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(54) Title: COMPOSITIONS AND METHODS FOR DETECTION AND TREATMENT OF CORONAVIRUS INFECTION

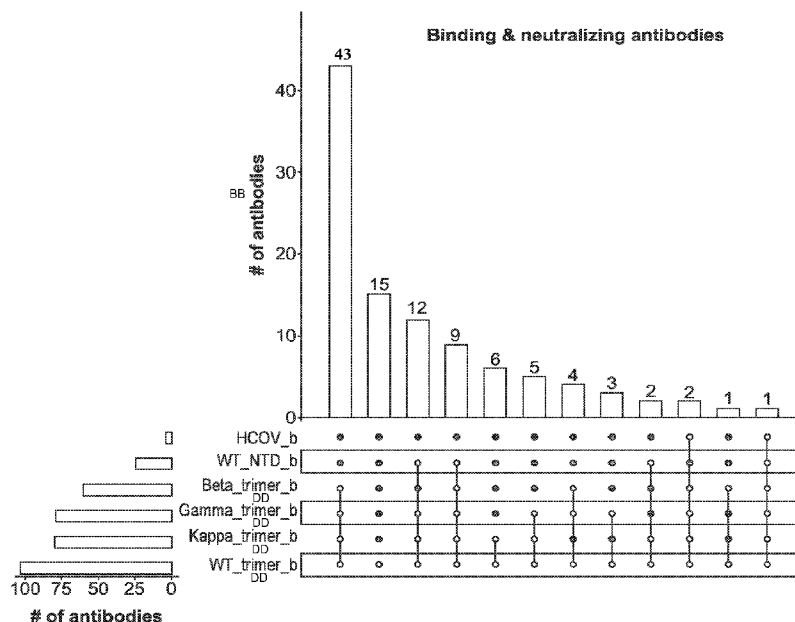


FIG. 26

(57) Abstract: The present disclosure relates generally to compositions comprising antigen-binding molecules that bind to a severe acute respiratory syndrome coronavirus (SARS-CoV), and/or comprising nucleic acids that encode such antigen-binding molecules, as well as therapeutic and diagnostic methods for using such compositions.

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COMPOSITIONS AND METHODS FOR DETECTION AND TREATMENT OF CORONAVIRUS INFECTION

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This application claims the benefit of and priority to U.S. Provisional Patent Application Serial Nos. 63/320,491, filed on March 16, 2022; 63/326,144, filed on March 31, 2022; and 63/377,521, filed on September 28, 2022. The disclosures of the above-referenced applications are herein expressly incorporated by reference in their entireties, including any drawings.

FIELD

[0002] The present disclosure relates generally to compositions comprising antigen-binding molecules that bind to a severe acute respiratory syndrome coronavirus (SARS-CoV), and/or comprising nucleic acids that encode such antigen-binding molecules, as well as therapeutic and diagnostic methods for using such compositions.

INCORPORATION OF THE SEQUENCE LISTING

[0003] This application contains a Sequence Listing, which is hereby incorporated herein by reference in its entirety. The accompanying Sequence Listing, named “057862-610001WO_SequenceListing_ST26.xml,” was created on March 7, 2023 and is 9.6 MB.

BACKGROUND

[0004] In the past decades, three novel coronaviruses (CoVs) have crossed from zoonotic hosts into humans and acquired the ability to spread by human-to-human transmission. Two of these pandemic CoVs, severe acute respiratory syndrome (SARS)-CoV in 2002 and Middle East respiratory syndrome (MERS)-CoV in 2012, caused relatively small outbreaks of human respiratory disease. The third, SARS-CoV-2 is a recently identified emerging coronavirus causing an acute respiratory distress syndrome known as COVID-19 that is similar to severe acute respiratory syