCACCATCAGC ACCCTGGAGCCTGAAGATTTT GCAGTGTATTTCTGTCAGCAG TATGCCAGTTCACGGACGTTC

	CTACGGGTTACTACTACATGGAC GTCTGGGGCAAAGGGACCACG (SEQ ID NO: 311) CDRH1: GGAGGCACCTTCAGCAGCTATG CT (SEQ ID NO: 305) CDRH2: ATCATCCCTATCCTTGGTATAGC A (SEQ ID NO: 306) CDRH3: GCGAGACATGGGGGGGTGGGAG CTACTACGGGTTACTACTACATG GACGTC (SEQ ID NO: 307)	GGCCAAGGGACCAGG (SEQ ID NO: 312) CDRL1: CAGACTGTCGGCGGCAGCTA C (SEQ ID NO: 308) CDRL2: GGTGCGTCC (SEQ ID NO: 309) CDRL3: CAGCAGTATGCCAGTTCACG GACG (SEQ ID NO: 310)
2C10	CAGGTGCAGCTACAGCAGTGGG GCGCAGGACTGTTGAAGCCTTC GGAGACCCTGTCCCTCACCTGCG GTGTCTATGGTGGGTCCTTCAGT GGTTACTACTGGAGCTGGATCCG CCAGTCCCCAGGGAAGGGGCTG GAGTGGATTGGGGAAATCAATT ATAGAGGAAACACCAACTACAA CCCGTCTCTCAAGAGTCGAGTCA CCATATCGGTAGACACGTCCAA AAACCAGTTCTCCCTAAACGTGA ACTCTGTGACCGCCGCGGACAC GGCTGTGTATTATTGTGCGAGAT GGGACGGTGGTAACTCCGTGGA CCACTGGGGCCAGGGAACCCTG (SEQ ID NO: 319) CDRH1: GGTGGGTCCTTCAGTGGTTACTA C (SEQ ID NO: 313) CDRH2: ATCAATTATAGAGGAAACACC (SEQ ID NO: 314) CDRH3: GCGAGATGGGACGGTGGTAACT CCGTGGACCAC (SEQ ID NO: 315)	CAGTCTGTCGTGACGCAGCCG CCCTCCGCGTCCGGGTCTCCT GGACAGTCAGTCACCATCTCC TGTTCTGGAAGCAGCTCCACC ATTGGAACTAATTATGTGGCC TGGTACCAGCAGCTCCCAGGA ACAGCCCCCAAACTCCTCATT TATGACAATTATAAGCGACCC TCGGGAATTCCTGACCGATTC TCTGGCTGGAGGTCTGGCACG TCAGCCACCCTGGTCATCAGC GGACTCCAGACCGGGGACGA GGCCGATTATTACTGCGGAAC GTGGGATAGTAGGCTGAGTGT TGGCGTGTTCGGCGGAGGGAC CAAG (SEQ ID NO: 320) CDRL1: AGCTCCACCATTGGAACTAA TTAT (SEQ ID NO: 316) CDRL2: GACAATTAT (SEQ ID NO: 317) CDRL3: GGAACGTGGGATAGTAGGCT GAGTGTTGGCGTG (SEQ ID NO: 318)

2C12	CAGGTGCAGCTGGTGGAGTCTG GGGGAGGCGTGGTCCAGCCTGG GAGGTCCCTGAGACTCTCCTGTG CAGCCTCTGGATTCACCTTCAGT AGCTATGCTATGCACTGGGTCCG CCAGGCTCCAGGCAAGGGGCTG GAGTGGGTGGCAGTTATATCAT ATGATGGAAGTAATAAATACTA TGCAGACTCCGTGAAGGGCCGA TTCACCATCTCCAGAGACAATTC CAAGAACACGCTGTATCTGCAA ATGAACAGCCTGAGAGCTGAGG ACACGGCTGTGTATTACTGTGCG AGAGGGGGACGATTCCACTACT ACTACTATGCCATGGACGTCTGG GGCCAAGGGACCACG (SEQ ID NO: 327) CDRH1: GGATTCACCTTCAGTAGCTATGC T (SEQ ID NO: 321) CDRH2: ATATCATATGATGGAAGTAATA AA (SEQ ID NO: 322) CDRH3: GCGAGAGGGGGACGATTCCACT ACTACTACTATGCCATGGACGTC (SEQ ID NO: 323)	GACATCCAGATGACCCAGTCT CCATCCTCCCTGTCTGCATCTA TAGGAGACAGAGTCACCATCA CTTGCCGGGCAAGTCAGAGCA TTAACATCTATTTAAATTGGT ATCAGCAGAAACCAGGGAAA GCCCCTAAGCTCCTGATCTAT GCTGCATCCAGTTTGCAAAGT GGGGTCCCGTCAAGGTTCAGT GGCAGTGGATCTGCGACAGAT TTCACTCTCACCATCAGCAGT CTGCAGCCTGAAGATTTTGCA ACTTACTACTGTCAACAGAGT TACATTACCCCTCAGACGTTC GGCCAAGGGACCAAG (SEQ ID NO: 328) CDRL1: CAGAGCATTAACATCTAT (SEQ ID NO: 324) CDRL2: GCTGCATCC (SEQ ID NO: 325) CDRL3: CAACAGAGTTACATTACCCC TCAGACG (SEQ ID NO: 326)
2D3	GAGGTCCAGCTGGTGCAGTCTG GGGCTGAGGTGAAGAAGCCTGG GTCCTCGGTGAAGGTCTCCTGCA AGGCTTCTGGAGGCACCTTCAGC AGCTATGCTATCAGCTGGGTGCG ACAGGCCCCTGGACAAGGGCTT GAGTGGATGGGAGGGATCATCC CTATCTTTGGTACAGCAAACTAC GCACAGAAGTTCCAGGGCAGAG TCACGATTACCGCGGACGAATC CACGAGCACAGCCTACATGGAG CTGAGCAGCCTGAGATCTGAGG ACACGGCCGTGTATTACTGTGCG AGCAGTGGCTGGTTAAGGGGTG	AATTTTATGCTGACTCAGCCC CACTCTGTGTCGGAGTCTCCG GGGAAGACGGTAACCATCTCC TGCACCGGCAGCAGTGGCAGC ATTGCCAGCAACTATGTGCAG TGGTACCAGCAGCGCCCGGGC AGTGCCCCCACCACTATTATC TATGAGGATAACCAAAGACCC TCTGGGGTCCCTGATCGGTTC TCTGGCTCCGTCGACAGCTCC TCCAACTCTGCCTCCCTCACC ATCTCTGGACTGAAGACTGAG GACGAGGCTGACTACTACTGT CAGTCTTATGATAGCAGCAAT

	CTTTTGATATCTGGGGCCAAGGGACAATG (SEQ ID NO: 335) CDRH1: GGAGGCACCTTCAGCAGCTATGCT (SEQ ID NO: 329) CDRH2: ATCATCCCTATCTTTGGTACAGCA (SEQ ID NO: 330) CDRH3: GCGAGCAGTGGCTGGTTAAGGGGTGCTTTTGATATC (SEQ ID NO: 331)	TGGGTGTTCGGCGGAGGGACCAAG (SEQ ID NO: 336) CDRL1: AGTGGCAGCATTGCCAGCAACTAT (SEQ ID NO: 332) CDRL2: GAGGATAAC (SEQ ID NO: 333) CDRL3: CAGTCTTATGATAGCAGCAATTGGGTG(SEQ ID NO: 334)
2G7	CAGGTGCAGCTACAGCAGTGGGGCGCAGGACTGTTGAAGCCTTCGGAGACCCTGTCCCTCACCTGCGCTGTCTATGGTGGGTCCTTCAGTGGTTACTACTGGAGCTGGATCCGCCAGCCCCCAGGGAAGGGGCTGGAGTGGATTGGGGAAATCAATCATAGTGGAAGCACCAACTACAACCCGTCCCTCAAGAGTCGAGTCACCATATCAGTAGACACGTCCAAGAACCAGTTCTCCCTGAAGCTGAGCTCTGTGACCGCCGCGGACACGGCTGTGTATTACTGTGCGAGAGGGAAATGGTTACGGGGTGCTTTTGATATCTGGGGCCAAGGGACAATG (SEQ ID NO: 343) CDRH1: GGTGGGTCCTTCAGTGGTTACTAC (SEQ ID NO: 337) CDRH2: ATCAATCATAGTGGAAGCACC (SEQ ID NO: 338) CDRH3: GCGAGAGGGAAATGGTTACGGGGTGCTTTTGATATC (SEQ ID NO: 339)	AATTTTATGCTGACTCAGCCCCACTCTGTGTCGGAGTCTCCGGGGAAGACGATAACCATCTCCTGCACCCGCAGCGGTGGCACCATTGGCAGCAACTATGTGCAGTGGTACCAGCAGCGCCCGGGCAGTTCCCCCACCACTGTGATCTATGAGGATAACCAAAGACCCTCTGGGGTCCCTGATCGGTTCTCTGGCTCCATCGACAGCTCCTCCAACTCTGCCTCCCTCACCATCTCTGGACTGAAGACTGAGGACGAGGCTGACTACTACTGTCAGTCTTATGATAGCAGCAATCGGGTGTTCGGCGGAGGGACCAAG (SEQ ID NO: 344) CDRL1: GGTGGCACCATTGGCAGCAACTAT (SEQ ID NO: 340) CDRL2: GAGGATAAC (SEQ ID NO: 341) CDRL3: CAGTCTTATGATAGCAGCAATCGGGTG (SEQ ID NO: 342)

2H4	CAGGTCCAGCTGGTACAGTCTG GGGCTGAGGTGACGAAGCCTGG GGCCTCAGTGAAGGTCTCCTGCA AGGCTTCTGGATACACCTTCAGC GGCTACTATATACACTGGGTGCG ACAGGCCCCTGGACAAGGGCTT GAGTGGATGGGGCGGGTCAACC CTAATAGTGGTGGCACAAAGTA TGCACAGAAGTTTCAGGACAGG GTCACGTTGACCAGGGACACGT CCATCAGTACTGCCTACATGGAA TTGACCAGTCTGAGATCTGACGA CACGGCCATGTATTTCTGTGCGA GAGGTGGCAGGCCCGGTTTACC TGCAGCTGGCTATATTGACTACT GGGGCCAGGGCACCCTG (SEQ ID NO: 351) CDRH1: GGATACACCTTCAGCGGCTACTA T (SEQ ID NO: 345) CDRH2: GTCAACCCTAATAGTGGTGGCA CA (SEQ ID NO: 346) CDRH3: GCGAGAGGTGGCAGGCCCGGTT TACCTGCAGCTGGCTATATTGAC TAC (SEQ ID NO: 347)	GAAACGACACTCACGCAGTCT CCAGCATTCGTGTCGGCGGCT CCCGGAGACAAAGTGTCCATC TCCTGCAAAGCCAGTGAATTC ATTGGAGATGATGTGAACTGG TACCAACAGAAACCAGGAGA GGCTCCTGTTTTCATCATTCAA GAGGCTCGTGTTCCCGTTCGT GGAATCCCACCCCGATTCAGT GGCAGCGGCTATGGAACAGA TTTTACCCTCACAATTGATGA CATACAATCTGAGGATTCTGC ATTTTACTTCTGTCTGCAATAT GATTCTTTCCCTCTCACTTTTG GCCAGGGGACCAAG (SEQ ID NO: 352) CDRL1: GAATTCATTGGAGATGAT (SEQ ID NO: 348) CDRL2: GAGGCTCGT (SEQ ID NO: 349) CDRL3: CTGCAATATGATTCTTTCCCT CTCACT (SEQ ID NO: 350)
3A11	GAGGTCCAGCTGGTACAGTCTG GAGCTGAGGTGAAGAAGCCTGG GGCCTCAGTGAAGGTCTCCTGCA AGGCTTCTGGTTACACGTTTAGC ACCTATGATATCAGCTGGGTGCG ACAGGCCCCTGGACAAGGGCTT GAGTGGATGGGATGGATCAGCA CTTACAATGGTGACACAAACTAT GCACAGAAGTTCCAGGGCAGAG TCACCATGACCACAGACACGTC CACGAGCACAATCTACATGGAG CTGAGGAGCCTGAGATCTGACG ACACGGCCGTCTATTACTGTGCG AGGGGAGATAGCAGTGTCGGGT	CAATCTGCCCTGACTCAGCCT GCCTCCGTGTCTGGGTCTCCT GGACAGGCGATCACCATGCCC TGCACTGGAACCAGCAGTGAC GTTGGTACTTATAACTATGTC TCCTGGTATCAACACTTCCCA GGCAAAGCCCCCAAACTCTTG ATTTATGATGTCAGTCATCGG CCCGCGGGGATTTCTGATCGC TTCTCTGGCTCCAAGTCTGGC AACACGGCCTCCCTGACCATC TCTGGCCTCCAGGCTGAGGAC GAAGCTGACTATTACTGCGCT TCATTTTCATCCAGCAGCACT

	ACGAATACTTCCAACACTGGGG CCAGGGAACCCTG (SEQ ID NO: 359) CDRH1: GGTTACACGTTTAGCACCTATGA T (SEQ ID NO: 353) CDRH2: ATCAGCACTTACAATGGTGACA CA (SEQ ID NO: 354) CDRH3: GCGAGGGGAGATAGCAGTGTCG GGTACGAATACTTCCAACAC (SEQ ID NO: 355)	CTCTTAGTGTTCGGCGGAGGG ACCAAG (SEQ ID NO: 360) CDRL1: AGCAGTGACGTTGGTACTTA TAACTAT (SEQ ID NO: 356) CDRL2: GATGTCAGT (SEQ ID NO: 357) CDRL3: GCTTCATTTTCATCCAGCAGC ACTCTCTTAGTG (SEQ ID NO: 358)
3C5	CAGGTGCAGCTACAGCAGTGGG GCGCAGGACTGTTGAAGCCTTC GGAGACCCTGTCCCTCACCTGCG GTGTCTATGGTGGGTCCTTAAGT GGTTACTACTGGAGCTGGATCCG CCAGCCCCCAGGGAAGGGGCTG GAGTGGATTGGGGAAATCAATC ATAGTGGAAGCACCAACTACAA CCCGTCCCTCAAGAGTCGAGTCA CCATATCAGTAGACACGTCCAA GAACCAGTTCTCCCTGAAGCTGA GCTCTGTGACCGCCGCGGACAC GGCTGTGTATTACTGTGCGAGAC GGTGGTGGCTACGAGGTGCTTTT GATATCTGGGGCCAAGGGACCA CG (SEQ ID NO: 367) CDRH1: GGTGGGTCCTTAAGTGGTTACTA C (SEQ ID NO: 361) CDRH2: ATCAATCATAGTGGAAGCACC (SEQ ID NO: 362) CDRH3: GCGAGACGGTGGTGGCTACGAG GTGCTTTTGATATC (SEQ ID NO: 363)	AATTTTATGCTGACTCAGCCC CACTCTGTGTCGGAGTCTCCG GGGAAGACGGTAACCATCTCC TGCACCGGCAGCAGTGGCAGC ATTGCCAGCAACTATGTGCAG TGGTACCAGCAGCGCCCGGGC AGTGCCCCCACCACTGTGATC TATGAGGATAACCAAAGACCC TCTGGGGTCCCTGATCGGTTC TCTGGCTCCATCGACAGCTCC TCCAACTCTGCCTCCCTCACC ATCTCTGGACTGAAGACTGAG GACGAGGCTGACTACTACTGT CAGTCTTATGATAGCAGCAAT TGGGTGTTCGGCGGAGGGACC AAG (SEQ ID NO: 368) CDRL1: AGTGGCAGCATTGCCAGCAA CTAT (SEQ ID NO: 364) CDRL2: GAGGATAAC (SEQ ID NO: 365) CDRL3: CAGTCTTATGATAGCAGCAA TTGGGTG (SEQ ID NO: 366)

3D2	CAGGTGCAGCTACAGCAGTGGG GCGCAGGACTGTTGAAGCCTTC GGAGACCCTGTCCCTCACCTGCG CTGTCTATGGTGGGTCCTTCAGT GGTTACTACTGGAGCTGGATCCG CCAGCCCCCAGGGAAGGGGCTG GAGTGGATTGGGGAAATCAATC ATAGTGGAAGCACCAACTACAA CCCGTCCCTCAAGAGTCGAGTCA CCATATCAGTAGACACGTCCAA GAACCAGTTCTCCCTGAAGCTGA GCTCTGTGACCGCCGCGGACAC GGCTGTGTATTACTGTGCGAGAC GGTGGTGGCTACGAGGTGCTTTT GATATCTGGGGCCAAGGGACCA CG (SEQ ID NO: 375) CDRH1: GGTGGGTCCTTCAGTGGTTACTA C (SEQ ID NO: 369) CDRH2: ATCAATCATAGTGGAAGCACC (SEQ ID NO: 370) CDRH3: GCGAGACGGTGGTGGCTACGAG GTGCTTTTGATATC (SEQ ID NO: 371)	AATTTTATGCTGACTCAGCCC CACTCTGTGTCGGAGTCTCCG GGGAAGACGGTAACCATCTCC TGCACCGGCAGCAGTGGCAGC ATTGCCCGCAACTATGTGCAT TGGTACCAGCAGCGCCCGGGC AGTGCCCCCACCACTGTGATC TATGAGGATAACCAAAGACCC TCTGGGGTCCCTGATCGGTTC TCTGGCTCCATCGACAGCTCC TCCAACTCTGCCTCCCTCACC ATCTCTGGACTGAAGACTGAG GACGAGGCTGACTACTACTGT CAGTCTTATGATAGGACCAAT AAGAGGGTTTTCGGCGGAGG GACCAGG (SEQ ID NO: 376) CDRL1: AGTGGCAGCATTGCCCGCAA CTAT (SEQ ID NO: 372) CDRL2: GAGGATAAC (SEQ ID NO: 373) CDRL3: CAGTCTTATGATAGGACCAA TAAGAGGGTT (SEQ ID NO: 374)
3D11	CAGGTGCAGCTACAGCAGTGGG GCGCAGGACTGTTGAAGCCTTC GGAGACCCTGTCCCTCACCTGCG CTGTCTATGGTGGGTCCTTCAGT GGTTACTACTGGAGCTGGATCCG CCAGCCCCCAGGGAAGGGGCTG GAGTGGATTGGGGAAATCAATC ATAGTGGAAGCACCAACTACAA CCCGTCCCTCAAGAGTCGAGTCA CCATATCAGTAGACACGTCCAA GAACCAGTTCTCCCTGAAGCTGA GCTCTGTGACCGCCGCGGACAC GGCTGTGTATTACTGTGCGAGAC GGTGGTGGCTACGAGGTGCTTTT	AATTTTATGCTGACTCAGCCC CACTCTGTGTCGGCGTCTCCG GGGAAGACGGTAACCATCCCC TGCACCGGCAGCAGTGGCAAC ATTGCCAGCAACTATGTGCAG TGGTACCAGCAGCGCCCGGGC AGTGCCCCCACCACTGTGATC TATGAGGATAACCAAAGACCC TCTGGGGTCCCTGATCGGTTC TCTGGCTCCATCGACAGCTCC TCCAACTCTGCCTCCCTCACC ATCTCTGGACTGAAGACTGAG GACGAGGCTGACTACTACTGT CAGTCTTATGATAATAACATT

	GATATCTGGGGCCAAGGGACCACG (SEQ ID NO: 383) CDRH1: GGTTACACCTTTACCAGCTATGGT (SEQ ID NO: 377) CDRH2: ATCAGCGCTTACAATGGTAACACA (SEQ ID NO: 378) CDRH3: GCGAGAGGCATTATTACTATGATATCGGACTAC (SEQ ID NO: 379)	CAGGTGTTCGGCGGAGGGACCAAG (SEQ ID NO: 384) CDRL1: AGTGGCAACATTGCCAGCAACTAT (SEQ ID NO: 380) CDRL2: GAGGATAAC (SEQ ID NO: 381) CDRL3: CAGTCTTATGATAATAACATTCAGGTG (SEQ ID NO: 382)
3E9	GAAGTGCAGCTGGTGCAGTCTGGAGCTGAGGTGAAGAAGCCTGGGGCCTCAGTGAAGGTCTCCTGCAAGGCTTCTGGTTACACCTTTACCAGCTATGGTATCAGCTGGGTGCGACAGGCCCCTGGACAAGGGCTTGAGTGGATGGGATGGATCAGCGCTTACAATGGTAACACAAACTATGCACAGAAGCTCCAGGGCAGAGTCACCATGACCACAGACACATCCACGAGCACAGCCTACATGGAGCTGAGGAGCCTGAGATCTGACGACACGGCCGTGTATTACTGTGCGAGAGGCATTATTACTATGATATCGGACTACTGGGGCCAGGGAACCCTG (SEQ ID NO: 391) CDRH1: GGATTCACCTTCAGTAGCTATGGC (SEQ ID NO: 385) CDRH2: ATATCATATGATGGAAGTAATAAA (SEQ ID NO: 386) CDRH3: GCGAGAGACGGTGGGGGAGGTATGGACGTC (SEQ ID NO: 387)	AATTTTATGCTGACTCAGCCCCACTCTGTGTCGGAGTCTCCGGGGAAGACGGTAACCATCTCCTGCACCGGCAGCAGTGGCAGCATTGCCAGCAACTATGTGCAGTGGTACCAGCAGCGCCCGGGCAGTGCCCCCACCACTGTGATCTATGAGGATAACCAAAGACCCTCTGGGGTCCCTGATCGGTTCTCTGGCTCCATCGACAGCTCCTCCAACTCTGCCTCCCTCACCATCTCTGGACTGAAGACTGAGGACGAGGCTGACTACTACTGTCAGTCTTATGATAGCAGCAACCTTCAGTGGGTGTTCGGCGGAGGGACCAAG (SEQ ID NO: 392) CDRL1: AGTGGCAGCATTGCCAGCAACTAT (SEQ ID NO: 388) CDRL2: GAGGATAAC (SEQ ID NO: 389) CDRL3: CAGTCTTATGATAGCAGCAACCTTCAGTGGGTG (SEQ ID NO: 390)

3F1	CAGGTGCAGCTGGTGCAATCTG GGGGAGGCGTGGTCCAGCCTGG GAGGTCCCTGAGACTCTCCTGTG CAGCCTCTGGATTCACCTTCAGT AGCTATGGCATGCACTGGGTCC GCCAGGCTCCAGGCAAGGGGCT GGAGTGGGTGGCAGTTATATCA TATGATGGAAGTAATAAATACT ATGCAGACTCCGTGAAGGGCCG ATTCACCATCTCCAGAGACAATT CCAAGAACACGCTGTATCTGCA AATGAACAGCCTGAGAGCTGAG GACACGGCTGTGTATTACTGTGC GAGAGACGGTGGGGGAGGTATG GACGTCTGGGGCCAAGGGACCA CG (SEQ ID NO: 399) CDRH1: GGATTCACCTTCAGTAGCTATGG C (SEQ ID NO: 393) CDRH2: ATATCATATGATGGAAGTAATA AA (SEQ ID NO: 394) CDRH3: GCGAGAGACGGTGGGGGAGGTA TGGACGTC (SEQ ID NO: 395)	AATTTTATGCTGACTCAGCCC CACTCTGTGTCGGAGTCTCCG GGGAAGACGGTCACCATCTCC TGCACCGCCAGCGGTGGCAGC ATTGCCGACAACTTTGTGCAG TGGTACCAGCAGCGCCCGGGC AGTGCCCCCACCACTCTGATC TATGACTATAGTCGAAGACCC TATGGGGTCCCAGATCGGTTC TCTGGCTCCATCGACAGGTCC TCCAATTCTGCCTCCCTCACC GTCTCTGGACTGATGACTGAG GACGAGGCTGACTACTATTGT CAGTCTTATGATATCAGCAAT CCGGTGTTCGGCGGAGGGACC AAG (SEQ ID NO: 400) CDRL1: GGTGGCAGCATTGCCGACAA CTTT (SEQ ID NO: 396) CDRL2: GACTATAGT (SEQ ID NO: 397) CDRL3: CAGTCTTATGATATCAGCAAT CCGGTG (SEQ ID NO: 398)
3F11	GAGGTCCAGCTGGTACAGTCTG GAGCTGAGGTGAAGAAGCCTGG GGCCTCAGTGAAGGTCTCCTGCA AGGCTTCTGGTTACACCTTTAGC AGCTCTGGTATCAGCTGGGTGCG ACAGGCCCCTGGACAAGGGCTT GAGTGGATGGGATGGATCAGCA CTTACAATGGTAACACAAACTAT GCACAGAATTTCCAGGGCAGAG TCACCATGACCACAGACACGTC CACGAGCACAGTCTACATGGAG TTGAGGGGCCTGACATCTGACG ACACGGCCGTGTATTACTGTGCT ACGAGTATAGCGGTGGCTGGTA TTGACTACTGGGGCCAGGGCAC CCTG (SEQ ID NO: 407)	GAAACGACACTCACGCAGTCT CCAGGCACCCTGTCCTTGTCT CCAGGGGAAAGCGCCACCCTC TCCTGCAGGGCCAGTCACAGT GATGGCAGGAATTACATTGCC TGGTACCAGCAGACACCTGGC CAGGCTCCCAGGCTCCTCGTT TATGATACGTCGAACAGGGCC GCTGGCGTCCCAGACAGGTTC AGAGGCAGTGGGTCTGGGAC AGACTTCACTCTCACCATCAG CAGACTGGAGCCTGAGGATTT TGCAGTTTATTTCTGTCATCAA TTTCGGAGGTCCGTGTCCACT TTTGGCCAGGGGACCAAA (SEQ ID NO: 408)

	CDRH1: GGTTACACCTTTAGCAGCTCTGGT (SEQ ID NO: 401) CDRH2: ATCAGCACTTACAATGGTAACACA (SEQ ID NO: 402) CDRH3: GCTACGAGTATAGCGGTGGCTGGTATTGACTAC (SEQ ID NO: 403)	CDRL1: CACAGTGATGGCAGGAATTAC (SEQ ID NO: 404) CDRL2: GATACGTCG (SEQ ID NO: 405) CDRL3: CATCAATTTCGGAGGTCCGTGTCCACT (SEQ ID NO: 406)
3H7	CAGGTGCAGCTGGTGCAATCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTGTCCTGTGCAGCGTCTGGATTCACCTTCAGTAACTATGGCATGCACTGGGTCCGCCAGGCTCCGGGCAAGGGGCTGGAGTGGGTGGCAGTTATATGGCATGATGGAACCAATAAATACTATGCAGACTCCGTGAAGGGCCGATTCACCGTCTCCAGAGACAATTCGAAGAACACTCTGTATTTGCAAATGGACACTCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGTGAGAGATCAGGGGGCCGGTGTTTGGAATGGTTATTCCTACTGGGGCCAGGGAACCCTG (SEQ ID NO: 415) CDRH1: GGATTCACCTTCAGTAACTATGGC (SEQ ID NO: 409) CDRH2: ATATGGCATGATGGAACCAATAAA (SEQ ID NO: 410) CDRH3: GTGAGAGATCAGGGGGCCGGTGTTTGGAATGGTTATTCCTAC (SEQ ID NO: 411)	AATTTTATGCTGACTCAGCCCCACTCTGTGTCGGAGTCTCCGGGGAAGACGGTAACCATCTCCTGCACCCGCAGCACTGACAGCATTGCCAGCAACTATGTGCAGTGGTACCAGCAGCGCCCGGGCAGTGCCCCCACCACTGTGATCTATGAAGATAACCAAAGACCCTCTGGGGTCCCTGATCGGTTCTCTGGCTCCATCGACAGCTCCTCCAACTCAGCCTCCCTCACCATCTCTGGACTGAAGACTGAGGACGAGGCTGACTACTACTGTCAGTCTTATGATGGCGTCAATCGCGGCGTGATATTCGGCGGAGGGACCAAG (SEQ ID NO: 416) CDRL1: ACTGACAGCATTGCCAGCAACTAT (SEQ ID NO: 412) CDRL2: GAAGATAAC (SEQ ID NO: 413) CDRL3: CAGTCTTATGATGGCGTCAATCGCGGCGTGATA (SEQ ID NO: 414)
3H11	CAGGTGCAGCTGGTGCAATCTGGGGCTGAGGTGAAGAAGCCTGG	AATTTTATGCTGACTCAGCCCCACTCTGTGTCGGAGTCTCCG

	GGCCTCAGTGAAGGTTTCCTGCA AGGCATCTGGATACACCTTCACC AGCTACTATATGCACTGGGTGCG ACAGGCCCCTGGACAAGGGCTT GAGTGGATGGGAATAATCAACC CTAGTGGTGGTAGCACAAGCTA CGCACAGAAGTTCCAGGGCAGA GTCACCATGACCAGGGACACGT CCACGAACACAGTCTACATGGA GCTGAGCAGCCTGAGATCTGAG GACACGGCCGTGTATTACTGTGC GAGCTCAGTAGTACCAGCTGCT ATTTACGACTACTACTACGGTAT GGACGTCTGGGGCCAAGGGACC ACG (SEQ ID NO: 423) CDRH1: GGATACACCTTCACCAGCTACTA T (SEQ ID NO: 417) CDRH2: ATCAACCCTAGTGGTGGTAGCA CA (SEQ ID NO: 418) CDRH3: GCGAGCTCAGTAGTACCAGCTG CTATTTACGACTACTACTACGGT ATGGACGTC (SEQ ID NO: 419)	GGGAAGACGGTAACCATCTCC TGCACCCGCAGCAGTGGCAAC ATTGCCAGTTACTATGTGCAG TGGTACCAGCAGCGCCCGGGC AGTTCCCCCACCACTGTGATC TATGAGGATAACCAAAGACCT TCTGGGGTCCCTGATCGGTTC TCTGGCTCCATCGACAGCTCC TCCAACTCTGCCTCCCTCACC ATCTCTGGACTGCAGACTGAG GACGAGGCTGACTACTACTGT CAGTCTTATGATCGTCCCAAT CATGTGGTGTTCGGCGGCGGG ACCAGG (SEQ ID NO: 424) CDRL1: AGTGGCAACATTGCCAGTTA CTAT (SEQ ID NO: 420) CDRL2: GAGGATAAC (SEQ ID NO: 421) CDRL3: CAGTCTTATGATCGTCCCAAT CATGTGGTG (SEQ ID NO: 422)
6F8	CAGGTGCAGCTGGTGGAGTCCG GGGGAGGCTTGGTACAGCCTGG GGGGTCCCTGAGACTCTCCTGTG CAGCCTCTGGGTTCACCGTCAGT AGCAACTACATGAGCTGGGTCC GCCAGGCTCCAGGGAAGGGGCT GGAGTGGGTCTCAGTTATTTATA GCGGTGGTAGCACATACTACGC AGACTCCGTGAAGGGCCGATTC ACCATCTCCAGAGACAATTCCA AGAACACGCTGTATCTTCAAATG AACAGCCTGAGAGCCGAGGACA CGGCCGTGTATTACTGTGCGAGA GACTACGGTGACTATTACTTTGA CTACTGGGGCCAGGGCACCCTG (SEQ ID NO: 431)	GAAATTGTGCTGACTCAGTCT CCAGGCACCCTGTCTTTGTCT CCAGGGGAAAGAGCCACCCT CTCCTGCACGGCCAGTCAGAC TATTAACAACAACTACTTAGC CTGGTACCAGCAGAAACCTGG CCAGGGTCCCAGCCTCCTCAT CTATGATGCATCCAGCAGGGC CACTGGCGTCCCAGACAGGTT CAGTGGCAGTGGGTCGGGGA CAGACTTCACTCTCACCATCA GCAGACTGGAGCCTGAAGATT TTGCAGTGTATTACTGTCAGC AGTATGGAAGCTCGCCTCGGA CGTTCGGCCAAGGGACCAAG (SEQ ID NO: 432)

	CDRH1: GGGTTCACCGTCAGTAGCAACT AC (SEQ ID NO: 425) CDRH2: ATTTATAGCGGTGGTAGCACA (SEQ ID NO: 426) CDRH3: GCGAGAGACTACGGTGACTATT ACTTTGACTAC (SEQ ID NO: 427)	CDRL1: CAGACTATTAACAACAACTA C (SEQ ID NO: 428) CDRL2: GATGCATCC (SEQ ID NO: 429) CDRL3: CAGCAGTATGGAAGCTCGCC TCGGACG (SEQ ID NO: 430)

[00203] Nucleic acid compositions encoding the anti-SARS-CoV-2-Spike antibodies and/or SARS-CoV-2-binding domains are also provided. As will be appreciated by those in the art, in the case of antigen binding domains, the nucleic acid compositions generally include a first nucleic acid encoding the heavy chain variable region and a second nucleic acid encoding the light chain variable region. In the case of scFvs, a single nucleic acid encoding the heavy chain variable region and light chain variable region, separated by a linker described herein, can be made. In the case of traditional antibodies, the nucleic acid compositions generally include a first nucleic acid encoding the heavy chain and a second nucleic acid encoding the light chain, which will, upon expression in a cell, spontaneously assemble into the "traditional" tetrameric format of two heavy chains and two light chains.

[00204] As is known in the art, the nucleic acids encoding the components of the invention can be incorporated into expression vectors, and depending on the host cells, used to produce the antibodies of the invention. These two nucleic acids can be incorporated into a single expression vector or into two different expression vectors. Generally, the nucleic acids can be operably linked to any number of regulatory elements (promoters, origin of replication, selectable markers, ribosomal binding sites, inducers, etc.) in an expression vector. The expression vectors can be extra-chromosomal or integrating vectors.

[00205] The nucleic acids and/or expression vectors of the current invention can be introduced into any type of host cells, which are well known in the art, including mammalian, bacterial, yeast, insect and fungal cells. After transfection, single cell clones can be isolated for cell bank generation using methods known in the art, such as limited dilution, ELISA, FACS, microscopy, or Clonepix. Clones can be cultured under conditions suitable for bio-

reactor scale-up and maintained expression of the antibodies. The antibodies can be isolated and purified using methods known in the art including centrifugation, depth filtration, cell lysis, homogenization, freeze-thawing, affinity purification, gel filtration, ion exchange chromatography, hydrophobic interaction exchange chromatography, and mixed-mode chromatography.

D. Therapeutic Applications

[0001] The current disclosure provides a method of treating a subject with SARS-CoV-2, and the method includes administering to the subject an effective amount of an anti-SARS-CoV-2 antibody described herein, or a pharmaceutical composition containing an anti-SARS-CoV-2 antibody.

[0002] In some embodiments, the methods of treating a subject with SARS-CoV-2 by the present disclosure comprises administering to the subject an effective amount of an anti-SARS-CoV-2 antibody that acts as a SARS-CoV-2 antagonist, or by administering a pharmaceutical composition containing an antagonistic anti-SARS-CoV-2 antibody.

[0003] In some embodiments, the methods encompassed by the present disclosure comprise methods of treating a subject with SARS-CoV-2, for example, by administering anti-SARS-CoV-2 antibodies that includes a heavy chain variable region comprising an amino acid sequence at least about 80% (*e.g.*, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:7, and a light chain variable region comprising amino acid sequence at least about 80% (*e.g.*, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:8; and/or a vhCDR1 comprising SEQ ID NO:1, a vhCDR2 comprising SEQ ID NO:2, a vhCDR3 comprising SEQ ID NO:3, a vlCDR1 comprising SEQ ID NO:4, a vlCDR2 comprising SEQ ID NO:5, and a vlCDR3 comprising SEQ ID NO:6.

[0004] The current disclosure also provides a method of modulating an immune response in a subject, and the method includes administering to the subject an effective amount of an anti-SARS-CoV-2 antibody described herein, or a pharmaceutical composition containing an anti- SARS-CoV-2 antibody.

[0005] In some embodiments, the methods of modulating an immune response encompassed by the present disclosure comprises stimulating an immune response in a subject, and in further embodiments, such methods comprise administering to the subject an effective amount of an anti-SARS-CoV-2 antibody that acts as a SARS-CoV-2 antagonist, or by administering a pharmaceutical composition containing an antagonistic anti-SARS-CoV-2 antibody.

[0006] In some embodiments, the methods encompassed by the present disclosure comprise methods of modulating an immune response in a subject, for example, by administering anti- SARS-CoV-2 antibodies that includes a heavy chain variable region comprising an amino acid sequence at least about 80% (*e.g.*, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:7, and a light chain variable region comprising amino acid sequence at least about 80% (*e.g.*, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:8; and/or a vhCDR1 comprising SEQ ID NO:1, a vhCDR2 comprising SEQ ID NO:2, a vhCDR3 comprising SEQ ID NO:3, a vlCDR1 comprising SEQ ID NO:4, a vlCDR2 comprising SEQ ID NO:5, and a vlCDR3 comprising SEQ ID NO:6.

E. Pharmaceutical Composition and Administration

[0007] The Anti-SARS-CoV-2-Spike antibodies described herein can be used in combination with additional therapeutic agents to treat Covid-19.

[0008] The present disclosure also features pharmaceutical compositions/formulations that contain a therapeutically effective amount of an anti-SARS-CoV-2 antibody described herein. The composition can be formulated for use in a variety of drug delivery systems. One or more physiologically acceptable excipients or carriers can also be included in the composition for proper formulation. Suitable formulations for use in the present disclosure are found in Remington's Pharmaceutical Sciences, Mack Publishing Company, Philadelphia, Pa., 17th ed., 1985. For a brief review of methods for drug delivery, see, *e.g.*, Langer (Science 249:1527-1533, 1990).

[0009] The antibodies of the present disclosure can exist in a lyophilized formulation or liquid aqueous pharmaceutical formulation. The aqueous carrier of interest herein is one which is pharmaceutically acceptable (safe and non-toxic for administration to a human) and is useful for the preparation of a liquid formulation. Illustrative carriers include sterile water for injection (SWFI), bacteriostatic water for injection (BWFI), a pH buffered solution (*e.g.*, phosphate-buffered saline), sterile saline solution, Ringer's solution or dextrose solution.

[0010] The antibodies of the present disclosure could exist in a lyophilized formulation including the proteins and a lyoprotectant. The lyoprotectant may be sugar, *e.g.*, disaccharides. In certain embodiments, the lyoprotectant is sucrose or maltose. The lyophilized formulation may also include one or more of a buffering agent, a surfactant, a bulking agent, and/or a preservative.

[0011] Actual dosage levels of the active ingredients in the pharmaceutical compositions of this invention may be varied so as to obtain an amount of the active ingredient which is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration, without being toxic to the patient. It may be administered in the range of 0.1 mg to 1 g and preferably in the range of 0.5 mg to 500 mg of active antibody per administration for adults. Alternatively, a patient's dose can be tailored to the approximate body weight or surface area of the patient. Other factors in determining the appropriate dosage can include the disease or condition to be treated or prevented, the severity of the disease, the route of administration, and the age, sex and medical condition of the patient. Further refinement of the calculations necessary to determine the appropriate dosage for treatment is routinely made by those skilled in the art, especially in light of the dosage information and assays disclosed herein. The dosage can also be determined through the use of known assays for determining dosages used in conjunction with appropriate dose-response data. An individual patient's dosage can be adjusted as the progress of the disease is monitored. Blood levels of the targetable construct or complex in a patient can be measured to see if the dosage needs to be adjusted to reach or maintain an effective concentration. Pharmacogenomics may be used to determine which targetable constructs and/or complexes, and dosages thereof, are most likely to be effective for a given individual (Schmitz et al., Clinica Chimica Acta 308: 43-53, 2001; Steimer et al., Clinica Chimica Acta 308: 33-41, 2001).

[0012] Doses may be given once or more times daily, weekly, monthly or yearly, or even once every 2 to 20 years. Persons of ordinary skill in the art can easily estimate repetition rates for dosing based on measured residence times and concentrations of the targetable construct or complex in bodily fluids or tissues. Administration of the present invention could be intravenous, intraarterial, intraperitoneal, intramuscular, subcutaneous, intrapleural, intrathecal, intracavitary, by perfusion through a catheter or by direct intralesional injection. This may be administered once or more times daily, once or more times weekly, once or more times monthly, and once or more times annually.

EXAMPLES

Example 1

A. Introduction

[00206] A naïve combinatorial human Fab library was screened for antibodies that target the SARS-CoV-2 Spike protein RBD and competitively block ACE2 binding. Antibodies were discovered that all exhibit effective receptor blockade but have different neutralization potencies against SARS-CoV-2. Taking these antibodies as mechanistic probes, it was shown that bivalent binding and receptor blockade are not the sole determinants of potent neutralization, In addition to blocking ACE2, these antibodies either inhibit or enhance syncytia formation in Vero E6 cells, suggesting that potentiation of cell-cell fusion by antibodies may compromise the effectiveness of viral neutralization in treatment of severe COVID-19. One potently neutralizing and potentially therapeutic antibody, designated 5A6, uniquely inhibits cell-cell fusion and syncytia formation and blocks receptor binding. High resolution cryogenic electron microscopy (cryo-EM) structures of multiple Spike-antibody complexes provide insight into determinants of viral neutralization potency, and reveal that 5A6 recognizes a quaternary epitope that conveys receptor blockade and inhibits syncytia by trapping the pre-fusion state. Methods for this study are described below:

B. Isolation of SARS-CoV-2 receptor-blocking antibodies from a naïve human library

[00207] Six antibodies that block the RBD/ACE2 interaction were identified with nanomolar EC50 values by phage display of a naïve combinatorial human Fab library

comprising 3 x 1010 random heavy and light IgG chain pairs drawn from health donors (Goh et al., 2014) (Figure 1A, Figure S1). Their germlines and degree of hypermutation are given in Table S1. Whereas the source Fabs had moderate intrinsic affinities for immobilized RBD, as high as 1.6 nM for 3D11 and 7.6 nM for 5A6, clones reformatted as IgGs showed sub-picomolar to picomolar binding avidity (Figure 1B, Figures 8-10). Biolayer interferometry (BLI) of free Fabs and their equivalent IgGs indicates that the greatly enhanced binding of the IgGs is primarily due to slower dissociation, likely due to bivalent binding of both Fab arms to their epitopes (Figure 1C, Figure 18). Stepwise binding BLI assays show that Fab fragments 5A6 and 3D11 have non-overlapping footprints on the RBD, while 5A6 shares at least partially overlapping epitopes with the other four antibodies (Figure 1D).

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C. SARS-CoV-2 neutralization by receptor blocking antibodies

[00208] Six receptor-blocking antibodies were evaluated for neutralizing activity against SARS-CoV-2 pseudovirus in CHO-ACE2 cells with a luciferase reporter (Figure 2A), and against live SARS-CoV-2 (Young et al., 2020) in Vero E6 cells by cell viability (Figure 2B). The antibodies neutralize pseudovirus with IC50 values ranging from 75.5 to 428.3 ng/mL, but while neutralization of live virus is 11- to 20-fold less potent for other antibodies, 5A6 retains similar potency with IC50 of 140.7 ng/ml (<2-fold weaker). This difference in neutralization potency in live virus and pseudovirus assays is most likely due to the non-replicating nature of pseudoviruses, which are thereby more sensitive to blockade of viral entry. A live virus neutralization of a subset of antibodies was validated (2H4, 3D11 and 5A6) using a RT-qPCR to quantify viral replication (Figure 11), and observed similar trends as obtained from cell viability assays (Figure 2B). To more accurately assess the therapeutic potential of 5A6, its neutralizing potency was studied in SARS-CoV-2 infection of human airway epithelia (HAE) (Pizzorno et al., 2020). SARS-CoV-2 replication in HAE was reduced 1000-fold by 5A6 at 75 ng/mL and 10,000-fold at 150ng/mL, and 5A6 also helped maintain epithelium integrity (represented by trans- epithelia electrical resistance), supporting its activity in a physiologically relevant in vitro model (Figure 2C).

[00209] All IgGs effectively block ACE2-RBD binding, with IC50 values below 50 nanomolar (Figure 7). Therefore, the relative viral neutralization potencies of these

antibodies cannot be ascribed to competitive receptor blocking alone. In order to interrogate other determinants of neutralization, we next compared the potency of each IgG antibody to their respective monomeric Fab fragments. A bivalent ACE2-Fc fusion protein was included as a reference for multivalent receptor blockade. All antibodies show dramatically increased potency against live virus compared to Fab, which is consistent with bivalent engagement of the Spike trimer by the IgG compared to the monovalent Fab fragment. The affinity or avidity for RBD is generally predictive of viral neutralization IC50, with two striking exceptions (Figure 2D, Table S2). Antibody 5A6 exhibits far greater viral neutralization potency than other antibodies with superior avidity. Conversely, 3D11 is among the least potent in viral neutralization despite displaying the strongest binding.

[00210] The discrepancy could arise from the differences in the structural arrangement of IgGs bound to the RBDs of intact, trimeric Spike on the virion. Surface plasmon resonance (SPR) to measure antibody binding to immobilized Spike trimers, as opposed to immobilized RBD (Figure S9, Table S2). Although kinetics of binding to trimer were largely similar, we noted that 5A6 IgG binds somewhat more tightly (3.6x) to the intact trimer than to the flexible Fc-RBD construct used for BLI, while 3D11 IgG binds much (18.7x) more weakly (but still apparently bivalently, with 21.7x tighter binding than 3D11 Fab). To further investigate the relationship of the antibodies to intact Spike assemblies, we purified SARS-CoV-2 pseudovirus by gradient centrifugation and immobilized the viral particles on ELISA plates (Figure 2E). The higher optical signal at saturation in concentration-dependent binding curves reveals that 5A6 IgG likely packs with higher density on the viral surface than the other four tested IgG antibodies or 5A6 Fab. It has been proposed that effective viral neutralization requires antibody packing density exceeding a critical threshold (Burton et al., 2001; Dowd and Pierson, 2011; Flamand et al., 1993) and 5A6 may possess a unique binding mode that accommodates a denser structural arrangement on the viral surface. Notably, 3D11 IgG exhibits a similarly high signal at saturation, but with lower affinity for the pseudoviral particles, despite having higher affinity than 5A6 for immobilized RBD or Spike trimer (Figure 2E, Figure 15). Finally, 2H4 and 1F4 IgGs saturate immobilized pseudovirus at 1/3 the density of 5A6 or 3D11,

while neutralizing live virus slightly more effectively than 3D11. These results suggest at least three different classes of receptor-blocking antibodies with distinct structural relationships to RBDs on viral particles.

D. Neutralizing antibodies inhibit or enhance Spike-mediated cell fusion

[00211] With receptor-blocking activity and avid binding eliminated as sole determinants of neutralization by prior experiments, 5A6 might interfere with additional functions of the SARS-CoV-2 Spike. The most prominent example is induction of fusion of infected cells with neighboring cells, leading to formation of syncytia (multinucleated giant cells), a phenomenon known to hasten disease progression in respiratory syncytial virus (McNamara and Smyth, 2002) and human immunodeficiency virus (Koot et al., 1993; Sylwester et al., 1997), and now widely observed in late-stage COVID-19 (Bussani et al., 2020). Therefore, it was assessed whether antibodies discovered in the campaign inhibit Spike-mediated syncytia formation. To directly examine syncytia formation by Spike alone, Spike protein was expressed with a C-terminal fluorescent tag in Vero E6 cells. Addition of trypsin as an exogenous Spike-processing enzyme resulted in cells with a diffuse fluorescent signal and multiple nuclei, indicative of syncytia formation. (Figure 3A). The impact of receptor-blocking antibodies was assayed on this trypsin-induced cell-cell fusion, using antibodies 2H4, 5A6 and 3D11, which represent different modes of viral neutralization. The 5A6 IgG has a dose-dependent inhibitory effect on syncytia (Figure 3B). By contrast 2H4 IgG has no significant effect. 3D11 potentiates cell-cell fusion. Furthermore, 5A6 Fabs also enhanced syncytial fusion, albeit weakly (Figure 3A-B). 5A6 IgG directly inhibits Spike-mediated fusion, while other receptor blocking antibodies fail to inhibit or even accelerate this process.

E. Structures of Spike-Fab complexes

[00212] The Spike trimer exists in equilibrium between the closed conformation, with all RBDs nestled closely around the S2 subunit, and "receptor seeking" states featuring one or more open RBDs that become erect and disengage from the S2 (Walls et al., 2020; Wrapp et al., 2020b; Yurkovetskiy et al., 2020). To provide structural insights into how antibodies targeting different RBD epitopes divergently modulate Sike protein function, the structures of

the trimeric Spike protein were determined alone (Figure 12A-12B), and in complex with Fab fragments of 3D11 (Figure 12C-12D), 2H4 (Figure 12E), and 5A6 (Figure 12F-12G). Consistent with epitope binning and functional characterization, these Fabs explore different regions of the RBD surface, are compatible with different (open or closed) RBD states in the Spike trimer, and bind with distinct geometries relative to the RBD and ACE2 interface (Figure 4). This form of three-dimensional epitope mapping provides atomic level understanding of the determinants of viral inhibition.

F. 2H4 is an orthosteric receptor-mimetic antibody

[00213] Multiple structures of 2H4 Fab were determined to be bound to Spike with resolution sufficient for unambiguously docking a model of 2H4, but precluding precise modelling of the epitope and complementarity determining regions (CDRs) (Figure 12E). Three major conformational states were identified by 3D classification, revealing either one, two, or three 2H4 Fabs bound to the Spike trimer. The receptor blocking activity of 2H4 is straightforward, as it recognizes an epitope that overlaps much of the ACE2 interface (Figure 4A). Binding of the 2H4 Fab is compatible with both major RBD conformations, and the structures are drawn from an ensemble of quaternary states reminiscent of those that follow ACE2 binding, and lead to S1 shedding and spike-mediated membrane fusion (Benton et al. 2020) (Figure 4B). The first of three predominant states features 2H4 bound to one open RBD, and the other two RBDs closed. The second state adds a second copy of 2H4, on a closed RBD counter-clockwise from the first. Density inspection and 3D variability analysis (3DVA) reveal that the third RBD is primarily open, and a trajectory of opening states correlate with binding the second Fab. The final state features three Fabs bound, and a strictly open third RBD. This restricted ensemble arises because when the bound RBD is closed, the Fab incurs clashes with the counter-clockwise adjacent RBD that can only be relieved by opening of that RBD and NTD, even beyond the degree of opening in the triple ACE2 complex with three open RBDs (Benton et.al. 2020) (Figure 4C). These observations suggest 2H4 directly blocks receptor binding, but also acts as a receptor-mimetic that admits the same cycle of Spike conformations as does ACE2. A neutralizing antibody against SARS-CoV has also been reported to engage in orthosteric receptor mimicry (Walls et al., 2019),

suggesting activation of fusion-associated conformational changes may be an intrinsic consequence of direct receptor interface binding in betacoronaviruses.

G. 3D11 allosterically blocks ACE2 binding and triggers Spike opening

[00214] The Spike:3D11 complex is relatively homogeneous, with only one major state (Figure 4D), and we determined its structure to ~3.0 Å resolution (Figure 12C). All three RBDs are bound to 3D11 Fab in the open conformation, with the Fab making a right angle to the long axis of the RBD, via an epitope exposed only in the open state and outside the RBM (Figure 4A). The epitope partly overlaps those of some other antibodies that bind outside the RBM (Liu et al., 2020; Yuan et al., 2020), but is distinct from those (Barnes et al., 2020; Pinto et al., 2020) that bind freely to a closed RBD (Figure 13D). Clashes between 3D11 and Spike NTDs also prevent 3D11 binding to closed RBDs, indicating 3D11 binds only to open RBDs. This restriction of binding to the subset of Spike conformations with open RBDs might account for lessened avidity of 3D11 IgG for the intact Spike trimer, as compared with RBD (Figure S9C). 3D classification reveals outward motions of the NTD and variation in Fab occupancy, but only open RBDs are observed (Figure 13A). As for 2H4, the 3D11 bound RBDs are "more open" (displaced further outward) than those in the triple ACE2 complex (Figure 4E).

[00215] Although its epitope does not significantly overlap with the ACE2-RBD interface, 3D11 nevertheless effectively blocks ACE2 binding and stabilizes a quaternary state of the Spike, with three open RBDs and NTDs, that closely resembles the penultimate stage of ACE2-induced Spike opening (Benton et al., 2020). We therefore term 3D11 an allosteric receptor-mimetic antibody, which does not directly target the ACE2 interface, yet prevents ACE2 binding and enhances Spike-mediated fusion by rapidly advancing the Spike conformational cycle to its final stages.

H. 5A6 traps a pre-fusion conformation to inhibit spike-mediated fusion

[00216] Multiple states of the Spike:5A6 complex were resolved to better than 3.0 Å, with local resolution sufficient for accurate modelling of the Fab-RBD interface (Figure S6G). 5A6 recognizes surface loops near the tip of the RBD, which are solvent

exposed even when all RBDs are closed. The binding geometry is permissive of any trimer configuration and any stoichiometry, without steric constraints from Spike or Fab. Yet despite this complete conformational freedom, all 5A6 complexes feature at least two 5A6 Fabs bound to an open RBD counter-clockwise adjacent in turn from a closed RBD (Figure 4F). The hallmark of these states is a cryptic, quaternary epitope in which a region of the Fab VL domain makes a second interaction with an adjacent, open RBD (Figure 4G). This new interaction is not possible with a closed RBD, and requires an adjustment away from the average positions of open RBDs in other structures (Figure 13B). The closed RBD bound via the main 5A6 interface is also displaced from other closed conformations.

[00217] CDR loops H1, H2, H3, and L1 engage the canonical epitope with a buried surface area of 850 Å2 (Figure 5A). Partial overlap of the RBM and Fab interface, and a clash induced between ACE2 and the Fab VL domain, are likely sufficient to exclude ACE2 from the RBD. The second interaction contributes an additional 363 Å2 (Figure 5B), and the CH1 and CL domains of 5A6 at the cryptic quaternary epitope induce an even more severe clash with ACE2 (Figure 4G). Two Fabs thus act synergistically to block ACE2 binding, while one Fab is capable of blocking ACE2 at two RBDs simultaneously. The secondary interface must be released in order for the bound RBD to open, and we hypothesize that 5A6 at its quaternary epitope locks one RBD closed, thereby arresting the trimer in its pre-fusion state. Precise conservation of binding mode and the cryptic quaternary epitope from free Fab to IgG is confirmed by a structure of 5A6 IgG complexed with Spike trimer at ~15 Å resolution (Figure 5C). Although the Fc domain is not well resolved due to the flexibility of the hinge region, the structures suggest 5A6 IgG may bind to two RBDs from the same trimer (Figure S7C), and shows that no steric effects preclude binding of three IgGs at sufficient concentration. Noting the weak potentiation of syncytia formation by 5A6 Fab, the cryptic epitope likely appears following initial Fab binding, and leads to cooperative action against SARS-CoV-2 by imbuing a second binding event with enhanced affinity and receptor blockade. The geometry of the quaternary epitope and avidity of 5A6 IgG drive robust pre-fusion conformational trapping and potent inhibition of Spike-mediated fusion and syncytia formation.

I. Methods

[00218] Antibody discovery from phage display library

[00219] Anti-SARS-CoV-2 Spike RBD antibodies were isolated from an HX02 human. Fab phage display library (Humanyx Pte Ltd) via in vitro selection. Briefly, biopanning was performed using SARS-CoV-2 RBD (YP_009724390.1) (Arg319-Phe541) with a mouse Fc tag (Sino Biological, 40592-V05H) biotinylated using the EZ-Link NHS-PEG4-Biotin labelling kit (Thermo Fisher Scientific, #A39259). In both rounds of biopanning, biotinylated SARS-CoV-2 RBD-mFc protein was immobilized on M280 streptavidin-coated magnetic beads (Life Technologies, #11205D); 3.5 x 1012 cfu phage in 1mL 1% casein-PBS blocking buffer was used in the first round, and 1.64 x 1011 cfu phage were used in the second round. During the biopanning process, binders to mouse Fc were removed by pre-incubation of phage with 2 μM mouse IgG before mixing with the RBD-mFc antigen. After two rounds of biopanning, the Fabs of selected clones were expressed in E. coli HB2151 cells (Stratagene) to screen for RBD binders by ELISA. Unique clones were identified by DNA sequencing.

[00220] IgG expression and purification

[00221] Fabs were reformatted into human IgG in the pTT5 vector (National Research Council of Canada) and the IgG antibodies were expressed using ExpiCHO expression system (Thermo Fisher Scientific) by transient co-transfection of plasmids expressing the heavy and light chain of each antibody clone. Eight days after transfection, ExpiCHO-S cell suspension was centrifuged for 10 min at 2000 rpm and filtered with 0.22 μm filter to remove the cells and debris. Antibodies were then purified from the culture supernatant using Protein G resin (Merck Millipore) following the manufacturer's instructions. After elution, the purified antibodies were dialyzed at 4°C. for 4-20 hours against 1x PBS, for 3 times and concentrated to 1-2 mg/ml using 10MWCO Vivaspin 20 (Sartorius).

[00222] Fab production and purification

[00223] The tag-less Fab fragments were produced using the ExpiCHO transient expression system. Eight days after transfection, ExpiCHO-S cell suspension was centrifuged and filtered; and Fab was purified from the filtered culture supernatant using cation exchange chromatography (CIEX) on AKTA FPLC System (GE Healthcare). In brief, the supernatant was concentrated to 2 ml using 10MWCO Vivaspin 20 (Sartorius), diluted 1:20 in Buffer A (20 mM Sodium Acetate, pH 5.2), filtered

through 0.22 μm filter, and loaded onto Mono-S 5/50 GL column at a flow rate of 1ml/min. Fab fragments were eluted in Buffer B (20 mM Sodium Acetate, pH 5.2 with 1 M Sodium Chloride) with a sequential linear gradient of 0% to 5% in 5 min, 5% to 15% in 30 min, and 15% to 100% in 20 min of Buffer B injection at a flow rate of 1 ml/min. The resulting purified Fab fragments were dialyzed at 4°C for 4-20 hours against 4 liters of 20 mM Histidine, 150 mM NaCl, pH 6.6, for 3 times and concentrated to 1-2 mg/ml using 10MWCO Vivaspin 6 (Sartorius).

[00224] Avidity binding ELISA to RBD proteins

[00225] Anti-SARS-CoV-2 Spike RBD IgG antibodies were tested in an ELISA against biotinylated recombinant SARS-CoV-2 Spike protein RBD-mFc (Sino Biological, 40592-V05H) or SARS-CoV Spike protein RBD-His (Sino Biological, 40150-V08B2) to assess binding avidity for the target. In brief, NeutrAvidin protein (Thermo Fisher Scientific, #31000) was coated at 5 μg/ml onto 96-well ELISA plates in coating buffer (8.4 g/L NaHCO3, 3.56 g/L Na2CO3, pH 9.5) overnight at 4°C. After blocking with 1% Casein (Thermo Fisher Scientific, #A37528) for two hours, biotinylated antigen at 0.2 μg/ml was added to the plates and captured by NeutrAvidin during one-hour incubation at room temperature. After washing with 0.05% PBST for 5 times, the IgG antibodies were added at different concentrations with 3-fold dilutions in triplicate and incubated for one hour. The wells were then washed again with 0.05% PBST, followed by addition of HRP conjugated anti-human Fc antibody (1:3000). Finally, the wells were washed and the HRP activity was measured at 450 nm with addition of 3,3',5,5'- tetramethylbenzidine (TMB) substrate (Surmodics, BioFX®, TMBW-1000-01).

[00226] Avidity binding ELISA to purified pseudovirus

[00227] Anti-SARS-CoV-2 Spike RBD IgG antibodies were tested in an ELISA against iodixanol-gradient-purified SARS-CoV-2 pseudoviruses with an isotype IgG used as a negative control antibody. In brief, 1 μg/ml of pseudoviral particles were coated in coating buffer onto 96-well ELISA plates overnight at 4°C. After blocking with 1% Casein (Thermo Fisher Scientific, #A37528) for two hours, serially diluted IgG antibodies starting from 100 nM with five-fold dilutions were added to the plates and incubated for an hour at room temperature. The wells were then washed again with 0.05% PBST, followed by addition of HRP conjugated anti-human Fc antibody (Thermo

Fisher Scientific, #A21445, 1:3000) for one-hour incubation before HRP activity was measured at 450 nm with addition of TMB substrate.

[00228] Competition ELISA

[00229] Anti-SARS-CoV-2 Spike RBD IgG antibodies were tested in a competition ELISA to assess their ability to block the Spike protein RBD from binding to human ACE2 protein. In brief, the recombinant human ACE2 protein with a human Fc tag (ACE2-Fc) was coated onto the 96-well ELISA plates in coating buffer overnight at 4°C and blocked with 1% Casein. Then different concentrations of anti-SARS-CoV-2 Spike RBD IgG antibodies were pre-incubated with 0.5 nM biotinylated Spike protein RBD-mFc for one hour at room temperature before they were added to the ELISA plates coated with ACE2-Fc. After one-hour incubation, the wells were washed with 0.05% PBST for five times and HRP conjugated streptavidin was added at a dilution of 1:3000, and incubated for another one hour before HRP activity was measured at 450 nm with addition of TMB substrate.

[00230] Cell lines and cell culture

[00231] The human embryonic kidney epithelial cell 293T (ATCC, CRL-3216) was cultured in Dulbecco's modified Eagle's medium (Hyclone, SH30022.01) supplemented with 10% heat-inactivated FBS (Gibco, 10270-106). A stable cell line expressing human ACE2, CHO-ACE2 (a kind gift from Professor Yee-Joo Tan, IMCB, A*Star) (Ng et al., 2014) was maintained in Dulbecco's modified Eagle's medium supplemented with 10% heat-inactivated FBS, 1% MEM Non-Essential Amino Acids Solution (Gibco, 11140-050) and 0.5 mg/ml of GeneticinTM Selective Antibiotic (Gibco, 10131-027). Every 2-3 days, cells were passaged by dissociating the cells with StemProTM AccutaseTM Cell Dissociation Reagent (Gibco, A1110501).

[00232] Conversion of IgG antibodies to Fab fragments

[00233] Digestion reaction for each IgG was prepared using immobilized FabALACTICA microspin columns (Genovis). 100 μL of IgG at 5 mg/mL concentration in digestion buffer (150 mM sodium phosphate, pH 7.0) were incubated overnight on each column. Digested sample was further purified using a HiTrap Protein L column followed by size-exclusion chromatography (Superdex 75 10/300 GL) using an Äkta Pure FPLC (all GE Healthcare).

[00234] Soluble SARS-CoV-2 Spike production

[00235] The expression plasmid containing the prefusion S ectodomain as used in Wrapp, et al. (Wrapp et al., 2020b) was kindly provided by Prof. Jason McLellan (University of Texas at Austin). This construct was used to transiently transfect high-density Chinese Hamster Ovary (ExpiCHO) cells with ExpiFectamine per the "Max Titer" protocol provided (Thermo Fisher). Six days post-transfection, 0.2 μm-filtered supernatant was collected and incubated with Ni-Sepharose Excel (Cytiva Life Sciences) for batch purification. Eluate was collected, concentrated in a 50 MWCO Amicon Ultra-15 centrifugal filter unit (MilliporeSigma), and injected onto a Superose6 10/300 GL column equilibrated in 10 mM HEPES, 200 mM NaCl, pH 8.0 to isolate trimeric, monodisperse material for Fab/IgG complexing.

[00236] Cryo-EM sample preparation and imaging

[00237] 2.5 μL of Spike-Fab complex at a concentration of 0.4 mg/mL was applied to a 300 mesh gold Quantifoil 1.2/1.3 holey carbon grid that was glow discharged for 30 sec at 15 mA immediately before sample application. Grids were blotted using Whatman #1 filter paper for 8 or 10 seconds at a blot force of 0 at 4°C and 100% humidity using a Mark IV Vitrobot (Thermo Fisher) and plunge frozen into liquid ethane. Samples were loaded onto a Titan Krios transmission electron microscope (Thermo Fisher) equipped with a Gatan K3 direct electron detector (Gatan) and a Quantum GIF energy filter (Gatan) operated with a 20 eV slit width during image acquisition. The K3 camera was operated in CDS mode using super resolution. A nominal magnification of 105,000x was used, for a pixel size of 0.835 Å (0.4175 Å super resolution pixel size) at the sample. A dose rate of 8 e-/(pix · sec), or 11.5 e-/(Å2 sec), and a frame rate of 0.05 sec/frame was used with a total exposure time of 5.9 sec, for a total dose of 67.7 e-/Å2. Automated data collection was performed using SerialEM (Mastronarde, 2005).

[00238] Image processing

[00239] Dose-weighted, motion-corrected sums down-sampled to the physical pixel size were obtained from the super-resolution DED movies using UCSF Motioncor2 (Zheng et al., 2017). For the Spike trimer, CTF estimation was performed in cryoSPARC (Punjani et al., 2017) followed by blob-based particle picking, 2D classification, ab initio modelling, 3D classification, and 3D refinement. For images of antibody complexes, particles were instead picked using templates generated from the apo trimer structure, and the apo trimer was likewise used as an initial model in 3D classification. The resolution of the

interface between the Spike RBD and the 5A6 Fab was further improved using naïve focused refinements. Processing details are given in Figure 17 and Figure 14.

[00240] Molecular modelling

[00241] For each Spike:Fab complex, a previously determined structure of the SARS-CoV-2 Spike protein, along with a full-length Fab homology model computed by MODELLER (Webb and Sali, 2016), were simultaneously docked into cryo-EM density using UCSF Chimera (Pettersen et al., 2004). Spike with one open RBD and one copy of ACE2 bound (PDB: 7a94) was used with 5A6, Spike with three open RBDs and three copies of ACE2 bound (PDB: 7a98) was used with 3D11, and Spike with two open RBDs and one copy of ACE2 bound (PDB: 7a95) was used with 2H4. Missing segments and side chains in the RBDs were built using Coot. Finally, real-space refinement in PHENIX (Liebschner et al., 2019), and density-restrained molecular dynamics simulations in ChimeraX (Goddard et al., 2018) and ISOLDE (Croll, 2018) were used to finalize the models. Models for the Spike:5A6 and Spike:3D11 complexes were first built into density maps from whole-particle cryo-EM reconstructions, and then further refined using maps from focused refinements of the Fab and Spike RBD. Maps of Spike:2H4 complexes were of lower resolution and model building was terminated after the docking step described above. Model statistics and density fit information are presented in Figure 19 and Figure 14.

[00242] Generation of pseudovirus particles

[00243] Pseudotyped viral particles expressing SARS-CoV-2 Spike protein were produced by transfecting of 30 million 293T cells with 12 µg pMDLg/pRRE (a gift from Didier Trono, Addgene #12251), 6 µg pRSV-Rev (a gift from Didier Trono, Addgene #12253), 24 µg pHIV-Luc-ZsGreen (a gift from Bryan Welm, Addgene #39196) and 12 µg pTT5LnX-CoV-SP (expressing SARS-CoV-2 Spike protein, Genbank: YP_009724390.1, a kind gift from DSO National Laboratories) using Lipofectamine 2000 transfection reagent (Invitrogen, 11668-019). The transfected cells were cultured at 37°C incubator for 3 days. Viral supernatant was harvested, centrifuged at 700 g for 10min to remove cell debris and filtered through a 0.45 µm filter unit (Sartorius, #16555). Lenti-X p24 rapid titer kit (Takara Bio, #632200) was used to quantify the viral titres following the manufacturer instructions. pTT5LnX-CoV-SP plasmid with D614G mutation was generated using QuickChange Lightning Multi Site-Directed Mutagenesis Kit (Agilent, #210513) and was

used to generate mutant pseudovirus expressing SARS-CoV-2 Spike protein carrying D614G mutation.

[00244] Purification of pseudovirus particles

[00245] To concentrate and purify the pseudovirus particles expressing the SARS-CoV-2 Spike glycoproteins, pre-cleared 40 mL viral supernatant was concentrated by 20% sucrose gradient centrifugation at 10,000 g for 4 hours at 4°C in an SW41 Ti rotor with no brake. Upon removal of supernatant, 1mL of PBS was added to the virus pellet and left at 4°C overnight. Concentrated virus was further purified by an OptiPrep (60% [wt/vol] iodixanol; #07820; STEMCELL Technologies Inc) velocity gradient. Iodixanol gradients were prepared in PBS in 1.2% increments ranging from 6 to 18%. Pseudoviruses were layered onto the top of the gradient and centrifuged for 1.5 hours at 200,000 g in an SW41 Ti rotor. Gradient fraction that contained pseudovirus pellet was collected.

[00246] Pseudovirus neutralization assay

[00247] CHO-ACE2 cells were seeded at a density of 3.2 x 104 cells in 100 μL of complete medium without Geneticin in 96-well Flat Clear Bottom Black Polystyrene TC-treated Microplates (Corning, #3904). Serially diluted IgG or Fab antibodies were incubated in a 96-well flat-bottom cell culture plate (Costar, #3596) with an equal volume of pseudovirus (12 ng of p24) at the final volume of 50μL at 37°C for one hour, and the mixture was added to the monolayer of pre-seeded CHO-ACE2 cells in triplicate. After one hour of pseudovirus infection at 37°C, 150μl of culture medium was added to each well and the cells were further incubated for another 48 hours. Upon removal of culture medium, cells were washed twice with sterile PBS, and then lysed in 20 μL of 1x Passive lysis buffer (Promega, E1941) with gentle shaking at 37°C for 30 minutes. Luciferase activity was then assessed using a Luciferase Assay System (Promega, E1510) on a Promega GloMax Luminometer. The relative luciferase units (RLU) were converted to percent neutralization and plotted with a non-linear regression curve fit using PRISM.

[00248] Live virus neutralization assay in Vero E6 cells

[00249] The potency of the IgG or Fab antibodies were determined in neutralizing live SARS-CoV-2 virus assays. In brief, 25 μl of 100 TCID50 of SARS-CoV-2 live virus (hCoV-19/Singapore/3/2020) isolated from a nasopharyngeal swab of a patient in Singapore (Young et al., 2020), was mixed with an equal volume of serially diluted IgG or Fab antibodies and incubated at 37°C for one hour before the mixture was added to 50 μl of Vero

E6 C1008 cells in suspension. The infected cells were incubated at 37°C incubator for four days and the cell viability was determined using Viral ToxGloTM Assay (Promega, #G8941). The potency of 2H4, 3D11 and 5A6 IgG antibodies in neutralizing live SARS-CoV-2 virus assays was also determined by measuring the viral genome copy number (GCN). 25 µl of 100 TCID50 of SARS-CoV-2 live virus (hCoV-19/Singapore/3/2020) was mixed with an equal volume of serially diluted 2H4, 3D11 or 5A6 IgG antibodies and incubated at 37°C for one hour before the mixture was added to 50 µl of 4x105 Vero E6 C1008 cells in suspension. The infected cells were incubated at 37°C incubator for 48 hrs after which supernatant was harvested and viral GCN was determined by subsequent RT-qPCR targeting the E gene using the RESOLUTE 2.0 kit as per manufacturer's instructions. Briefly, 2.5 µl of supernatant was diluted with 2.5 µl of Milli-Q water and added to 20 µl of RT-PCR master mix. PCR was carried out as follows: reverse transcription at 55°C for 15min, inactivation at 95°C for 4min, followed by 45 cycles of amplification consisting of denaturation at 95°C for 3s and annealing/extension at 62°C for 30s and GCN values determined by comparing Ct values against a logGCN standard curve.

[00250] Live virus neutralization assay in HAE

[00251] MucilAirTM HAE (human airway epithelia) reconstituted from human primary cells obtained from nasal or bronchial biopsies were provided by Epithelix SARL (Geneva, Switzerland) and maintained in air-liquid interphase with specific culture medium in Costar Transwell inserts (Corning, NY, USA) according to the manufacturer's instructions. The potency of 5A6 IgG was tested in neutralizing a live virus strain (BetaCoV/France/IDF0571/2020) isolated from one of the first COVID-19 cases confirmed in France: a 47-year old female patient hospitalized in January 2020 in the Department of Infectious and Tropical Diseases, Bichat Claude Bernard Hospital, Paris (Lescure et al., 2020). The complete viral genome sequence was obtained using Illumina MiSeq sequencing technology, was then deposited after assembly on the GISAID EpiCoV platform (Accession ID EPI_ISL_411218) under the name BetaCoV/France/IDF0571/2020. Briefly, the apical poles of HAE were gently washed twice with warm Opti-MEM medium (Gibco, Thermo Fisher Scientific) and then infected directly with a 150 µl dilution of live SARS-CoV-2 virus (strain: BetaCoV/France/IDF0571/2020) in Opti-MEM medium, at a multiplicity of infection (MOI) of 0.1. Viral suspensions were pre-incubated 60 min with antibody 5A6 IgG (75 ng/ml or 150 ng/ml) or an anti-Ebola glycoprotein control antibody (150 ng/ml) before infection. A

control infection was performed in absence of antibody. For mock infection, the same procedure was followed using Opti-MEM as inoculum. Viral replication was quantified as the measured copy number of the viral genomes inside, and at the apical poles of, nasal and bronchial HAE. Samples collected from apical washes at 48 hours post-infection were separated into 2 tubes: one for TCID50 viral titration (stored at - 80°C) and one for RT-qPCR. HAE cells were harvested in RLT buffer (Qiagen) and total RNA was extracted using the RNeasy Mini Kit (Qiagen) for subsequent RT-qPCR. Variations in trans epithelial electrical resistance (Δ TEER) were measured using a dedicated volt-ohm meter (EVOM2, Epithelial Volt/Ohm Meter for TEER) and expressed as Ohm/cm2.

[00252] Cell-cell fusion assay

[00253] Vero E6 cells were transfected with S protein bearing furin recognition mutation (R682RAR to A682AAR) with C-terminal GFP tag by Lipofectamin 2000 (Invitrogen) and were cultured on μ-Slide 8 well chamber slides (Ibidi). The transfection efficiency was monitored by percentage of GFP positive cells and optimized within 15-30% to achieve the best signal-to-noise ratio in the following cell-cell fusion assay. After 48 hours, cells were treated with various antibodies diluted in DMEM without FBS for 1 hour at 37°C. Cells were then treated with 15 μg/ml trypsin and incubated at 37°C for another 2 hours. After trypsin treatment, cells were fixed with 4% PFA at room temperature for 15 mins and the cell nuclei were stained with DAPI. Images were taken by Olympus confocal microscope.

[00254] Fab affinity measurement by BLI

[00255] Binding affinity of purified Fab to RBD was measured on the Octet96Red system (ForteBio). Anti-human IgG Fc (AHC) sensors were first loaded with 1 μg/ml system (ForteBio). Anti-human IgG Fc (AHC) sensors were first loaded with 1 μg/ml supplemented with 0.1% Tween-20 and 0.1% BSA) for 5 min to establish a stable baseline. The sensors were then dipped into different concentrations of each Fab from 100 nM to 3.125 nM in two-fold dilutions for 6 min, and then in kinetics buffer again for 10 min to measure association and dissociation. Assays were run at 25°C and data was analysed on the Octet System Data Acquisition Software version 9.0.0.4. using the 1:1 Langmuir binding model.

[00256] Avidity binding by BLI

[00257] Avidity of anti-SARS-CoV-2 Spike RBD IgG antibodies for RBD was measured on the Octet96Red system. Anti-hIgG Fc capture (AHC) sensors were used. The sensors were loaded with 1 μg/ml of Fc-RBD (made in-house) in assay buffer (phosphate-buffered

saline buffer supplemented with 0.1% Tween-20 and 0.1% BSA) for 10 min, quenched in 0.5 mg/ml of isotype IgG in assay buffer for 10 min, then dipped in assay buffer for 12 min for the system to stabilize. To measure the association of 5A6, the sensors were dipped in a range of 5A6 IgG concentrations (25-0.39 nM in 2-fold serial dilutions) in assay buffer for 6 min. To measure dissociation, the sensors were dipped in assay buffer for 10 min. The experiment was conducted at 25°C. Data analysis was done in the Octet System Data Acquisition Software version 9.0.0.4. using the 1:2 bivalent model.

[00258] Epitope binning by BLI

[00259] Epitope binning was done using a classical sandwich assay. The AR2G sensor tips (ForteBio) were activated in freshly prepared 20mM EDC (1-ethyl-3-[3-dimethylaminopropyl]-carbodiimide hydrochloride), 10mM NHS (N-hydroxysuccinimide) solution and the 5A6 antibody was immobilized to the sensor tips using a concentration of 7.5 µg/ml of 5A6 in 10 mM sodium acetate pH 6 buffer. After quenching in 1M ethanolamine, the 5A6-immobilized sensor tips were dipped in 5 µg/ml of tagless RBD for 600s, then in 10µg/ml of the second antibody for 300s. The assay was run at 25°C. Sensor tips were regenerated in 10 mM glycine at pH 2.7 and neutralized in PBS with 0.1% Tween-20 before another cycle of sandwich assay was performed. Each sensor tip was used in a total of 3 cycles. Data analysis was done in the Octet System Data Acquisition Software version 9.0.0.4.

[00260] IgG and Fab affinity for Spike trimer by SPR

[00261] StreptagII-tagged prefusion S ectodomain, diluted to 10 µg/mL in 10 mM HEPES, 150 mM NaCl, 3 mM EDTA, 0.05% PS-20, pH 7.4, was captured on a StreptactinXT-immobilized (Iba Life Sciences) CM5 Series S sensor chip at an average level of 224 or 347 RU (response units) for IgG and Fab kinetics measurements, respectively using a Biacore T200 (Cytiva Life Sciences). 2-fold serial dilutions of purified IgG from 12.5 nM to 0.39 nM or Fab from 100 nM to 3.125 nM were flowed over the captured prefusion S ectodomain at 30 µL/minute for 90 seconds followed by 420 seconds of dissociation flow. Following each cycle, the chip surface was regenerated with 3 M guanidine hydrochloride. The resulting reference flow cell and blank-injection subtracted sensorgrams were fit to a 1:1 Langmuir binding model using the Biacore T200 Evaluation Software (Cytiva Life Sciences).

[00262] Statistical analysis.

[00263] Data were analysed using GraphPad Prism version 7.03. Statistical tests are indicated in the figure legends. EC50 values were calculated by non-linear regression analysis on the binding curves using GraphPad Prism and IC50 values were calculated either using the [Inhibitor] vs response variable slope four parameter non-linear regression model of GraphPad Prism, or the four parameter logistic regression model in the Quest Graph™ IC50 Calculator from AAT Bioquest, Inc (https://www.aatbio.com/tools/ic50-calculator). One-way analysis of variance (ANOVA) was used to compare differences between groups. Differences were considered statistically significant at confidence levels $*P < 0.05$ or $**P < 0.01$, $***P < 0.001$.

[00264] The examples set forth above are provided to give those of ordinary skill in the art a complete disclosure and description of how to make and use the embodiments of the compositions, systems and methods of the invention, and are not intended to limit the scope of what the inventors regard as their invention. Modifications of the above-described modes for carrying out the invention that are obvious to persons of skill in the art are intended to be within the scope of the following claims. All patents and publications mentioned in the specification are indicative of the levels of skill of those skilled in the art to which the invention pertains. All references cited in this disclosure are incorporated by reference to the same extent as if each reference had been incorporated by reference in its entirety individually.

[00265] All headings and section designations are used for clarity and reference purposes only and are not to be considered limiting in any way. For example, those of skill in the art will appreciate the usefulness of combining various aspects from different headings and sections as appropriate according to the spirit and scope of the invention described herein.

[00266] All references cited herein are hereby incorporated by reference herein in their entireties and for all purposes to the same extent as if each individual publication or patent or patent application was specifically and individually indicated to be incorporated by reference in its entirety for all purposes.

[00267] Many modifications and variations of this application can be made without departing from its spirit and scope, as will be apparent to those skilled in the art. The specific embodiments and examples described herein are offered by way of example only, and the application is to be limited only by the terms of the appended claims, along with the full scope of equivalents to which the claims are entitled.

WHAT IS CLAIMED IS:

1. A method of preventing formation of syncytia comprising a fusion between a SARS-CoV-2 infected cell displaying a SARS-CoV-2 Spike protein on its surface, and a second cell displaying an ACE-2 receptor on its surface, the syncytia formation mediated by the SARS-CoV-2 Spike protein binding to the ACE-2 receptor, the method comprising contacting a cell infected with SARS-CoV-2, or at risk of being infected with SARS-CoV-2 with an isolated anti-SARS-CoV-2-Spike antibody or an antigen binding fragment thereof specifically binding to the Spike protein, trapping the Spike protein in a pre-fusion state, thereby preventing the formation of the syncytia.

2. The method according to claim 1, wherein the isolated anti-SARS-CoV-2-Spike antibody or antigen binding fragment is an IgG, IgM, IgA, Fab, single domain antibody.

3. The method according to claim 1, wherein the isolated anti-SARS-CoV-2-Spike antibody or antigen binding fragment binds to a quaternary epitope of the Spike protein.

4. The method according to claim 3, wherein the isolated anti-SARS-CoV-2-Spike antibody binds to the quaternary epitope through residues in the CDR.

5. The method according to any preceding claim, wherein the isolated anti-SARS-CoV-2-Spike antibody or antigen binding fragment comprises a heavy chain variable domain sequence that is at least 90% identical to SEQ ID NO. 7.

6. The method according to any preceding claim, wherein the isolated anti-SARS-CoV-2-Spike antibody or antigen binding fragment comprises a light chain variable domain sequence that is at least 90% identical to SEQ ID NO. 8.

7. The method according to any preceding claim, wherein the isolated anti-SARS-CoV-2-Spike antibody or antigen binding fragment comprises a heavy chain variable region comprising complementarity determining regions (CDRs), wherein:

a. the heavy chain CDR1 is SEQ ID NO. 1;

b. the heavy chain CDR2 is SEQ ID NO. 2; and

c. the heavy chain CDR3 is SEQ ID NO. 3;

and a light chain variable region comprising CDRs, wherein:

d. the light chain CDR1 is SEQ ID NO. 4;

e. the light chain CDR2 is SEQ ID NO. 5; and

f. the light chain CDR3 is SEQ ID NO. 6.

8. The method according to claim 5, wherein heavy chain variable region, SEQ ID NO. 7, comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 mutations at E38, S57, Y58, D59, G62, S63, N64, and/or R106.

9. The method according to claim 8, wherein the mutation at position D59 is selected from D59G, D59L, D59K, D59I, D59M, D59W, D59T, D59F, or D59Y.

10. The method according to claim 8, wherein the mutation at position N64 is selected from N64R or N64I.

11. The method according to claim 8, wherein the mutation at position R106 is selected from R106E, R106D, R106N, R106Q, R106A, R106V, or R106L.

12. The method according to claim 6, wherein the light chain variable region, SEQ ID NO. 8, comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 mutations at S69, L114, and/or R116.

13. The method according to any preceding claim, wherein the isolated anti-SARS-CoV-2-Spike antibody is a human antibody.

14. The method according to any preceding claim, wherein the isolated anti-SARS-CoV-2-Spike antibody is a humanized antibody.

15. The method according to any preceding claim, wherein the isolated anti-SARS-CoV-2-Spike antibody is a monoclonal antibody.

16. A method of treating a SARS-CoV-2 infection in a subject in need of such treatment, the method comprising administering to the subject an antibody according to any previous claim.

17. The method according to claim 16, wherein the isolated anti-SARS-CoV-2-Spike antibody is in a pharmaceutical formulation comprising a pharmaceutically acceptable carrier.

18. An isolated antibody, wherein the isolated antibody or antigen binding fragment comprises a heavy chain variable domain sequence that is at least 90% identical to SEQ ID NO. 7.

19. The isolated anti-SARS-CoV-2-Spike antibody according to claim 18, wherein the isolated antibody or antigen binding fragment comprises a light chain variable domain sequence that is at least 90% identical to SEQ ID NO. 8.

20. The isolated antibody according to any preceding claim, wherein the isolated anti-SARS-CoV-2-Spike antibody or antigen binding fragment comprises a heavy chain variable region comprising complementarity determining regions (CDRs), wherein:

a. the heavy chain CDR1 is SEQ ID NO. 1; binds through T29, S36, Y37, E38)

b. the heavy chain CDR2 is SEQ ID NO 2 (ISYDGSNK); binds through V55, I56, S57, Y58, D59, N64, Y66; and

c. the heavy chain CDR3 is SEQ ID NO. 3 (ARLITMVRGEDY; binds through R106, L107, T109, M110, V112, R113, G114, E115),

and a light chain variable region comprising CDRs, wherein:

d. the light chain CDR1 is SEQ ID NO. 4 (QSISSY; binds through S36, Y38)

e. the light chain CDR2 is SEQ ID NO. 5 (AAS; binds through S69, G70); and

f. the light chain CDR3 is SEQ ID NO. 6 (QQSYNLPRT; binds through S107, Y108, N109, L114, R116)

21. The isolated anti-SARS-CoV-2-Spike antibody according any previous claim, wherein heavy chain variable region, SEQ ID NO. 7, comprises at least one mutation at E38, S57, Y58, D59, G62, S63, N64, and/or R106.

22. The isolated anti-SARS-CoV-2-Spike antibody according to claim 21, wherein the mutation at position D59 is selected from D59G, D59L, D59K, D59I, D59M, D59W, D59T, D59F, or D59Y.

23. The isolated anti-SARS-CoV-2-Spike antibody according to claim 21, wherein the mutation at position N64 is selected from N64R or N64I.

24. The isolated antibody according to claim 21, wherein the mutation at position R106 is selected from R106E, R106D, R106N, R106Q, R106A, R106V, or R106L.

25. The isolated anti-SARS-CoV-2-Spike antibody according to any previous claim, wherein light chain variable region, SEQ ID NO. 8, comprises a mutation at S69, L114 and/or R116,

26. The isolated anti-SARS-CoV-2-Spike antibody according to any preceding claim, wherein the isolated antibody is a human antibody.

27. The isolated anti-SARS-CoV-2-Spike antibody according to any preceding claim, wherein the isolated antibody is a humanized antibody.

28. The isolated anti-SARS-CoV-2-Spike antibody according to any preceding claim, wherein the isolated antibody is a monoclonal antibody.

29. An isolated polynucleotide composition comprising a first nucleic acid encoding the VH region of any of claim 20-28, and a second nucleic acid encoding the VL region of any preceding claim.

30. A plasmid comprising at least one polynucleotide sequence of claim 29.

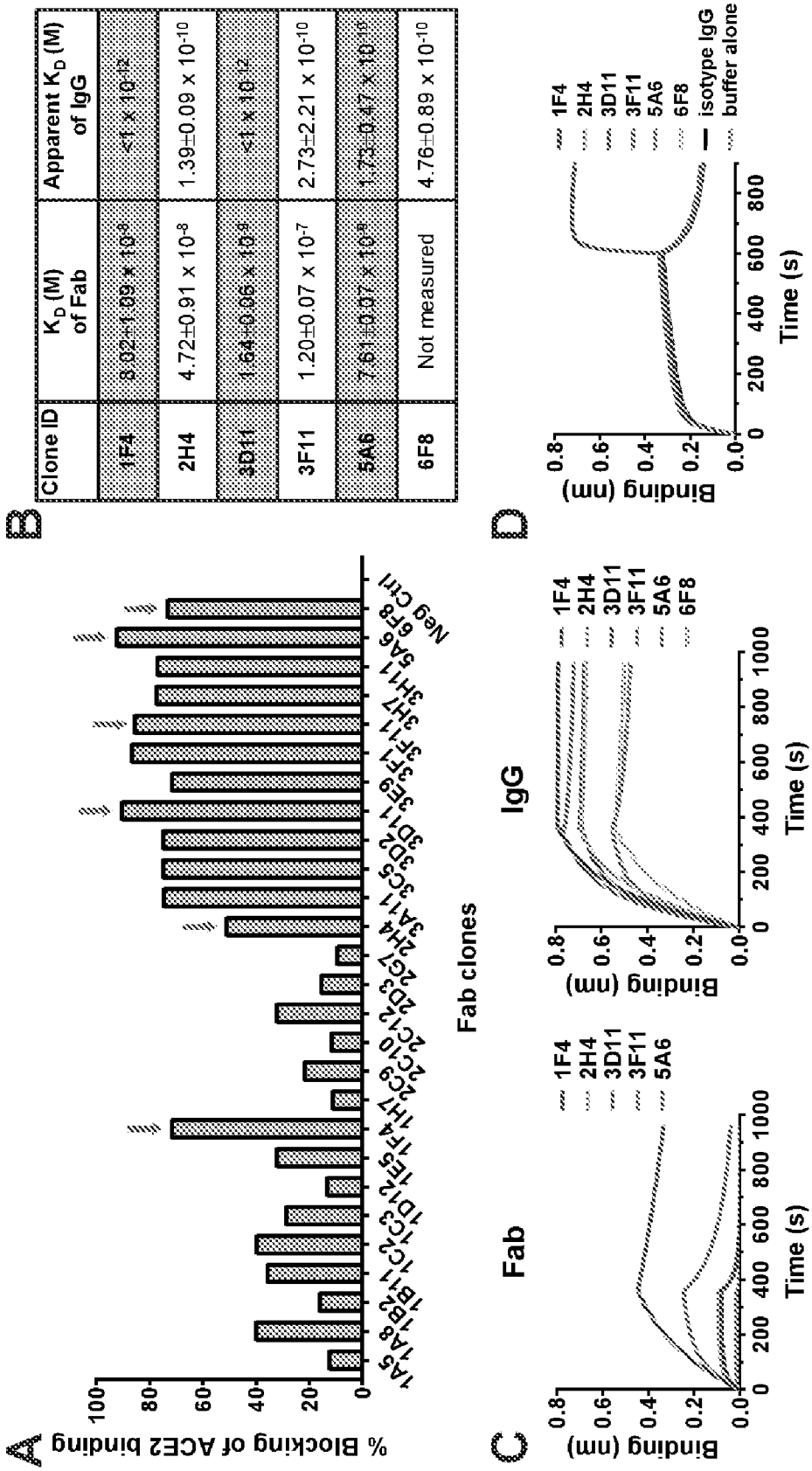
31. A host cell comprising a polynucleotide sequence of claim 30.

32. A method of producing an antibody comprising culturing the host cell of claim 31 under conditions that promote the production of the antibody.

33. A pharmaceutical composition comprising as an active ingredient, at least one isolated antibody or antigen binding fragment thereof of any preceding claim and a pharmaceutically acceptable carrier.

34. The pharmaceutical composition of claim 33 for use in preventing or retarding formation of SARs-CoV-2 mediated syncytia formation by binding to RBD and stabilizing a SARs-CoV-2 Spike protein conformation retarding or preventing S1 shedding and trapping a pre-fusion state of the SARs-CoV-2.

FIGURE 1



Clone ID	K_D (M) of Fab	Apparent K_D (M) of IgG
1F4	8.02±1.09 x 10^{-8}	<1 x 10^{-12}
2H4	4.72±0.91 x 10^{-8}	1.39±0.09 x 10^{-10}
3D11	1.64±0.06 x 10^{-8}	<1 x 10^{-12}
3F11	1.20±0.07 x 10^{-7}	2.73±2.21 x 10^{-10}
5A6	7.61±0.07 x 10^{-8}	1.73±0.47 x 10^{-10}
6F8	Not measured	4.76±0.89 x 10^{-10}

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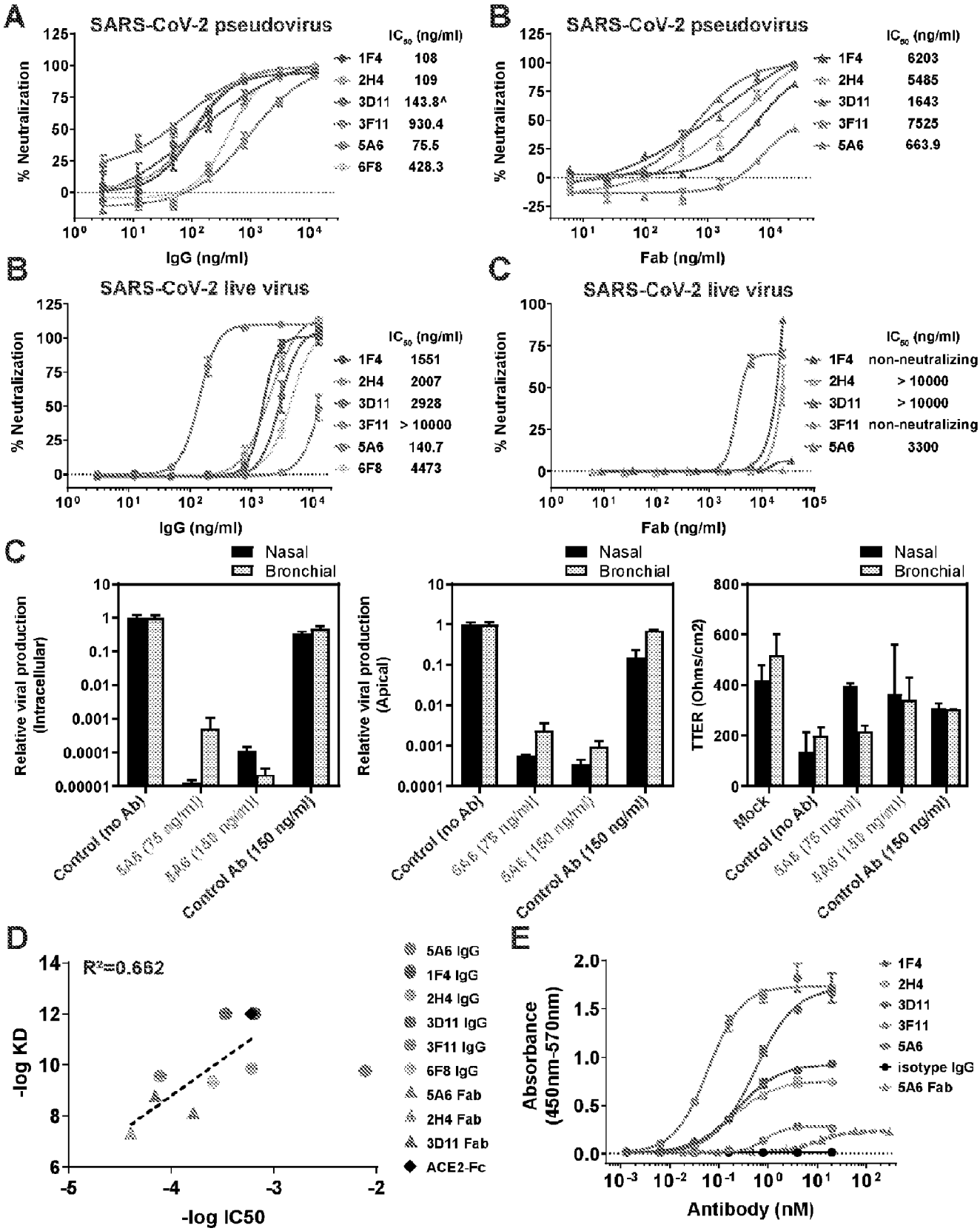

A
SARS-CoV-2 pseudovirus
% Neutralization
IgG (ng/ml)
IC50 (ng/ml)
1F4 108
2H4 109
3D11 143.8^
3F11 930.4
5A6 75.5
6F8 428.3
B
SARS-CoV-2 pseudovirus
% Neutralization
Fab (ng/ml)
IC50 (ng/ml)
1F4 6203
2H4 5485
3D11 1643
3F11 7525
5A6 663.9
B
SARS-CoV-2 live virus
% Neutralization
IgG (ng/ml)
IC50 (ng/ml)
1F4 1551
2H4 2007
3D11 2928
3F11 > 10000
5A6 140.7
6F8 4473
C
SARS-CoV-2 live virus
% Neutralization
Fab (ng/ml)
IC50 (ng/ml)
1F4 non-neutralizing
2H4 > 10000
3D11 > 10000
3F11 non-neutralizing
5A6 3300
C
Nasal
Bronchial
Relative viral production (Intracellular)
Control (no Ab)
5A6 (75 ng/ml)
5A6 (150 ng/ml)
Control Ab (150 ng/ml)
Relative viral production (Apical)
TTER (Ohms/cm2)
Mock
D
R²=0.662
-log KD
-log IC50
5A6 IgG
1F4 IgG
2H4 IgG
3D11 IgG
3F11 IgG
6F8 IgG
5A6 Fab
2H4 Fab
3D11 Fab
ACE2-Fc
E
Absorbance (450nm-570nm)
Antibody (nM)
1F4
2H4
3D11
3F11
5A6
isotype IgG
5A6 Fab

FIGURE 2

FIGURE 3

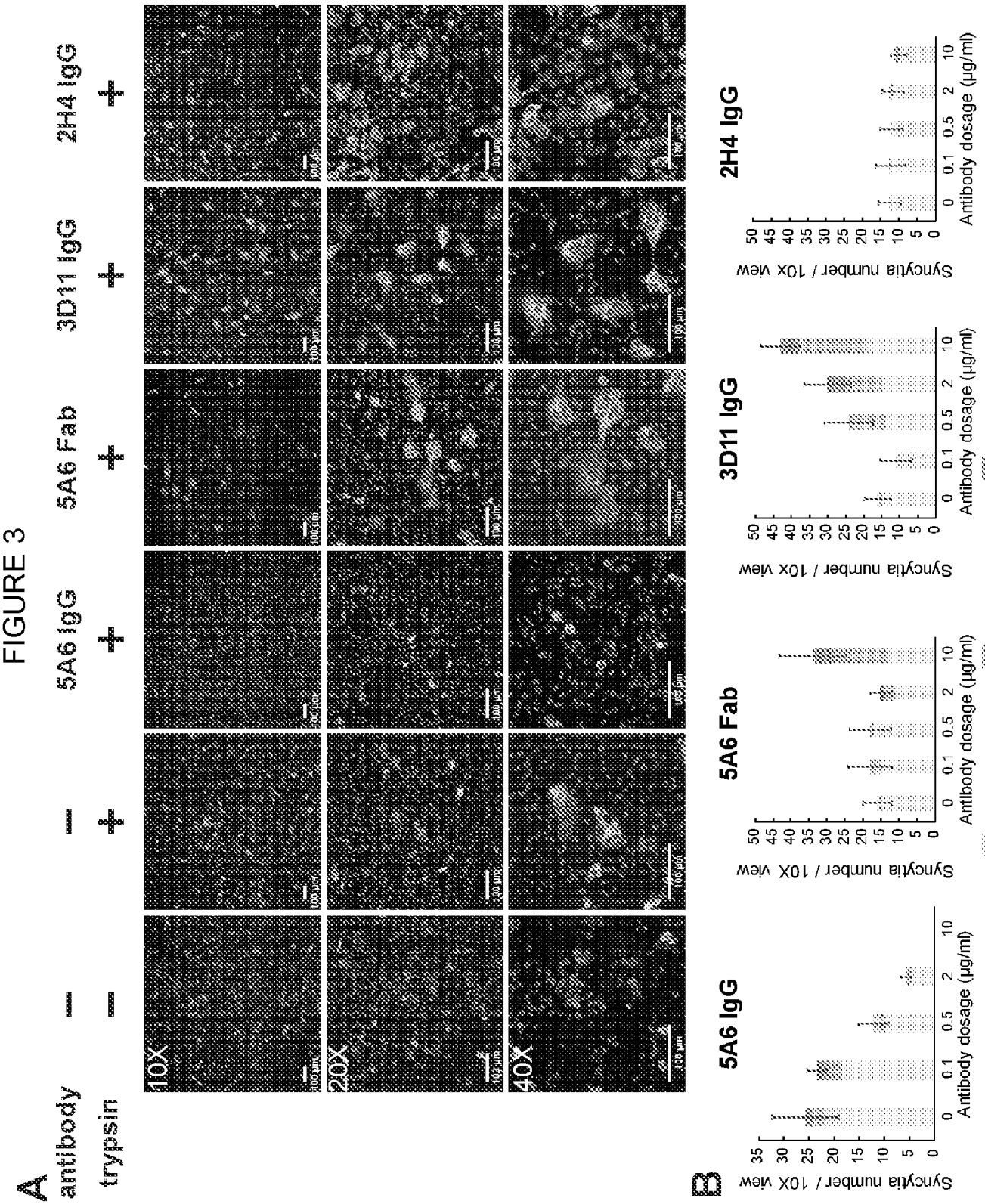

A
antibody
trypsin
5A6 IgG
5A6 Fab
3D11 IgG
2H4 IgG
10X
20X
40X
B
5A6 IgG
5A6 Fab
3D11 IgG
2H4 IgG
Syncytia number / 10X view
Antibody dosage (μg/ml)
3-4 nuclei
5-7 nuclei
8-10 nuclei

FIGURE 4

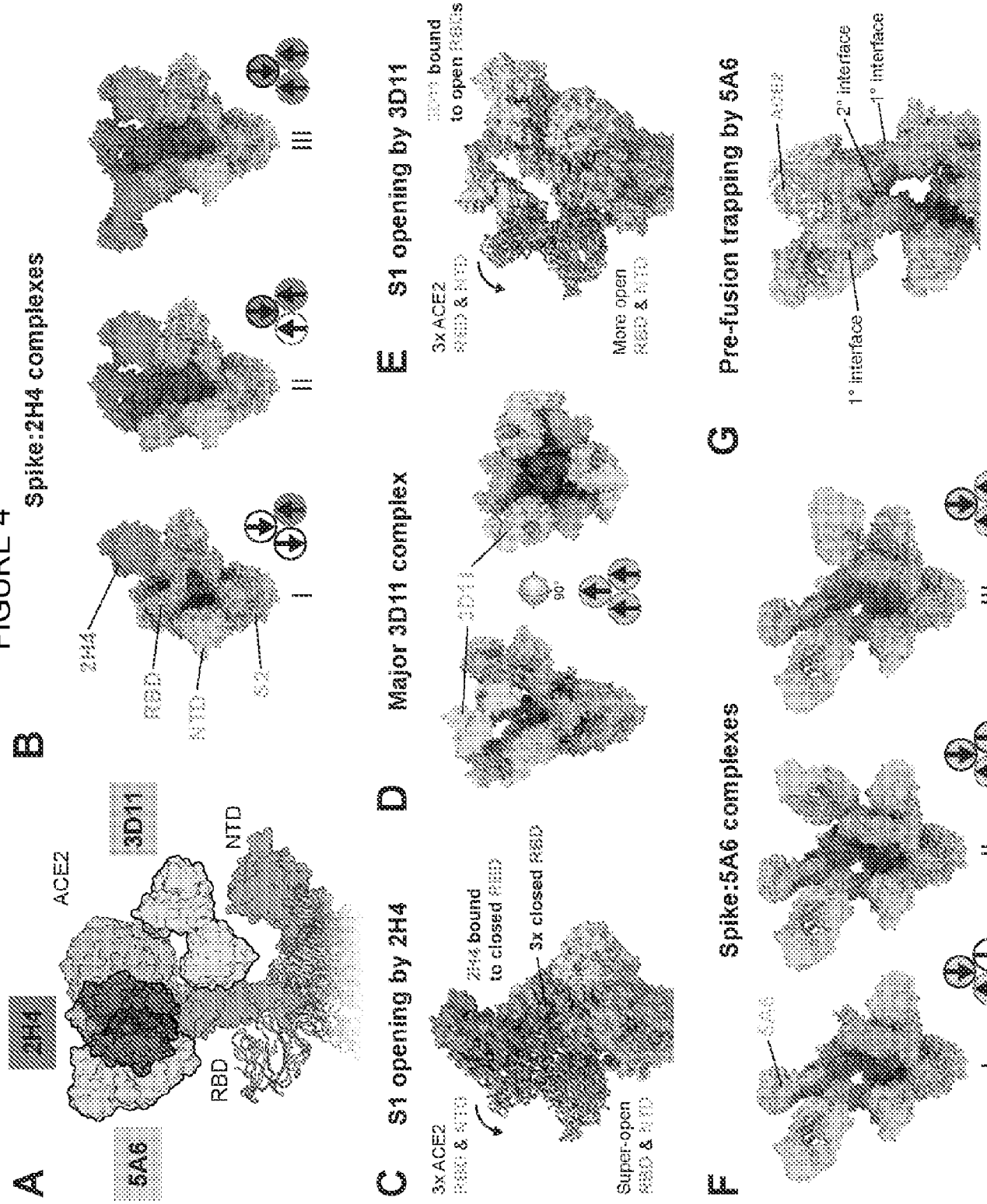

A
2H4
3D11
ACE2
5A6
RBD
NTD
B
Spike:2H4 complexes
2H4
RBD
S1 NTD
S2
I
II
III
C
S1 opening by 2H4
3x ACE2
RBD & NTD
2H4 bound
to closed RBD
3x closed RBD
Super-open
RBD & NTD
D
Major 3D11 complex
3D11
90°
E
S1 opening by 3D11
3x ACE2
RBD & NTD
3D11 bound
to open RBDs
More open
RBD & NTD
F
Spike:5A6 complexes
5A6
I
II
III
G
Pre-fusion trapping by 5A6
NTD
2° interface
1° interface
1° interface

FIGURE 5

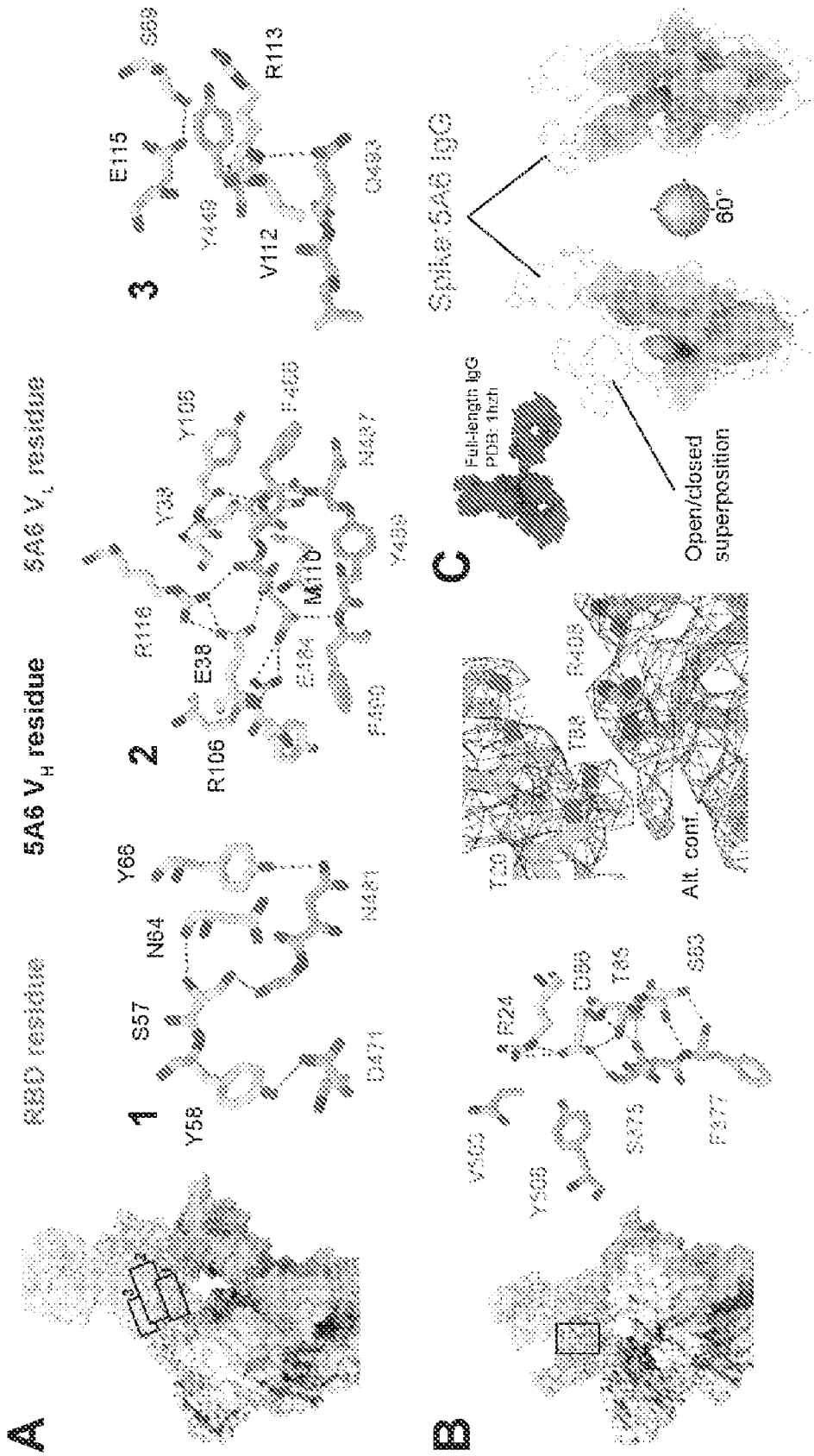

A
RBD residue
5A6 V_H residue
5A6 V_L residue
1
2
3
S57
N64
Y66
Y58
D471
N481
R106
E38
R116
Y33
Y105
E384
M110
R408
N437
Y489
E115
S69
Y449
R113
V112
Q493
B
Y505
R24
D33
T85
S53
S375
F377
T28
R408
Alt. conf.
C
Full-length IgG
PDB: 1hzh
Spike:5A6 IgG
Open/closed
superposition
60°

FIGURE 6

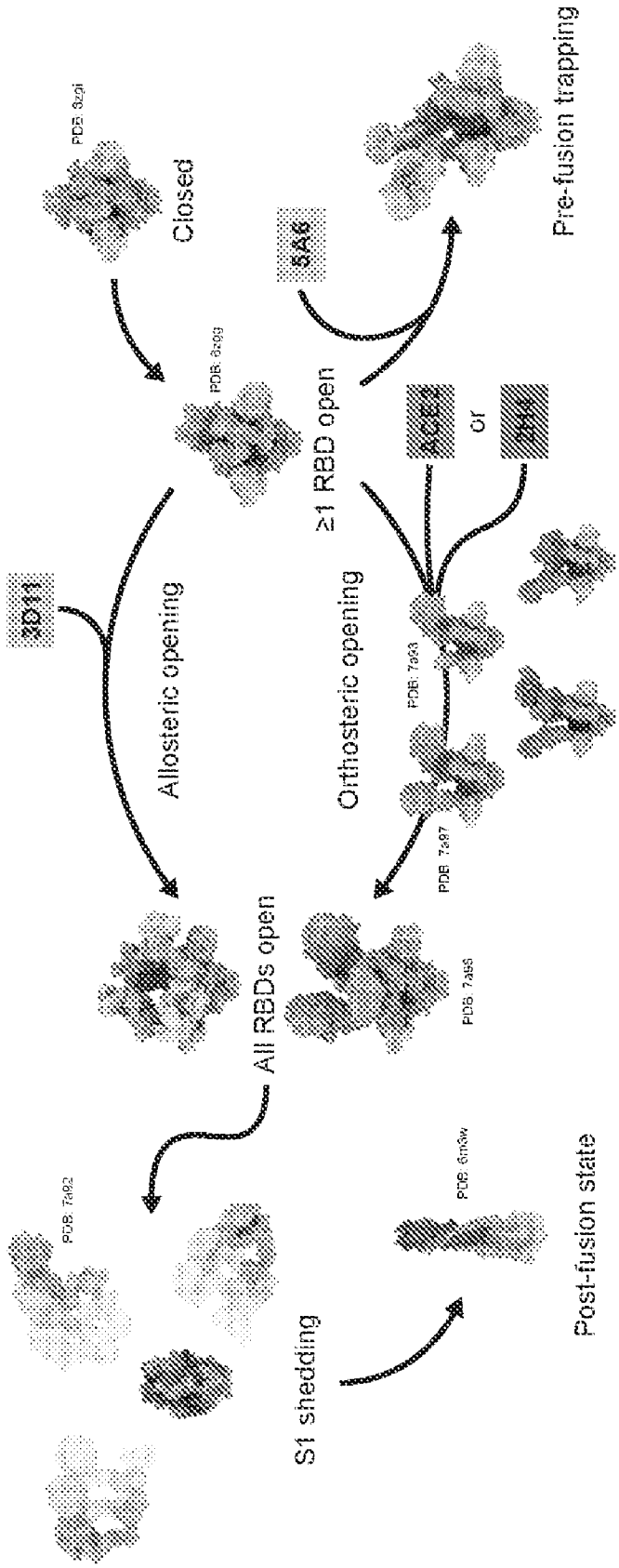

PDB 6zgi
Closed
PDB 6vsb
2D11
Allosteric opening
All RBDs open
PDB 7a92
S1 shedding
PDB 6m0w
Post-fusion state
≥1 RBD open
S2A6
Pre-fusion trapping
ACE2
or
PDB 7a93
PDB 7a97
PDB 7a98
Orthosteric opening

Figure 7

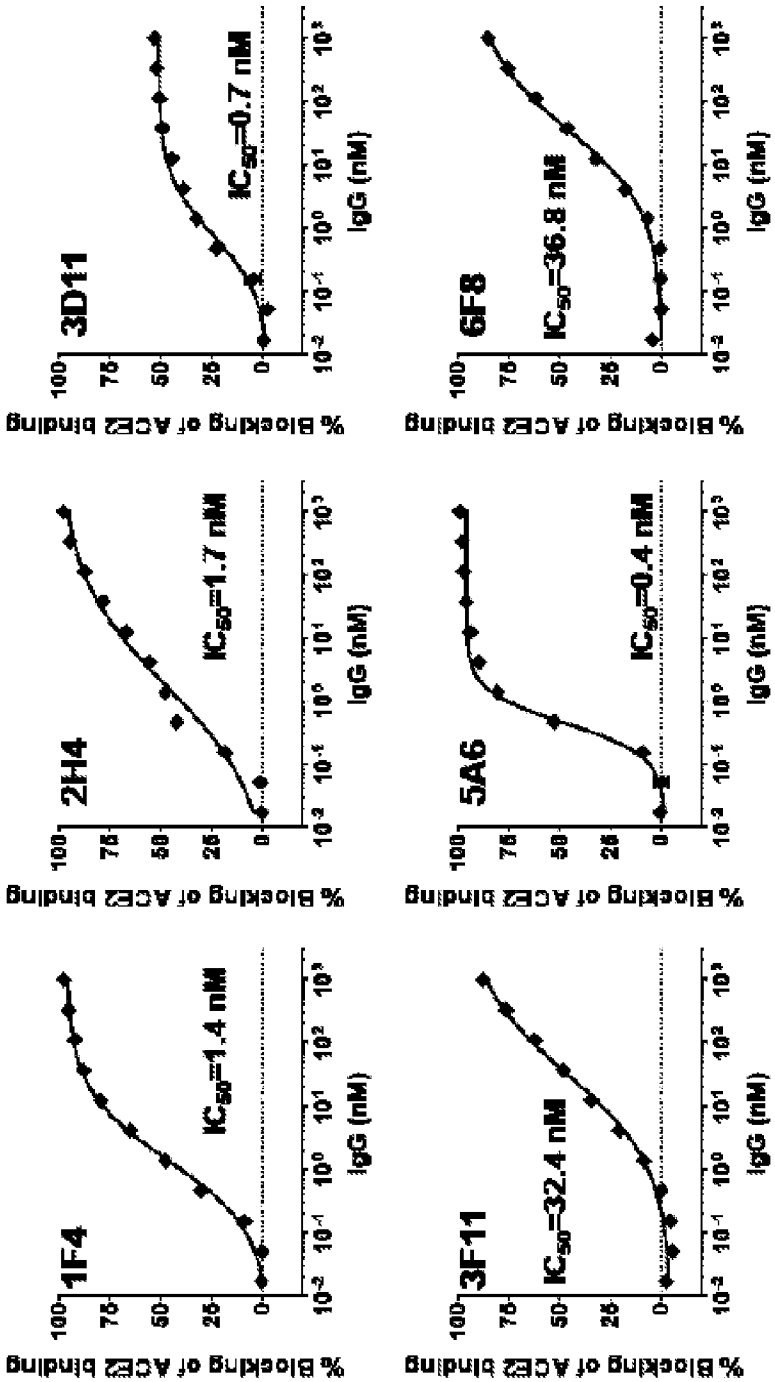

3D11
IC50=0.7 nM
6F8
IC50=36.8 nM
2H4
IC50=1.7 nM
5A6
IC50=0.4 nM
1F4
IC50=1.4 nM
3F11
IC50=32.4 nM
% Blocking of ACE2 binding
IgG (nM)

Figure 8

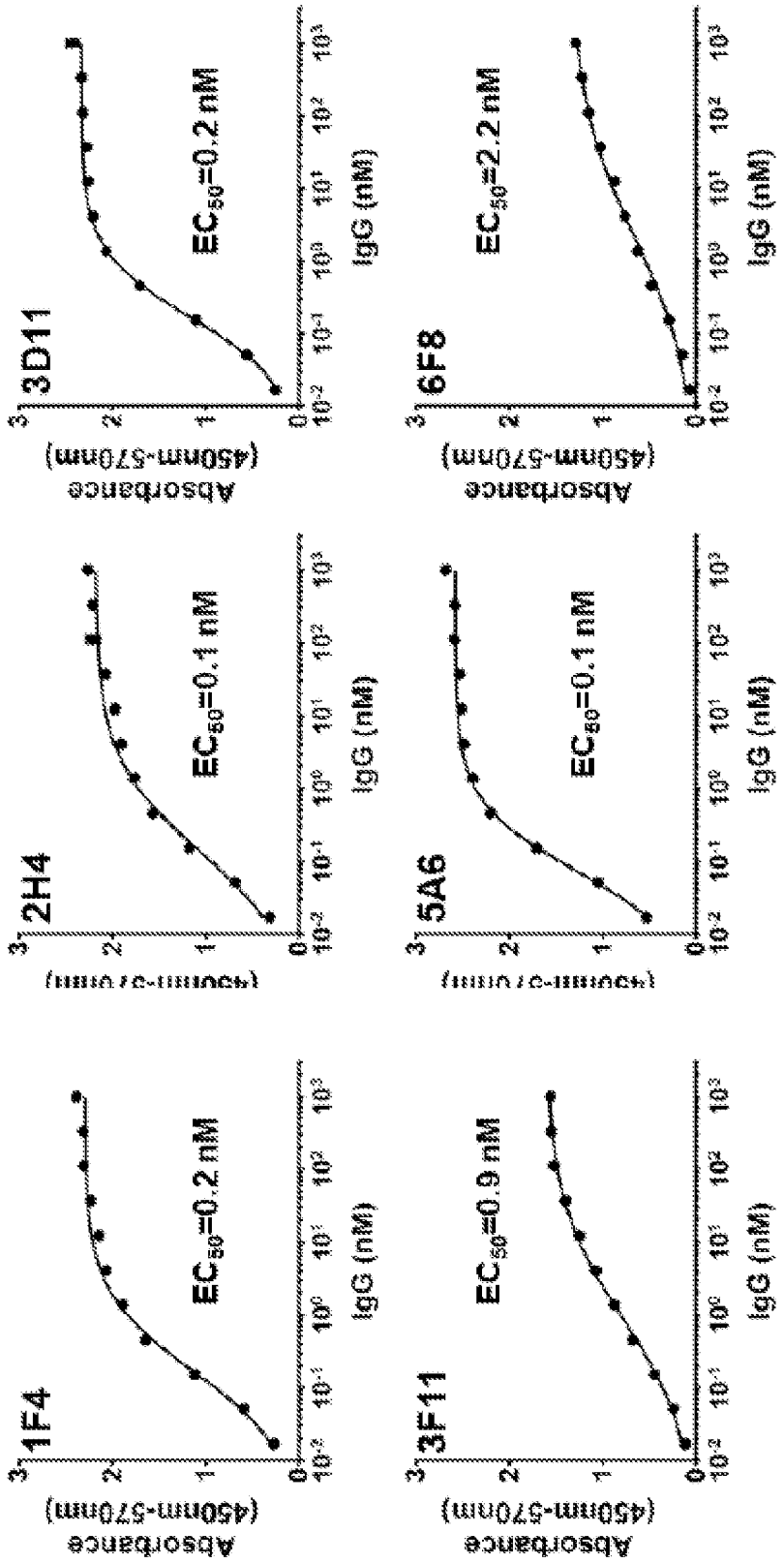

1F4
EC50=0.2 nM
2H4
EC50=0.1 nM
3D11
EC50=0.2 nM
3F11
EC50=0.9 nM
5A6
EC50=0.1 nM
6F8
EC50=2.2 nM
Absorbance (450nm-570nm)
IgG (nM)

Figure 9

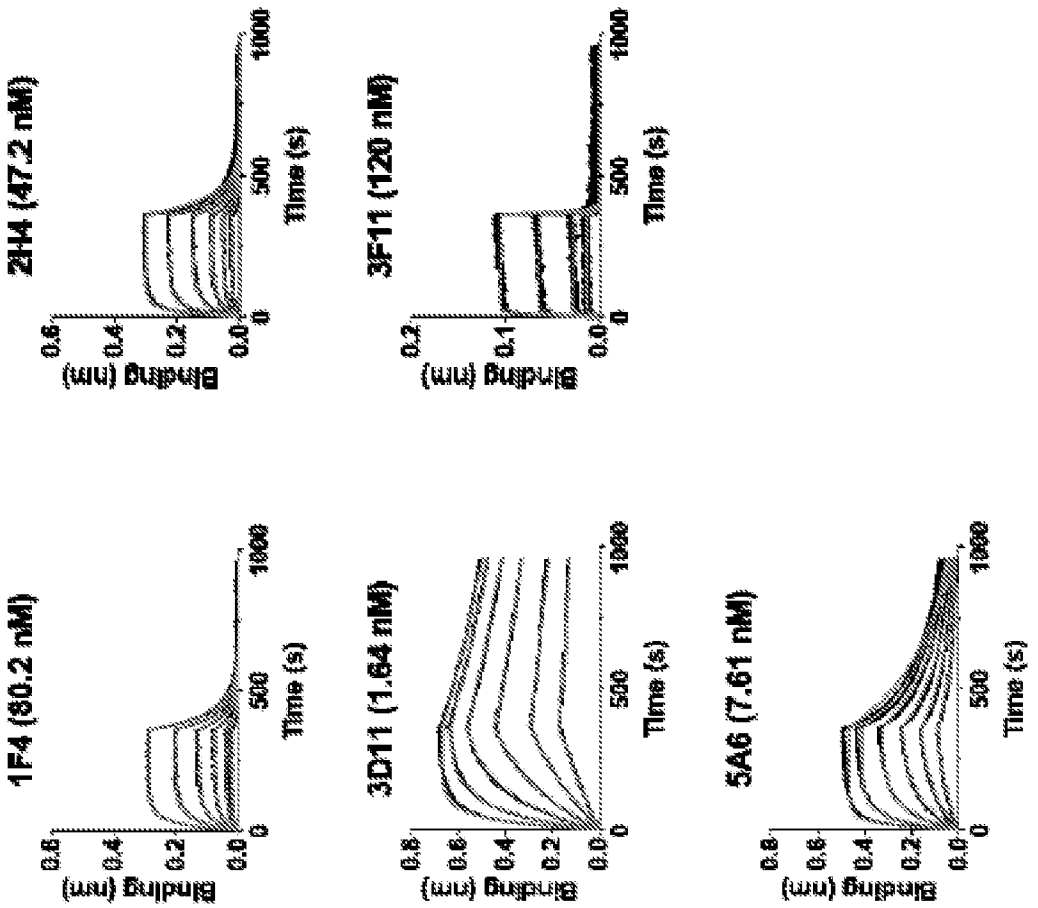

2H4 (47.2 nM)
3F11 (120 nM)
1F4 (80.2 nM)
3D11 (1.64 nM)
5A6 (7.61 nM)
Binding (nm)
Time (s)

Figure 10

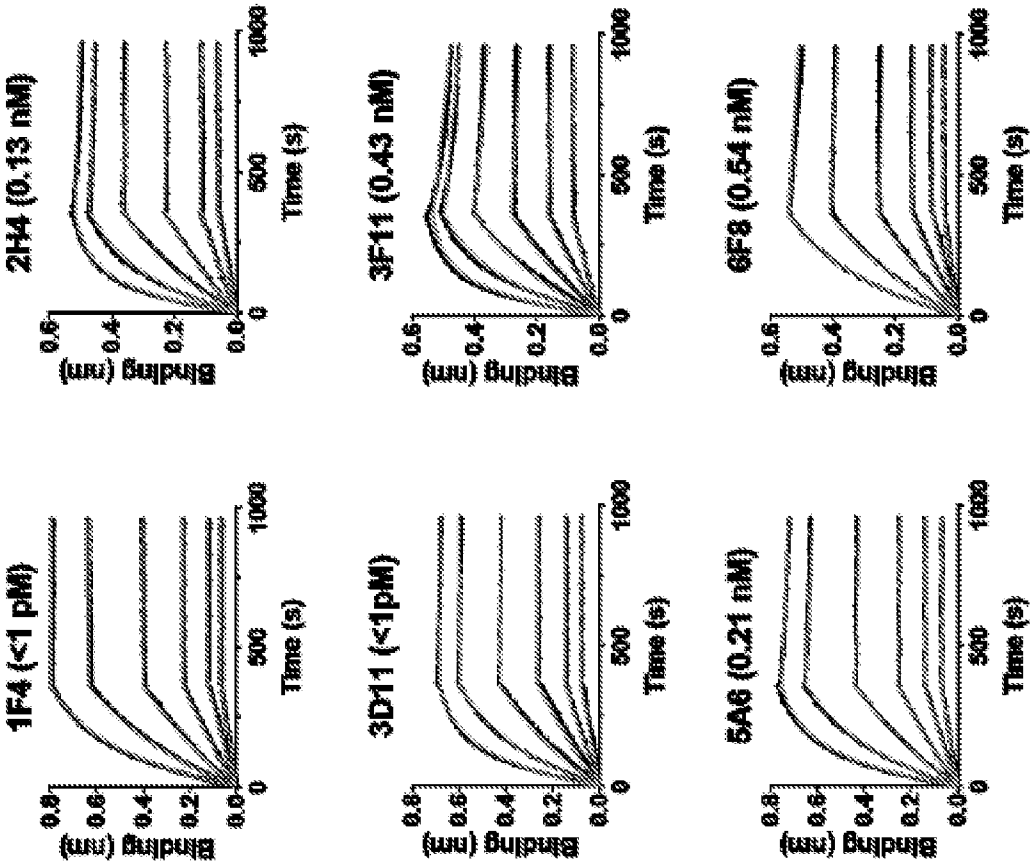

2H4 (0.13 nM)
3F11 (0.43 nM)
6F8 (0.54 nM)
1F4 (<1 pM)
3D11 (<1pM)
5A6 (0.21 nM)
Binding (nm)
Time (s)

Figure 11

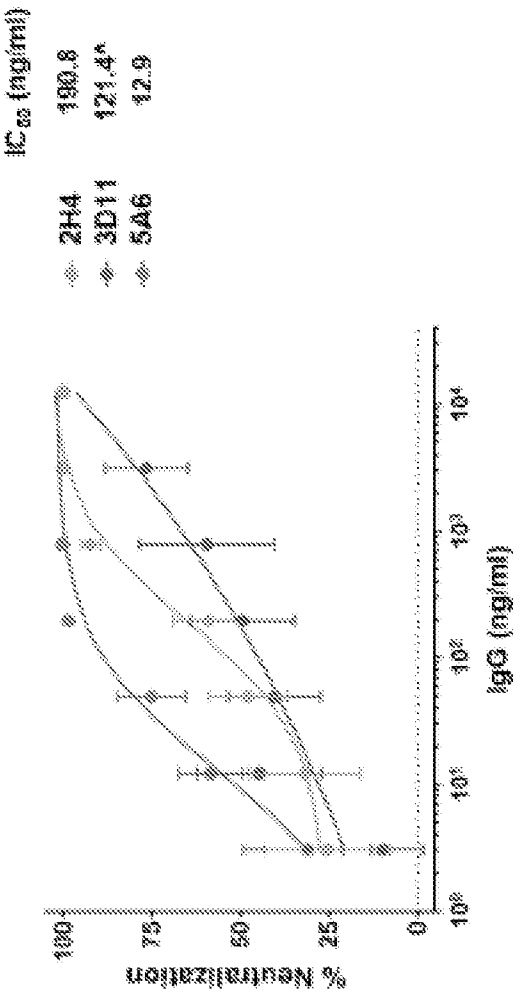

IC50 (ng/ml)
2H4 190.8
3D11 121.4^
5A6 12.9
% Neutralization
100
75
50
25
0
10²
10³
10⁴
IgG (ng/ml)

Figure 12

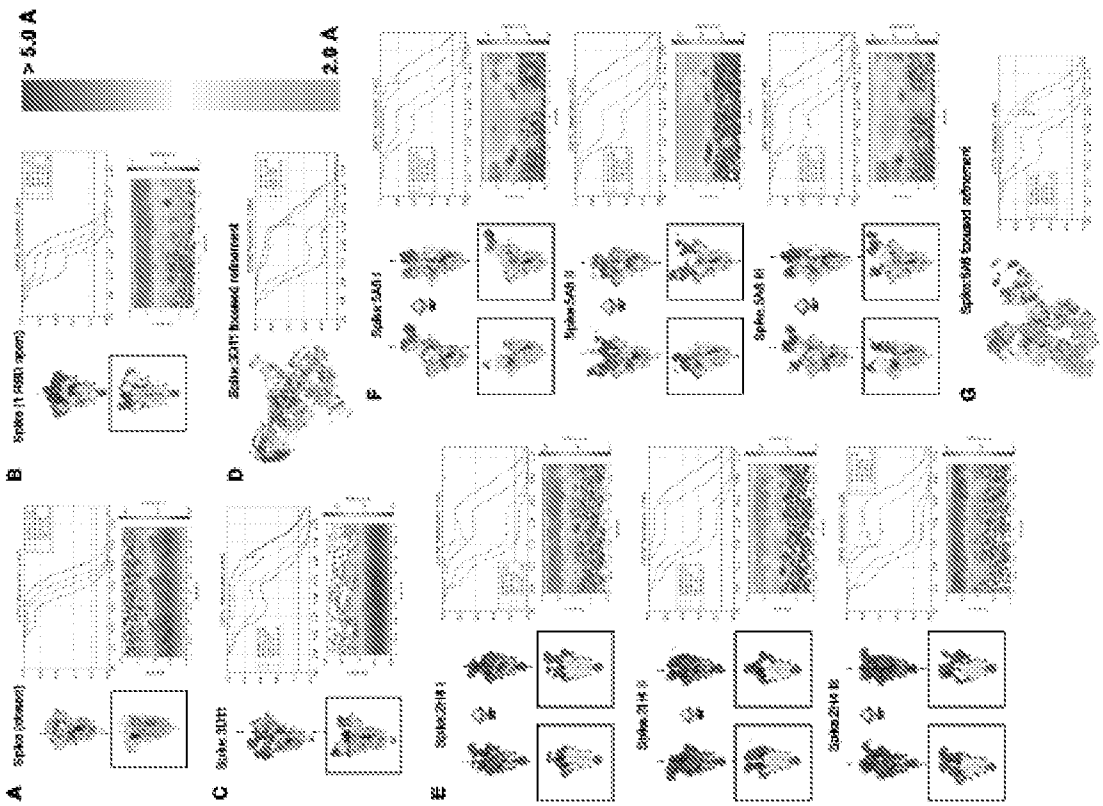


Figure 13

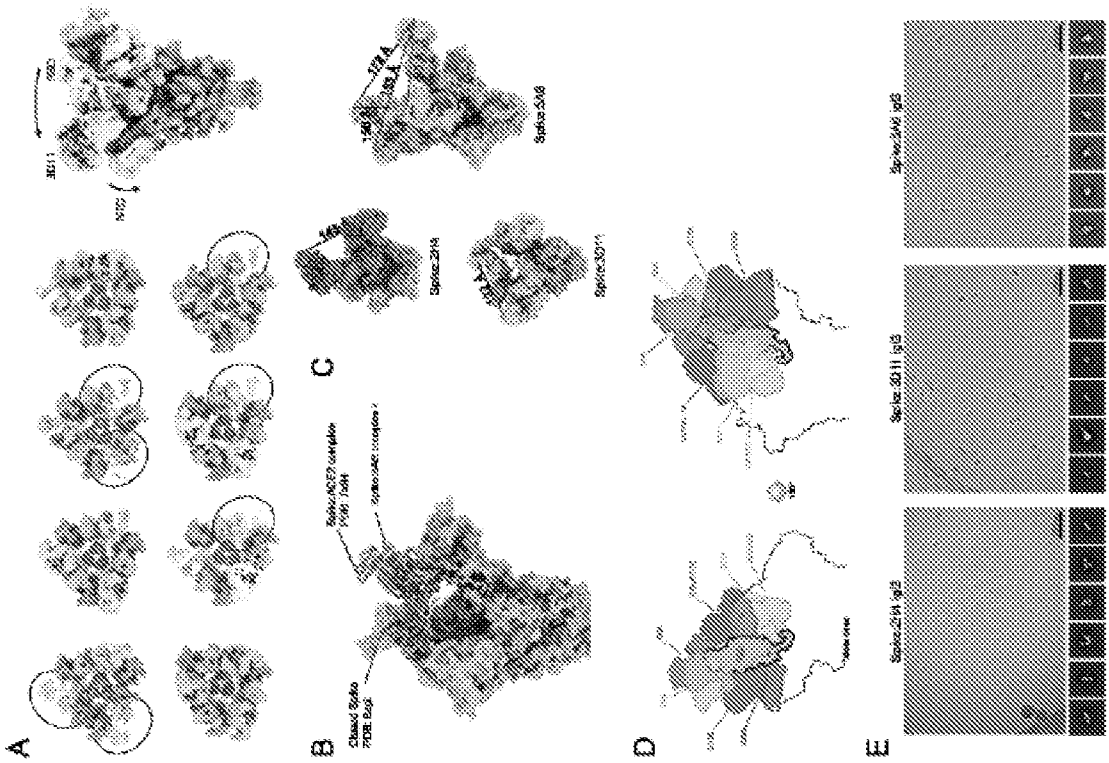


Figure 14

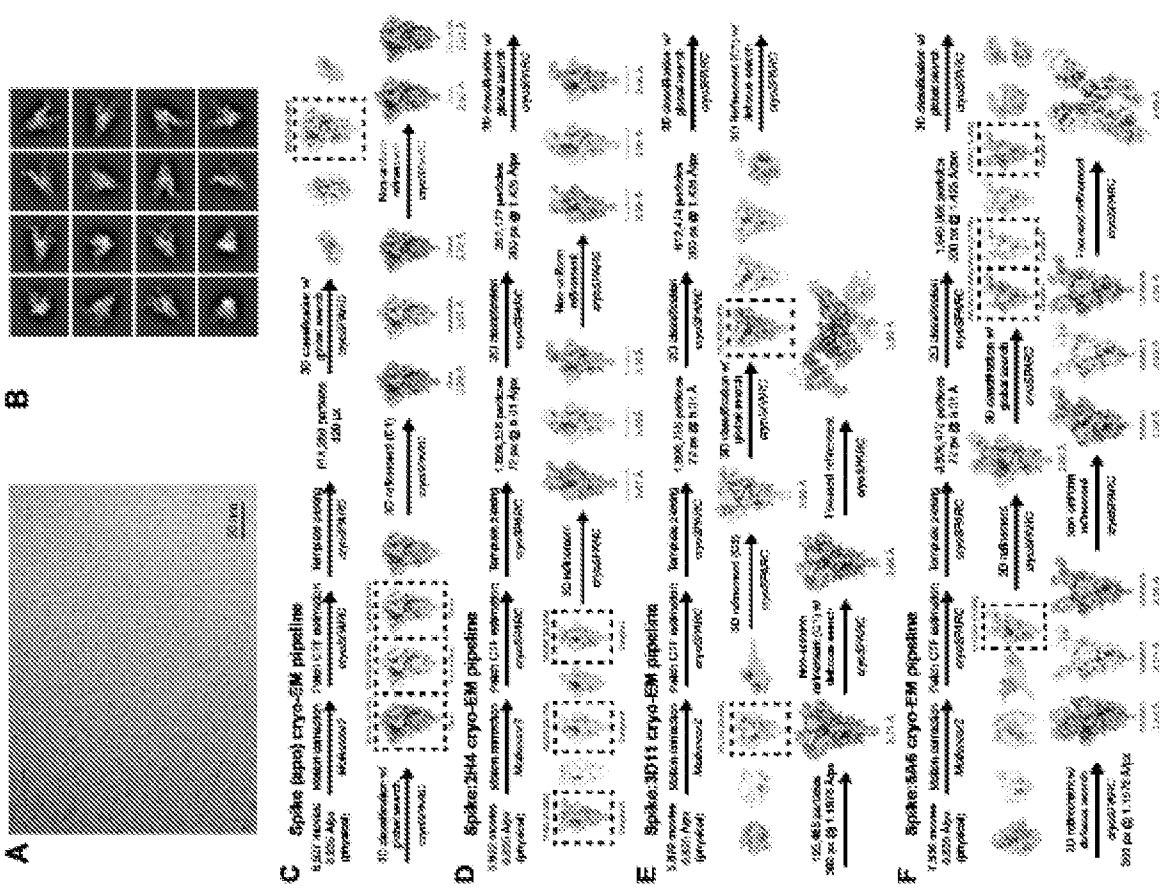

A
B
C Spike (apo) cryo-EM pipeline
D Spike:3H4 cryo-EM pipeline
E Spike:3D11 cryo-EM pipeline
F Spike:5A6 cryo-EM pipeline

Figure 15

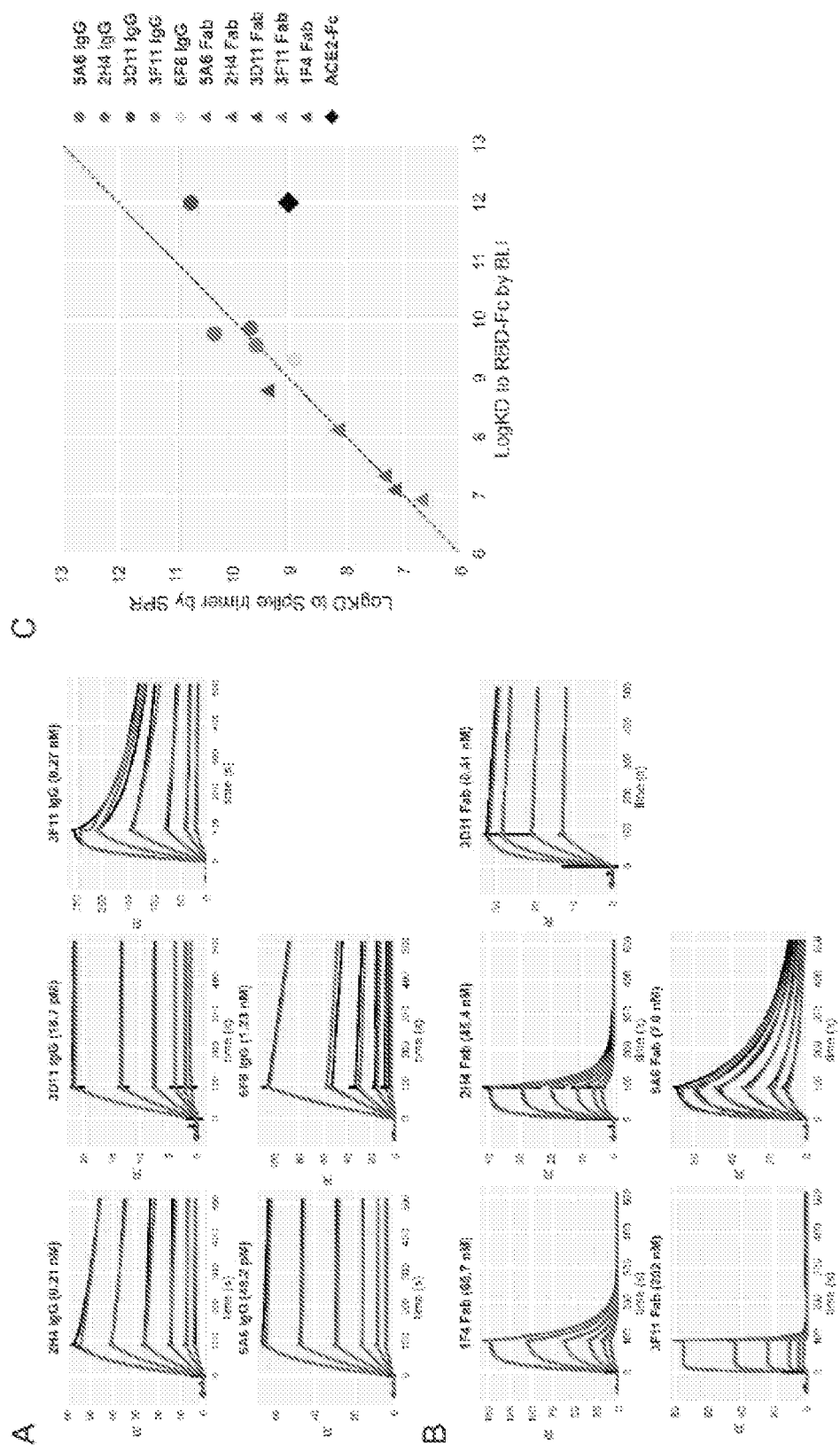

A
B
C
LogKD to Spike trimer by SPR
LogKD to RBD-Fc by BLI
6
7
8
9
10
11
12
13
SAB IgG
2H4 IgG
3D11 IgG
3F11 IgG
6F8 IgG
SAB Fab
2H4 Fab
3D11 Fab
3F11 Fab
1F4 Fab
ACE2-Fc

Figure 16


A
5A6 IgG
WT
D614G
IC_{50} (ng/ml)
22.2
1.95^
% Neutralization
IgG (ng/ml)
B
3D11 IgG
WT
D614G
IC_{50} (ng/ml)
155.5^
839.8
% Neutralization
IgG (ng/ml)

Figure 17

Table S1. Percent framework identity to the germline sequences

mAb	VH (% identity)	VL (% identity)
1F4	IGHV6-1*01 (100.0)	IGLV1-47*01 (87.2)
2H4	IGHV1-2*06 (88.8)	IGKV5-2*01 (82.3)
3D11	IGHV4-34*01 (100.0)	IGLV6-57*02 (97.5)
3F11	IGHV1-18*01 (92.5)	IGKV3-20*01 (86.1)
5A6	IGHV3-30*01 (92.5)	IGKV1-39*01 (97.5)
6F8	IGHV3-66*01 (98.8)	IGKV3-20*01 (94.9)

VH and VL % identity refers to variable region compared to germline (IMGT).

Figure 18

Table S2. Binding kinetics of antibodies and Fabs measured against Fc-RBD by BLI or Spike trimer by SPR.

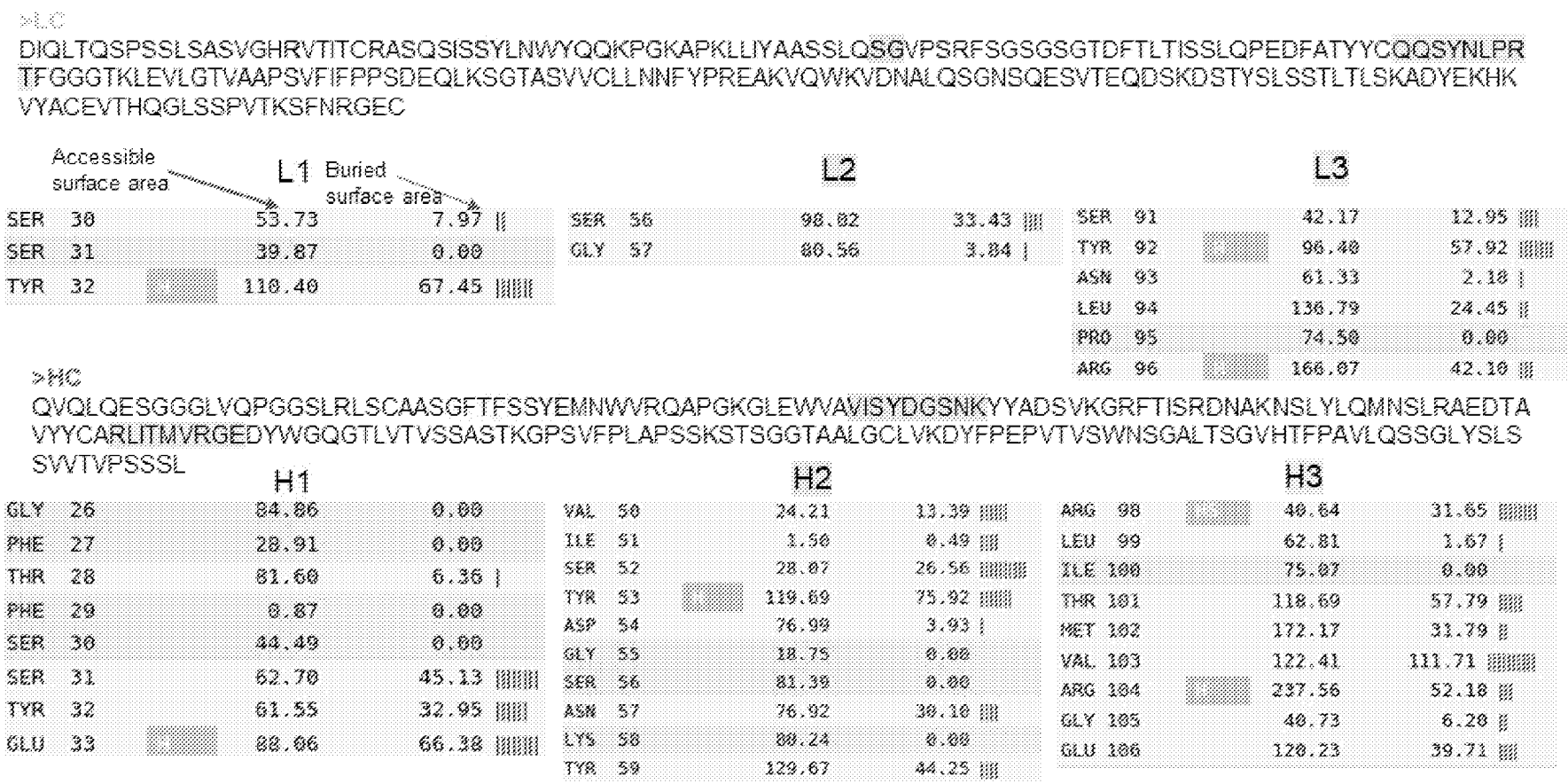
mAb		k_a RBD ($M^{-1}s^{-1}$)	k_d RBD (s^{-1})	K_D RBD	k_a trimer ($M^{-1}s^{-1}$)	k_d trimer (s^{-1})	K_D trimer
1F4	Fab	2.14E+05	1.70E-02	8.02E-08	4.432E+05	3.046E-02	6.874E-08
	IgG	2.50E+05	<1.0E-07	<1.00E-12	-	-	-
2H4	Fab	3.58E+05	1.66E-02	4.72E-08	7.130E+05	3.340E-02	4.536E-08
	IgG	4.38E+05	6.10E-05	1.39E-10	2.042E+06	4.264E-04	2.088E-10
3D11	Fab	2.99E+05	4.90E-04	1.64E-09	5.098E+05	2.063E-04	4.047E-10
	IgG	3.44E+05	<1.0E-07	<1.00E-12	1.164E+06	2.173E-05	1.867E-11
3F11	Fab	7.68E+05	9.20E-02	1.20E-07	8.776E+05	1.775E-01	2.023E-07
	IgG	4.78E+05	1.23E-04	2.73E-10	8.487E+06	2.250E-03	2.651E-10
5A6	Fab	4.69E+05	3.57E-03	7.61E-09	8.557E+05	6.011E-03	7.025E-09
	IgG	3.39E+05	5.92E-05	1.73E-10	2.029E+06	9.772E-05	4.816E-11
6F8	Fab	-	-	-	-	-	-
	IgG	1.83E+05	8.76E-05	4.76E-10	3.617E+05	4.441E-04	1.228E-09
ACE2-Fc		1.43E+05	<1.0E-07	1.00E-12	3.751E+05	3.637E-04	9.699E-10

Figure 19

Table S3. Cryo-EM data collection, refinement and validation statistics

	Spike:5A6 complex I (EMDB-22893) (PDB 7KQB)	Spike:5A6 Fab and RBDs only	Spike:3D11 complex (EMD-22997) (PDB 7KQE)	Spike:3D11 Fab and RBD only	Spike:2H4 complex Rigid body docking (EMDB-22994)
Data collection and processing					
Magnification	EFTEM 105,000		EFTEM 105,000		EFTEM 105,000
Voltage (kV)	300		300		300
Electron exposure (e–/Å^2)	66.7		66.7		66.7
Defocus range (μm)	-0.5-1.5		-0.5-1.5		-0.5-1.5
Pixel size (Å)	0.835		0.835		0.835
Symmetry imposed	C1		C1		C1
Initial particle images (no.)	3,826,472		1,890,759		1,689,358
Final particle images (no.)	380,163		195,465		104,986
Map resolution (Å)	2.42	2.66	2.64	2.95	3.38
FSC threshold 0.143					
Map resolution range (Å)					
Refinement					
Initial model used (PDB code)	7a94	7a94	7a98	7a98	7a95
Model resolution (Å)	3.9	3.0	8.3	3.1	
FSC threshold 0.5					
Model resolution range (Å)					
Map sharpening *B* factor (Å^2)	-74.9	-87.7	-76.3	-57.1	-58.0
Model composition					
Non-hydrogen atoms	32,217	6,590	34,626	4,870	34,977
Protein residues	4,105	852	4,467	635	4511
Ligands	0	0	0	0	0
B factors (Å^2)					
Protein (min/max/mean)	1.84/281.53/94.83	1.84/115.96/25.03	0/609.22/243.17	0/609.22/185.68	0/754.58/163.41
Ligand	-/-/-	-/-/-	-/-/-	-/-/-	-/-/-
R.m.s. deviations					
Bond lengths (Å)	0.012	0.012	0.012	0.012	0.017
Bond angles (°)	1.916	2.069	1.805	2.039	2.003
Validation					
MolProbity score	0.87	1.23	1.03	1.02	2.61
Clashscore	0.09	0.77	0.2	0.21	27.30
Poor rotamers (%)	0.98	1.22	1.08	1.28	2.04
Ramachandran plot					
Favored (%)	95.27	93.72	93.59	94.75	93.02
Allowed (%)	4.65	6.16	6.3	4.93	6.08
Disallowed (%)	0.07	0	0.11	0.32	0.90

Figure 20



Interface residues highlighted yellow, non-interfacing residues highlighted blue; | - hydrogen bond; || - hydrogen bond/salt bridge; |||||| - buried area percentage, correlates with dense packing of the interfacial residues

Figure 21

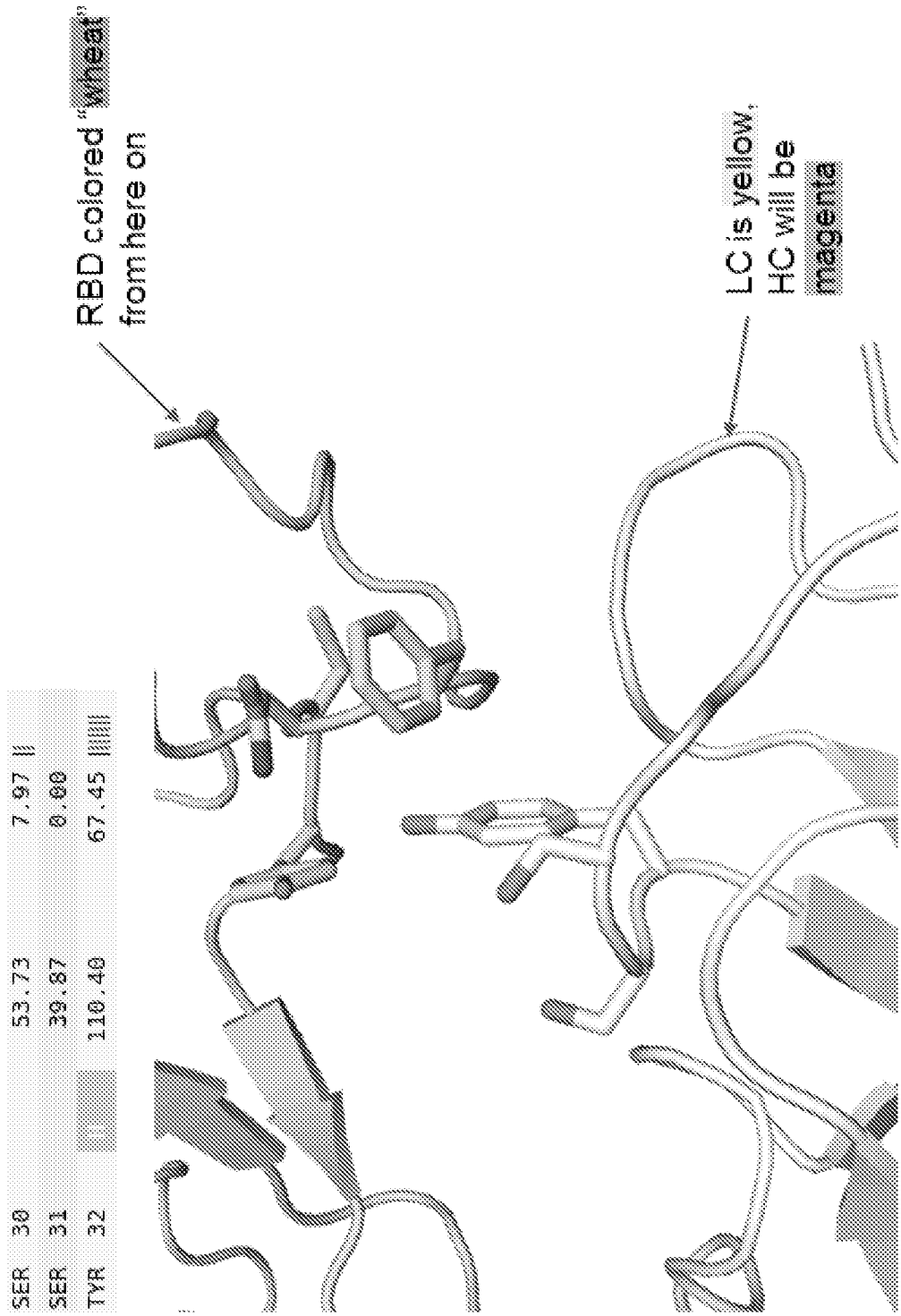

L1
SER 30 53.73 7.97
SER 31 39.87 0.00
TYR 32 110.40 67.45
RBD colored "wheat" from here on
LC is yellow, HC will be magenta

Figure 22

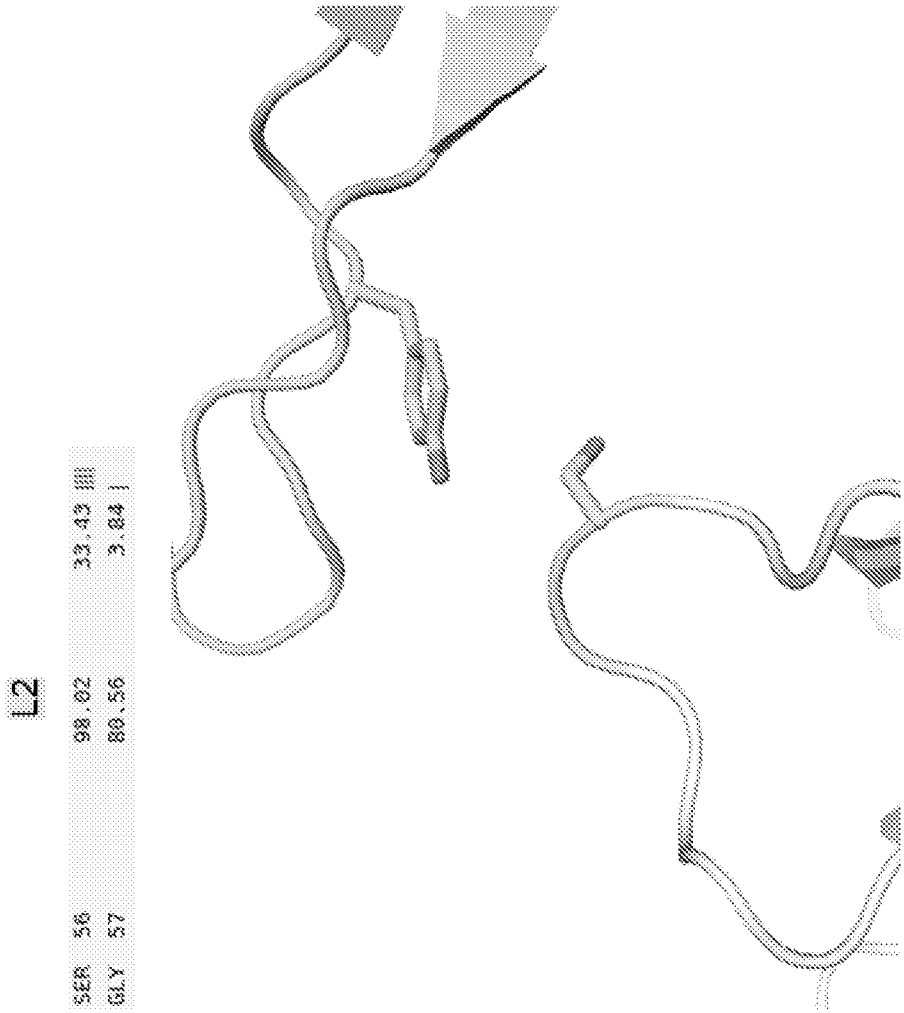


Figure 23

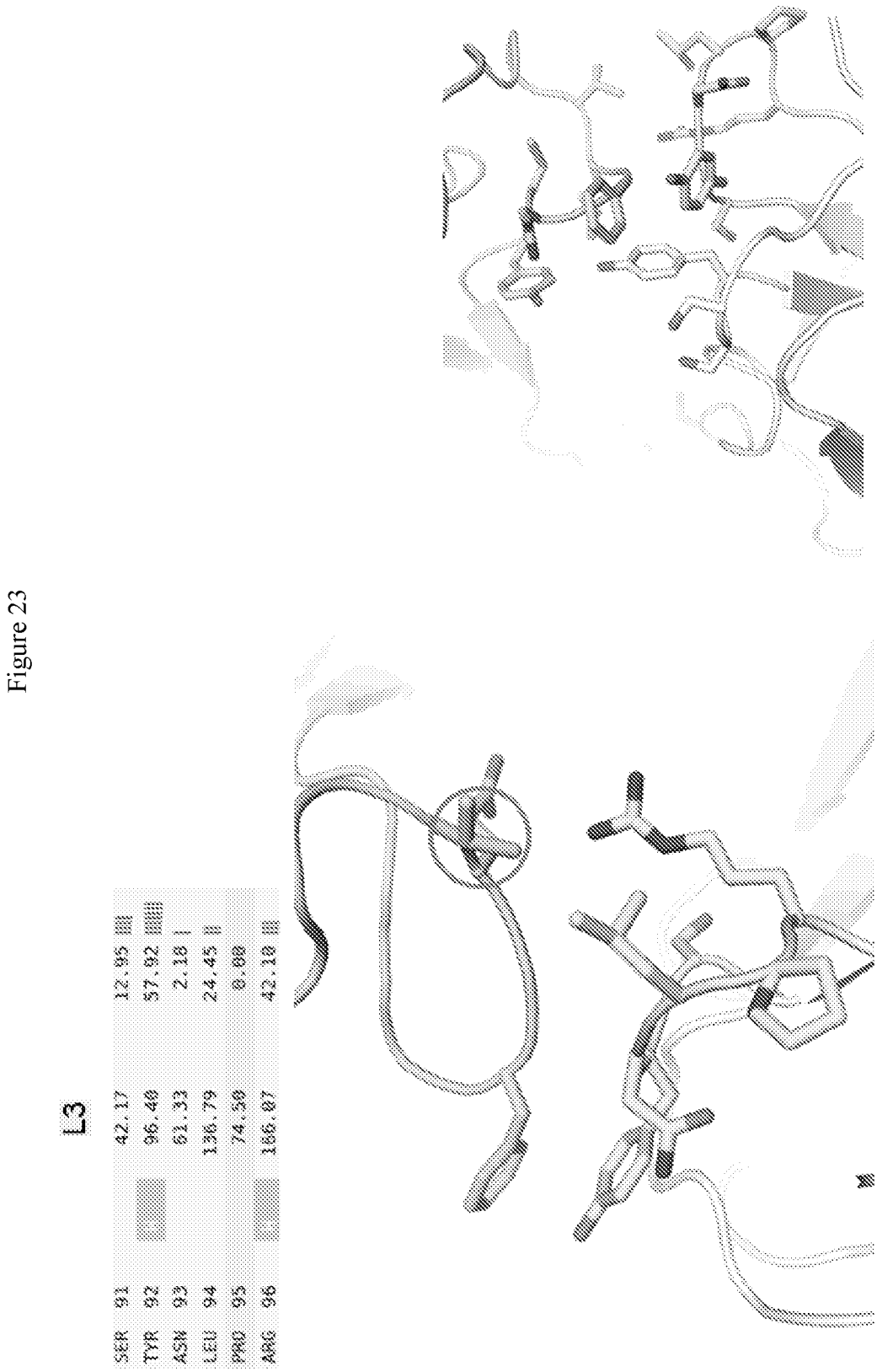

L3
SER 91 42.17 12.95
TYR 92 96.40 57.92
ASN 93 61.33 2.18
LEU 94 136.79 24.45
PRO 95 74.50 0.00
ARG 96 166.07 42.10

Figure 24

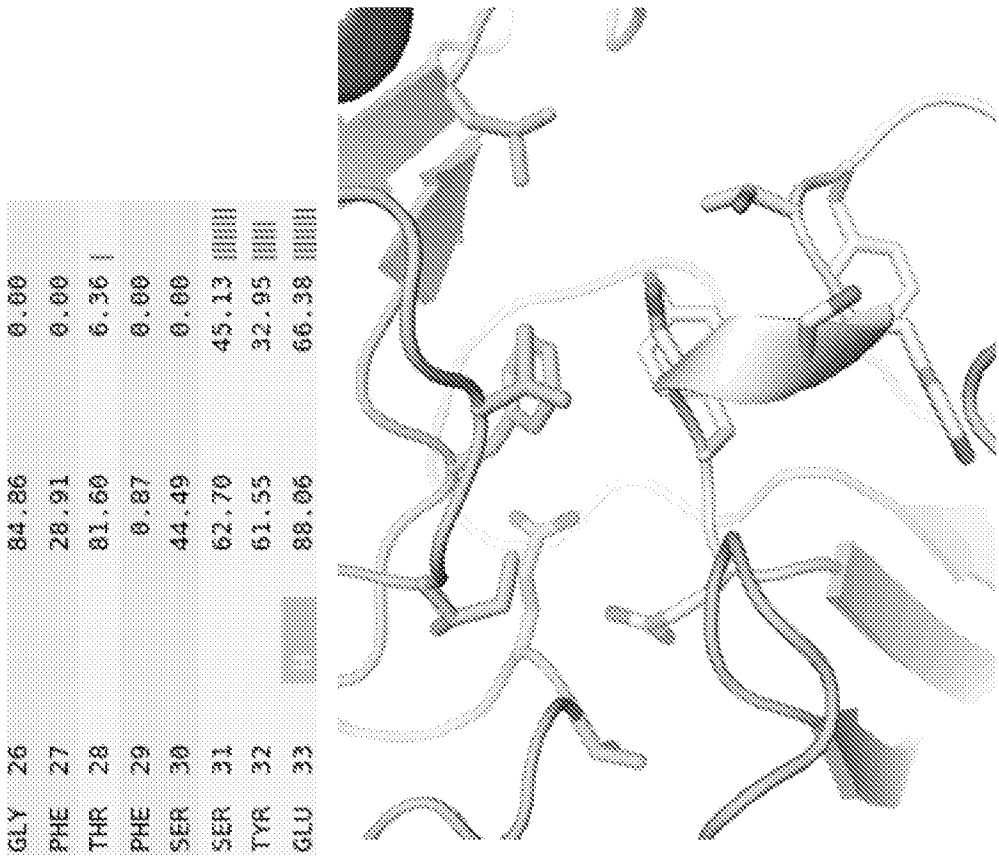

H1
GLY 26 84.86 0.00
PHE 27 28.91 0.00
THR 28 81.60 6.36
PHE 29 0.87 0.00
SER 30 44.49 0.00
SER 31 62.70 45.13
TYR 32 61.55 32.95
GLU 33 88.06 66.38

Figure 25

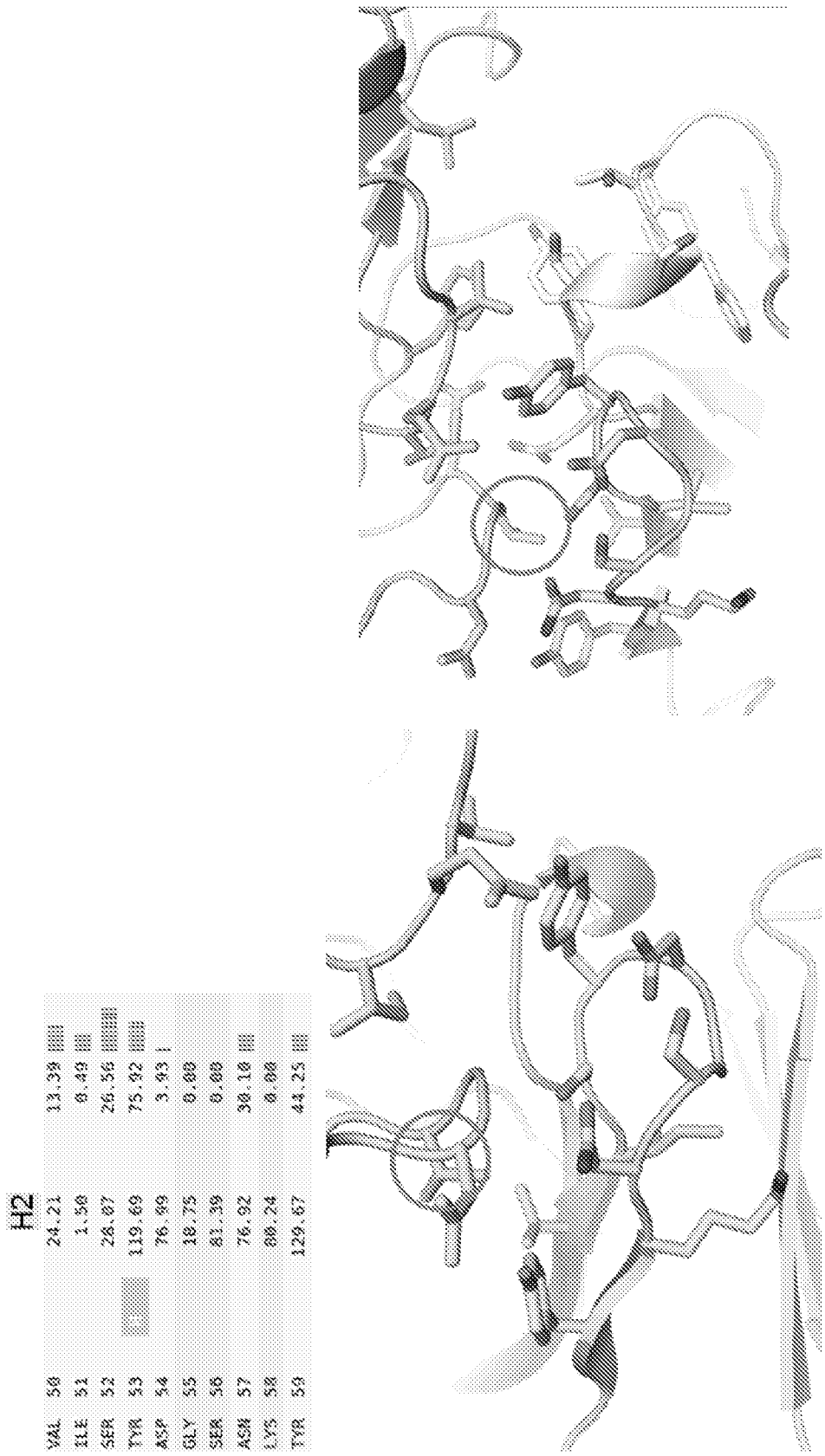
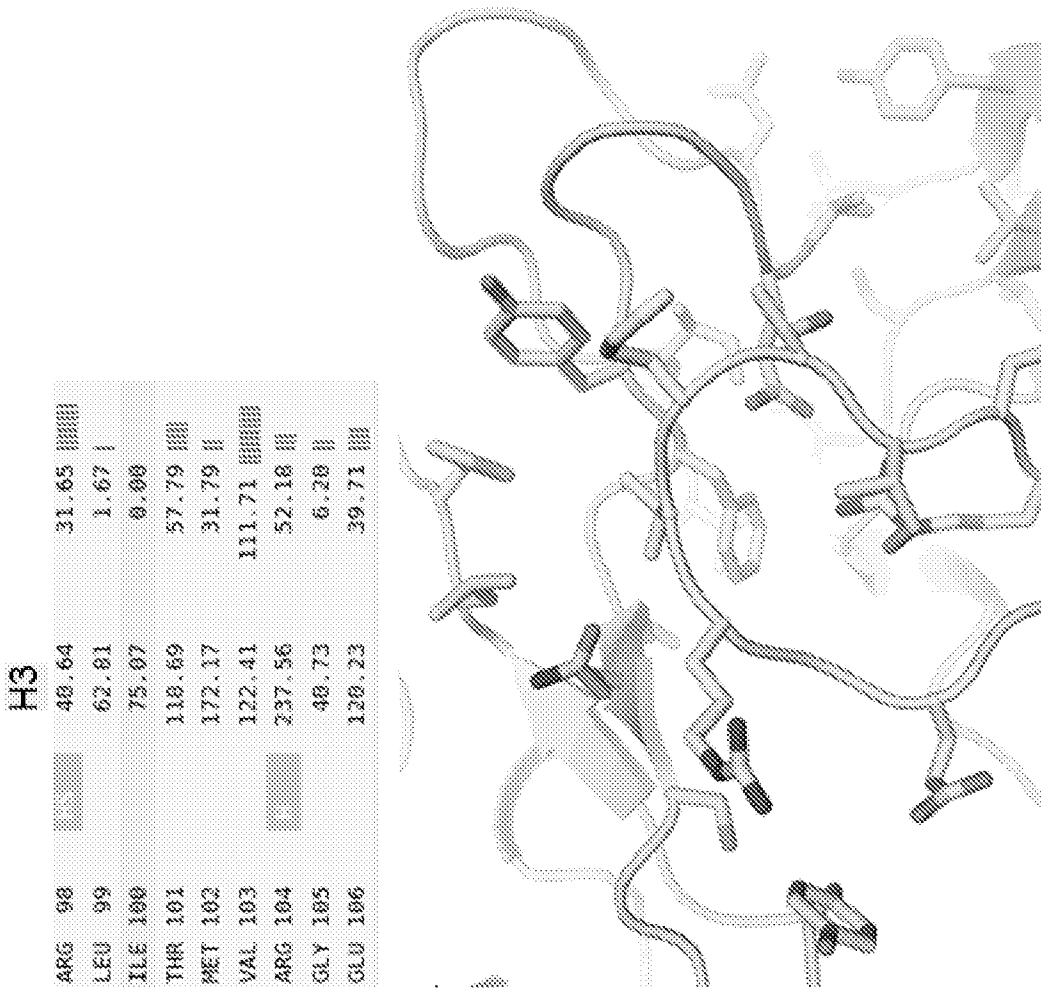

H2
VAL 50 24.21 13.39
ILE 51 1.50 0.49
SER 52 28.07 26.56
TYR 53 119.69 75.92
ASP 54 76.99 3.93
GLY 55 18.75 0.00
SER 56 81.39 0.00
ASN 57 76.92 30.10
LYS 58 80.24 0.00
TYR 59 129.67 44.25

Figure 26


H3
ARG 98 40.64 31.65
LEU 99 62.81 1.67
ILE 100 75.07 0.00
THR 101 118.69 57.79
MET 102 172.17 31.79
VAL 103 122.41 111.71
ARG 104 237.56 52.18
GLY 105 40.73 6.28
GLU 106 120.23 39.71

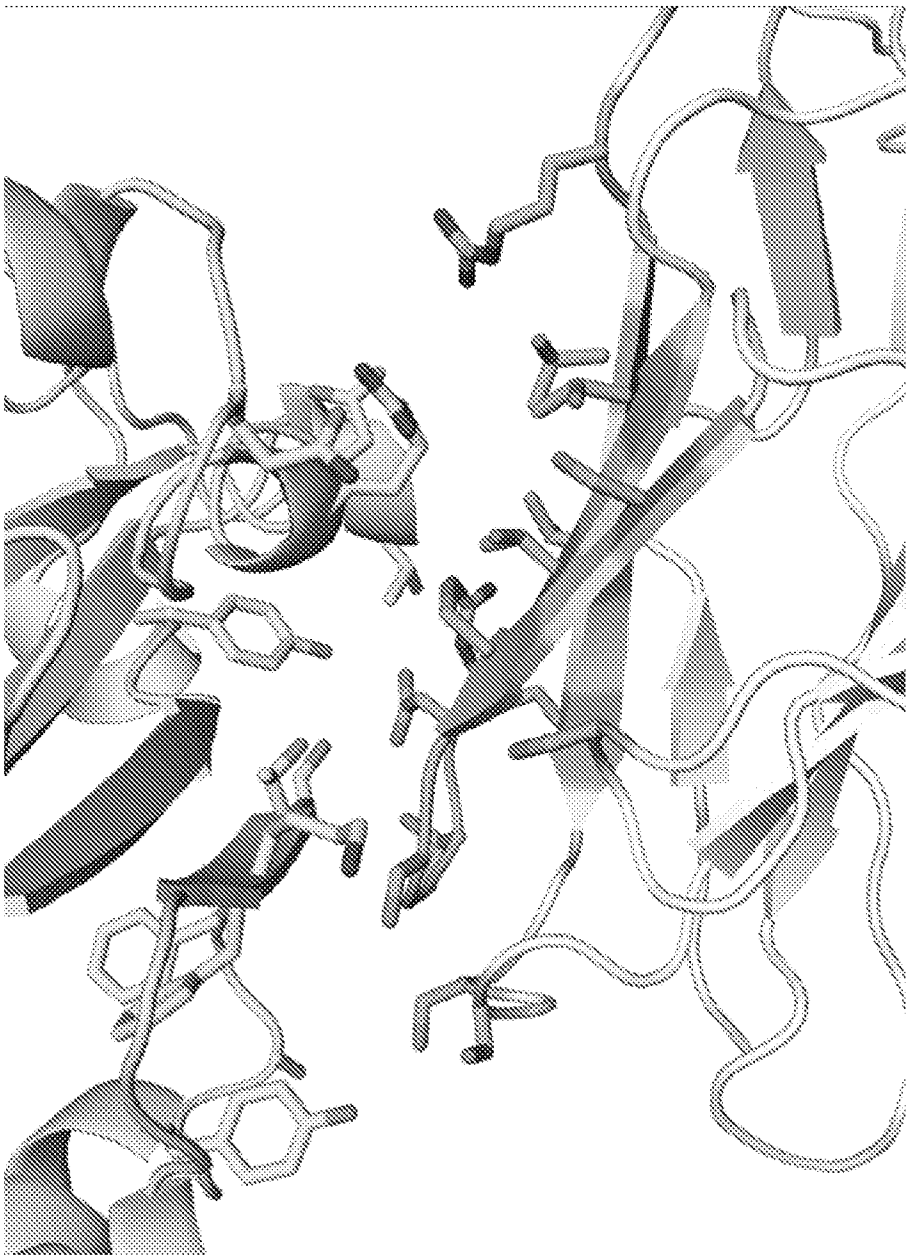


Figure 27

Figure 28

>LC
DIQLTQSPSSLSASVGHRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYNLPR
TFGGGTKLEVLGTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHK
VYACEVTHQGLSSPVTKSFNRGEC

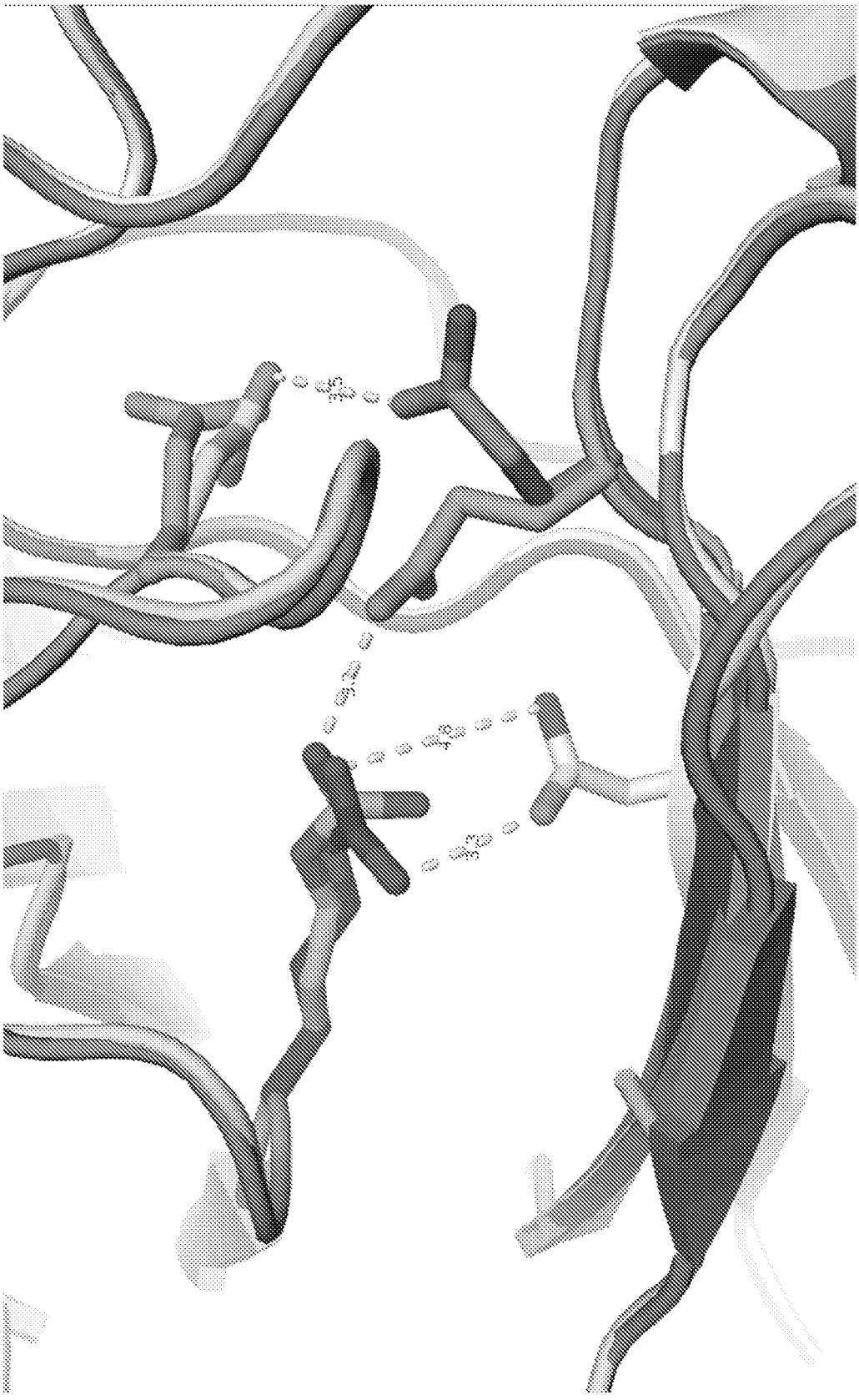


Figure 29

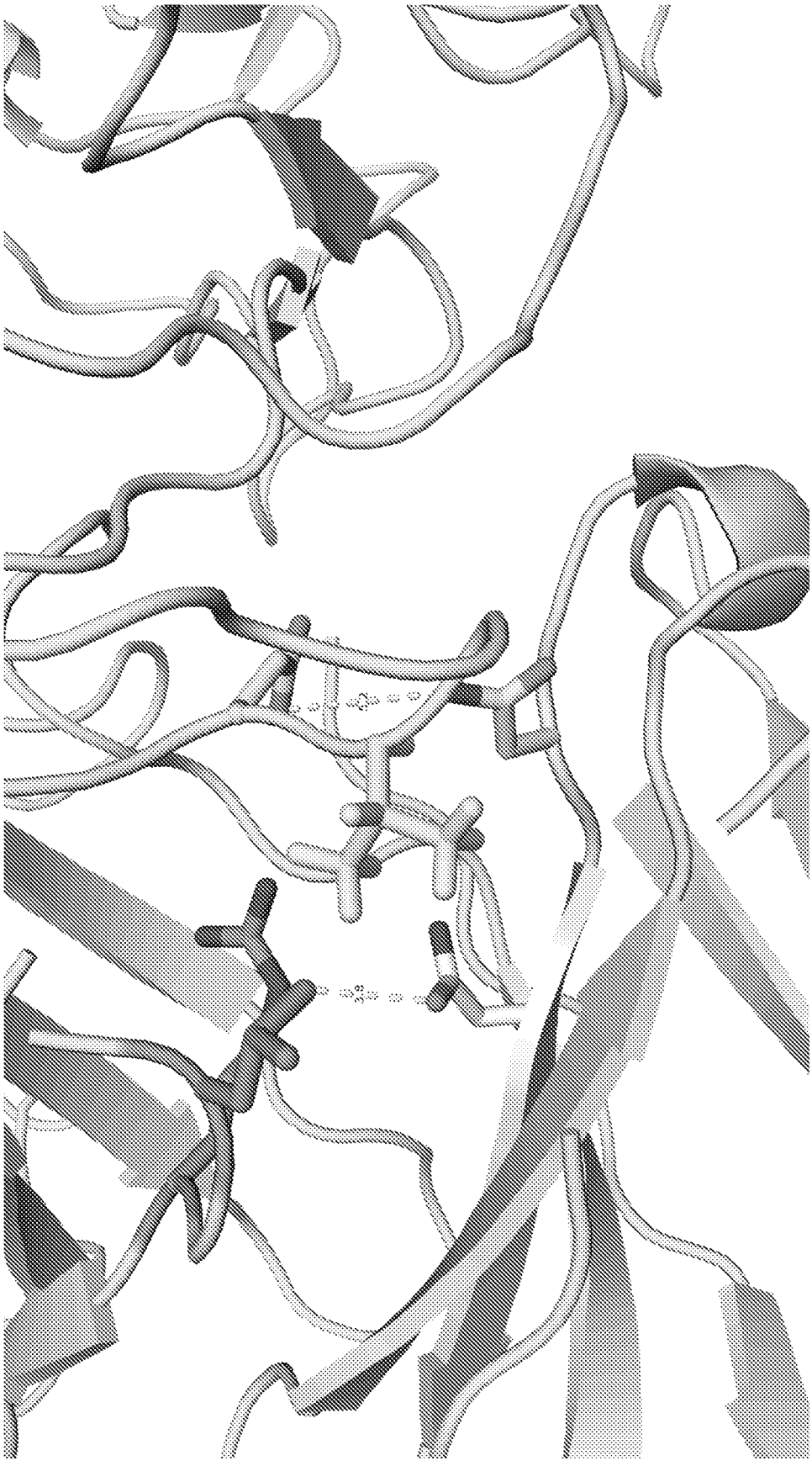


Figure 30

Figure 31

Single point mutants at Heavy Chain position S52

Construct	Light Chain	Heavy Chain	Koff (1/s)
5A6 WT			1.14E-02
1	WT	S52G	5.25E-02
2	WT	S52A	3.05E-02
3	WT	S52V	5.11E-02
4	WT	S52L	No binding
5	WT	S52E	No binding
6	WT	S52R	No binding
7	WT	S52K	2.04E-02
8	WT	S52I	3.34E-02
9	WT	S52P	3.35E-02
10	WT	S52Y	No binding
11	WT	S52Q	No binding
12	WT	S52M	No binding
13	WT	S52W	No binding
14	WT	S52T	4.68E-02
15	WT	S52F	No binding
16	WT	S52D	4.25E-02
17	WT	S52H	No binding
18	WT	S52N	4.47E-03

Antigen: MBP-RBD

Figure 32

Single point mutants at Heavy Chain position Y53

Construct	Light Chain	Heavy Chain	Koff (1/s)
5A6 WT			1.14E-02
1	WT	Y53G	3.38E-02
2	WT	Y53A	2.10E-02
3	WT	Y53V	1.11E-02
4	WT	Y53L	7.81E-03
5	WT	Y53E	No binding
6	WT	Y53R	2.79E-02
7	WT	Y53K	7.24E-03
8	WT	Y53I	1.63E-02
9	WT	Y53P	1.60E-02
10	WT	Y53S	5.37E-03
11	WT	Y53Q	1.46E-02
12	WT	Y53M	3.25E-02
13	WT	Y53W	1.36E-02
14	WT	Y53T	1.02E-02
15	WT	Y53F	1.49E-02
16	WT	Y53D	6.61E-02
17	WT	Y53H	1.76E-02
18	WT	Y53N	2.27E-02

Antigen: MBP-RBD

Figure 33

Single point mutants at Heavy Chain position D54

Construct	Light Chain	Heavy Chain	Koff (1/s)
5A6 WT			1.14E-02
1	WT	D54G	1.60E-03
2	WT	D54A	9.12E-03
3	WT	D54V	3.37E-03
4	WT	D54L	2.66E-03
5	WT	D54E	8.57E-03
6	WT	D54R	3.38E-03
7	WT	D54K	1.66E-03
8	WT	D54I	1.42E-03
9	WT	D54P	7.25E-03
10	WT	D54S	2.93E-03
11	WT	D54Q	3.89E-03
12	WT	D54M	1.21E-03
13	WT	D54W	4.61E-04
14	WT	D54T	2.42E-03
15	WT	D54F	5.10E-04
16	WT	D54Y	6.72E-04
17	WT	D54H	8.32E-03
18	WT	D54N	1.12E-02

Antigen: MBP-RBD

Figure 34

Single point mutants at Heavy Chain position G55

Construct	Light Chain	Heavy Chain	Koff (1/s)
5A6 WT			1.14E-02
1	WT	G55D	3.16E-02
2	WT	G55A	1.52E-02
3	WT	G55V	No binding
4	WT	G55L	2.57E-02
5	WT	G55E	2.37E-02
6	WT	G55R	1.88E-02
7	WT	G55K	2.14E-02
8	WT	G55I	3.33E-02
9	WT	G55P	4.38E-01
10	WT	G55S	2.10E-02
11	WT	G55Q	2.08E-02
12	WT	G55M	2.12E-02
13	WT	G55W	1.43E-02
14	WT	G55T	2.34E-02
15	WT	G55F	3.44E-02
16	WT	G55Y	1.60E-02
17	WT	G55H	3.03E-02
18	WT	G55N	2.09E-02

Antigen: MBP-RBD

Figure 35

Single point mutants at Heavy Chain position S56

Construct	Light Chain	Heavy Chain	Koff (1/s)
5A6WT			1.14E-02
1	WT	S56D	8.43E-03
2	WT	S56A	7.44E-03
3	WT	S56V	5.98E-03
4	WT	S56L	7.02E-03
5	WT	S56E	8.17E-03
6	WT	S56R	3.11E-03
7	WT	S56K	6.31E-03
8	WT	S56I	6.31E-03
9	WT	S56P	1.16E-02
10	WT	S56G	5.30E-03
11	WT	S56Q	7.79E-03
12	WT	S56M	3.90E-03
13	WT	S56W	3.91E-03
14	WT	S56T	1.03E-02
15	WT	S56F	6.85E-03
16	WT	S56Y	8.19E-03
17	WT	S56H	7.17E-03
18	WT	S56N	7.73E-03

Antigen: MBP-RBD

Figure 36

Single point mutants at Heavy Chain position N57

Construct	Light Chain	Heavy Chain	Koff (1/s)
5A6WT			1.14E-02
1	WT	N57D	3.01E-02
2	WT	N57A	2.68E-02
3	WT	N57V	5.37E-03
4	WT	N57L	1.63E-02
5	WT	N57E	6.34E-02
6	WT	N57R	1.48E-02
7	WT	N57K	2.30E-03
8	WT	N57I	2.05E-02
9	WT	N57P	No binding
10	WT	N57S	1.12E-02
11	WT	N57Q	2.96E-02
12	WT	N57M	1.84E-02
13	WT	N57W	2.13E-02
14	WT	N57T	2.55E-02
15	WT	N57F	2.80E-02
16	WT	N57Y	9.27E-03
17	WT	N57H	7.19E-03
18	WT	N57G	1.98E-02

Antigen: MBP-RBD

Figure 37

Single point mutants at Light Chain position L94

Construct	Heavy Chain	Light Chain	Koff (1/s)
5A6WT			4.59E-04
1	WT	L94D	2.40E-03
2	WT	L94A	1.13E-03
3	WT	L94V	1.39E-03
4	WT	L94N	1.32E-02
5	WT	L94E	3.18E-02
6	WT	L94R	8.15E-04
7	WT	L94K	7.23E-03
8	WT	L94I	1.09E-03
9	WT	L94P	4.04E-03
10	WT	L94S	1.19E-03
11	WT	L94Q	1.64E-03
12	WT	L94M	2.46E-03
13	WT	L94W	2.34E-02
14	WT	L94T	1.03E-03
15	WT	L94F	3.13E-03
16	WT	L94Y	6.66E-03
17	WT	L94H	1.38E-02
18	WT	L94G	3.39E-03

Antigen: Fc_TEV_RBD (avidity)

Figure 38

Single or double point mutants at Light Chain R96 and S56

Construct	Heavy Chain	Light Chain	Koff (1/s)
5A6 WT			9.85E-03
1	WT	R96A	No binding
2	WT	R96I	No binding
3	WT	R96L	No binding
4	WT	S56Y, R96A	No binding
5	WT	S56Y, R96I	No binding
6	WT	S56Y, R96L	No binding

Antigen: MBP-RBD

Figure 39

Single point mutants at Heavy Chain E33 with single or double mutants at Light Chain R96 and S56

Construct	Heavy Chain	Light Chain	Koff (1/s)
5A6 WT			1.06E-02
1	E33A	R96A	No binding
2	E33A	R96I	No binding
3	E33A	R96L	No binding
4	E33A	S56Y, R96A	No binding
5	E33A	S56Y, R96I	No binding
6	E33A	S56Y, R96L	No binding
7	E33A	S56Y	No binding
8	E33I	R96A	No binding
9	E33I	R96I	No binding
10	E33I	R96L	No binding
11	E33I	S56Y, R96A	No binding
12	E33I	S56Y, R96I	No binding
13	E33I	S56Y, R96L	No binding
14	E33I	S56Y	No binding
15	E33L	R96A	No binding
16	E33L	R96I	No binding
17	E33L	R96L	No binding
18	E33L	S56Y, R96A	No binding
19	E33L	S56Y, R96I	No binding
20	E33L	S56Y, R96L	No binding
21	E33L	S56Y	No binding
22	E33N	R96A	No binding
23	E33N	R96I	No binding
24	E33N	R96L	No binding
25	E33N	S56Y, R96A	No binding
26	E33N	S56Y, R96I	No binding
27	E33N	S56Y, R96L	No binding
28	E33N	S56Y	No binding

Antigen: MBP-RBD

Figure 40

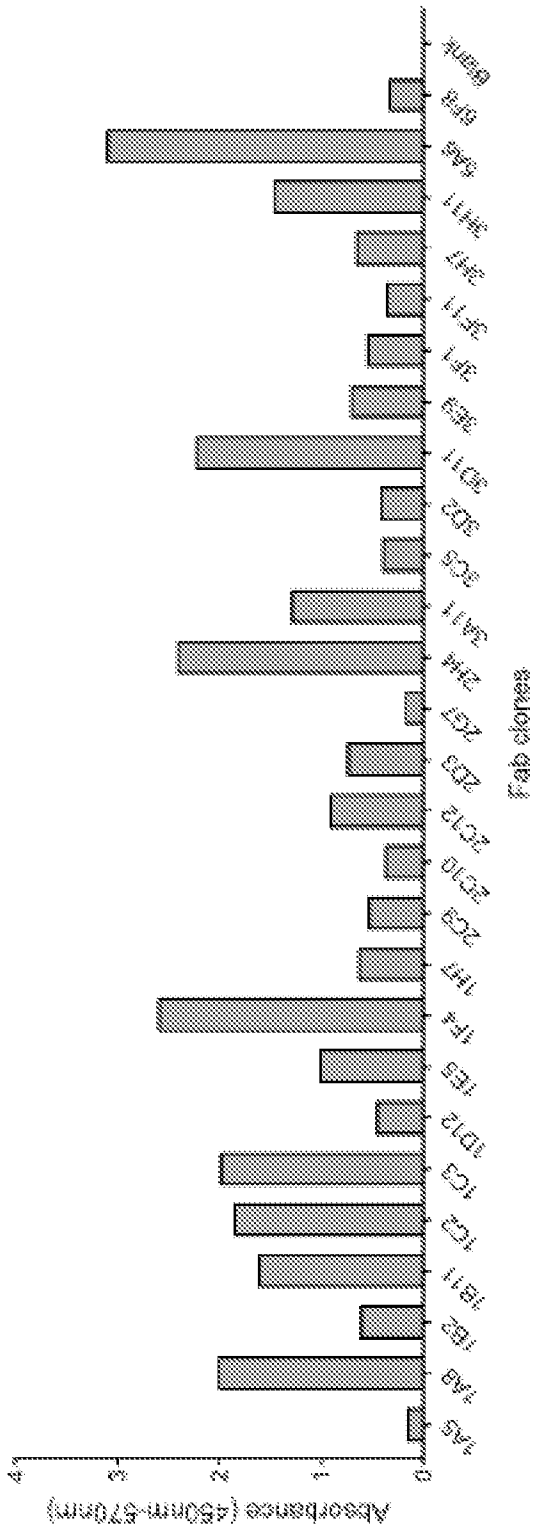

Absorbance (450nm-570nm)
0
1
2
3
4
Fab clones
1A5
1A8
1B2
1B11
1C2
1C3
1D12
1E3
1F4
1H7
2C3
2D10
2C12
2E3
2G3
2H4
3A11
3C5
3D2
3D11
3E3
3F1
3F11
3H7
4A5
4B3
4B8

Figure 41

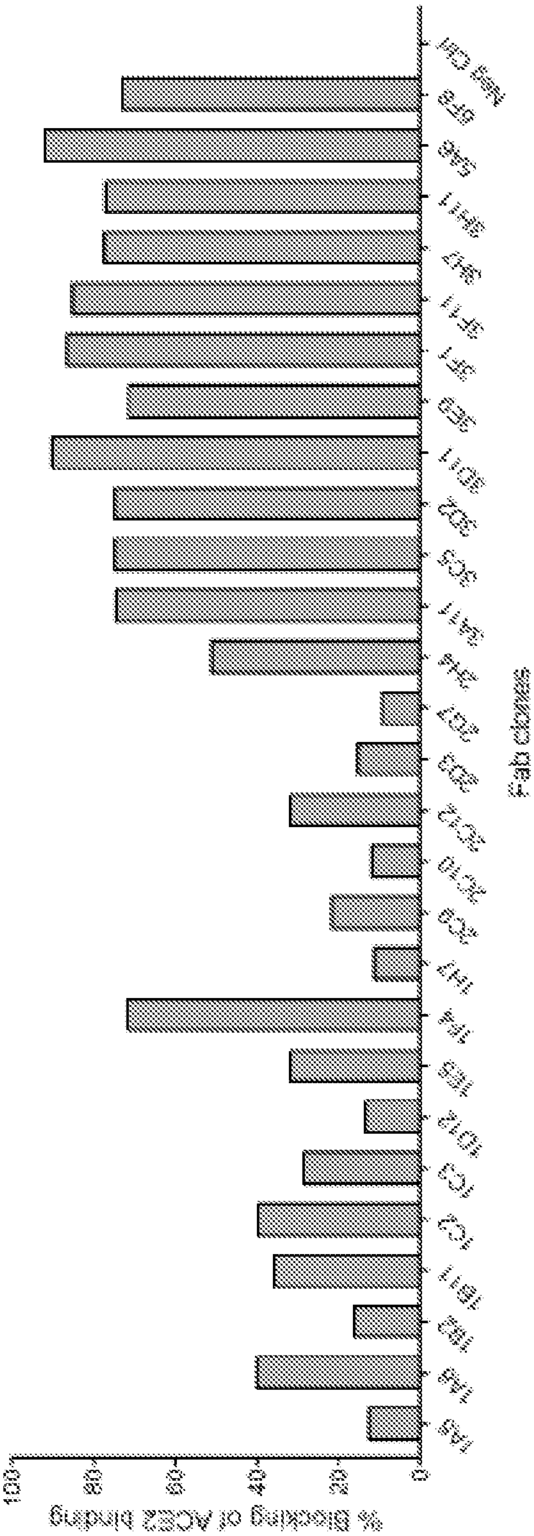

% Blocking of ACE2 binding
0
20
40
60
80
100
1A5
1A9
1B2
1B11
1C2
1C3
1D12
1E5
1F4
1H7
2C9
2C10
2C12
2D3
2G7
3A4
3A11
3C5
3D2
3D11
3E9
3F1
3F11
3H7
3H11
5A6
5F8
Neg Ctrl
Fab clones

Figure 42

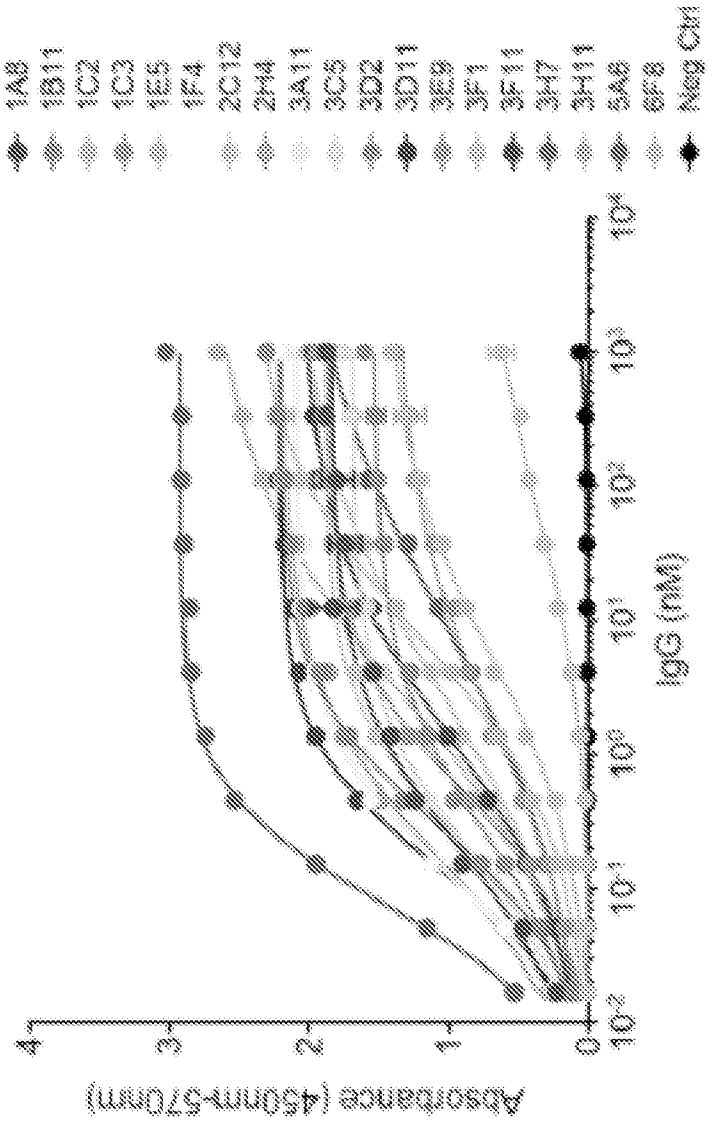

1A8
1B11
1C2
1C3
1E5
1F4
2C12
2H4
3A11
3C5
3D2
3D11
3E9
3F1
3F11
3H7
3H11
5A8
6F8
Neg Ctrl
Absorbance (450nm-570nm)
IgG (nM)

Figure 43

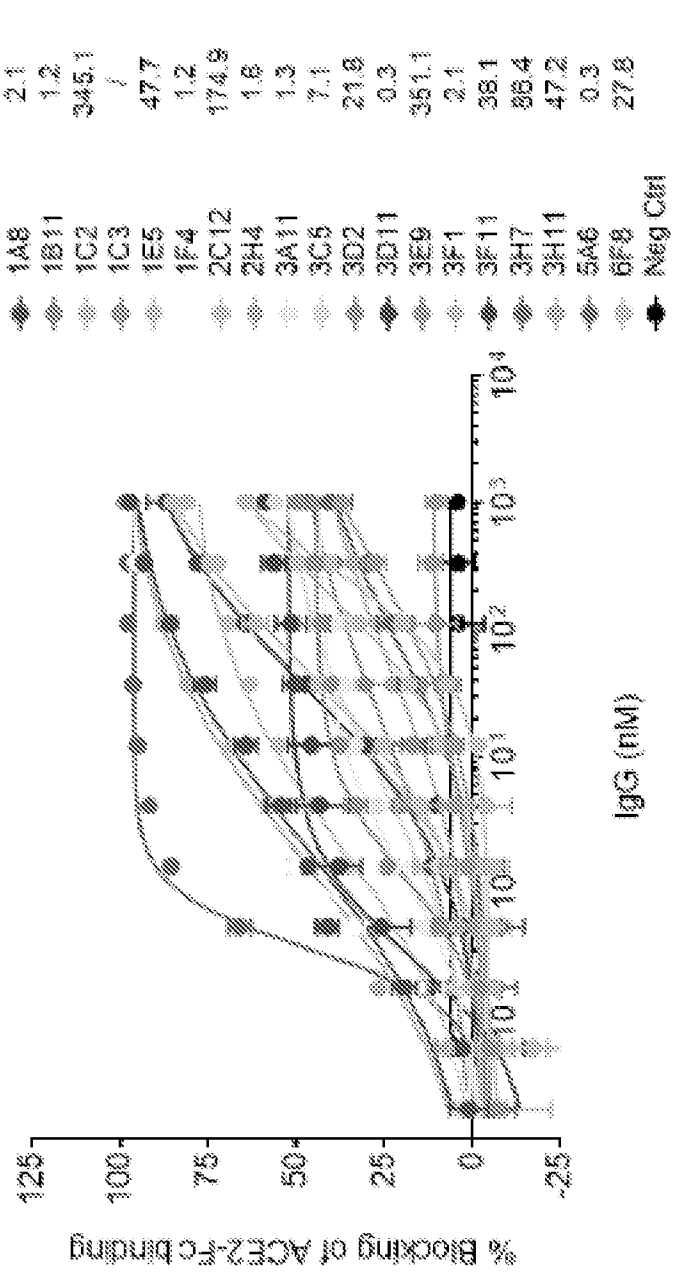

EC50 (nM)
1A8 2.1
1B11 1.2
1C2 345.1
1C3 /
1E5 47.7
1F4 1.2
2C12 174.9
2H4 1.6
3A11 1.3
3C5 7.1
3D2 21.6
3D11 0.3
3E9 351.1
3F1 2.1
3F11 38.1
3H7 88.4
3H11 47.2
5A6 0.3
6F8 27.8
Neg Ctrl
% Blocking of ACE2-Fc binding
125
100
75
50
25
0
-25
IgG (nM)

Figure 44

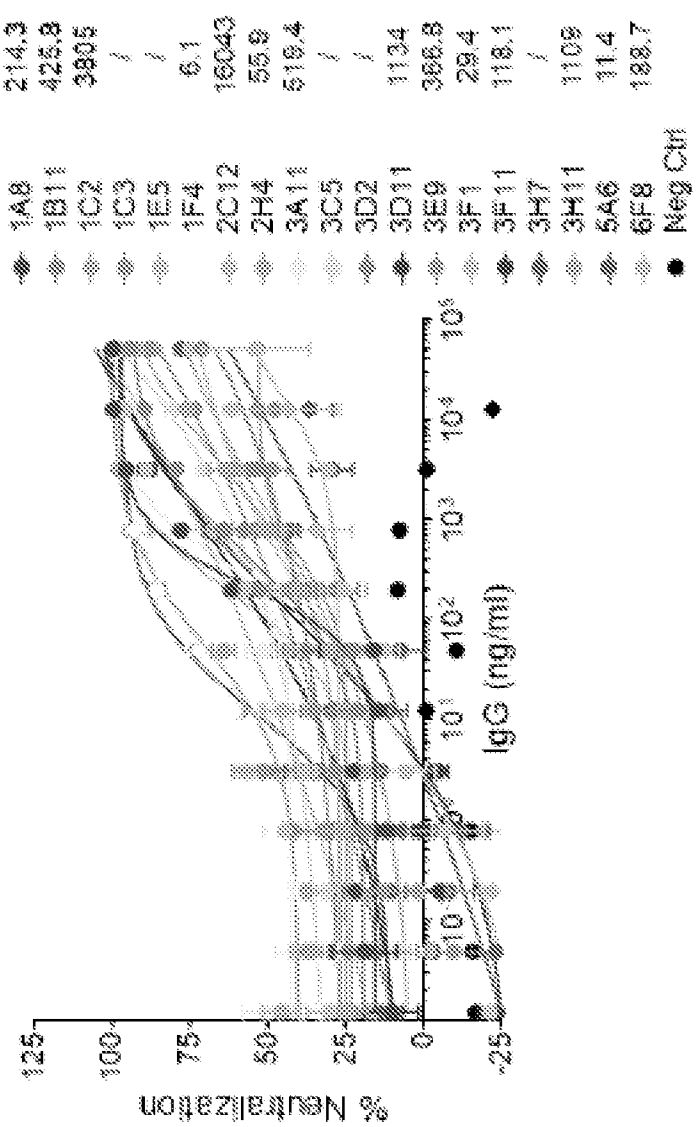

EC50
1A9 214.3
1B11 425.8
1C2 3805
1C3 /
1E5 /
1F4 6.1
2C12 16043
2H4 55.9
3A11 619.4
3C5 /
3D2 /
3D11 1134
3E9 366.8
3F1 29.4
3F11 118.1
3H7 /
3H11 1109
5A6 11.4
6F8 188.7
Neg Ctrl
% Neutralization
125
100
75
50
25
0
-25
10
10¹
10²
10³
10⁴
10⁵
IgG (ng/ml)

Figure 45

Vk	IMGT		Vk	IMGT		Vk	IMGT		Vk	IMGT		Vk	IMGT
D	1		I	21		G	47		R	75		E	97
I	2		[illegible]	[illegible]		K	48		F	76		D	98
Q	3		C	23		A	49		[illegible]	[illegible]		F	99
L	4		[illegible]	[illegible]		P	50		G	78		A	100
T	5		A	25		K	51		[illegible]	[illegible]		T	101
Q	6		S	26		L	52		[illegible]	[illegible]		Y	102
S	7		Q	27		L	53		[illegible]	[illegible]		Y	103
P	8		[illegible]	[illegible]		I	54		[illegible]	[illegible]		C	104
S	9	CDR1	I	29		Y	55		[illegible]	[illegible]	CDR3	Q	105
S	10		[illegible]	[illegible]	CDR2	A	56		[illegible]	[illegible]		Q	106
L	11		S	37		A	57		F	87		[illegible]	[illegible]
S	12		Y	38		[illegible]	[illegible]		[illegible]	[illegible]		[illegible]	[illegible]
A	13		L	39		S	66		L	89		[illegible]	[illegible]
S	14		N	40		L	67		[illegible]	[illegible]		L	[illegible]
V	15		W	41		Q	68		I	91		P	115
C	16		Y	42		S	69		S	92		[illegible]	[illegible]
H	17		Q	43		G	70		S	93		T	117
[illegible]	[illegible]		Q	44		V	71		L	94		F	118
V	19		K	45		P	72		Q	95		G	
[illegible]	[illegible]		P	46		S	74		P	96		G	

Figure 46

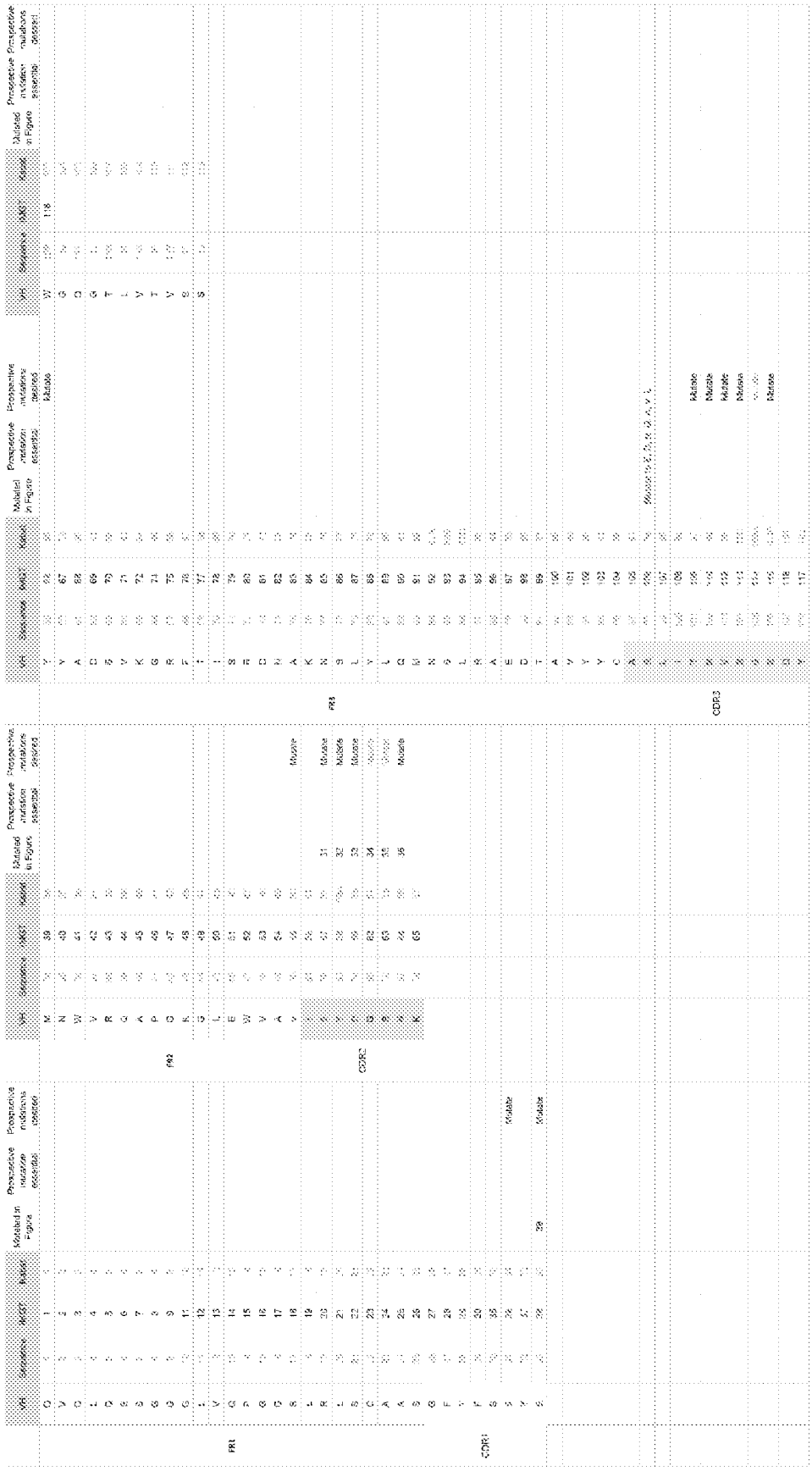


Figure 47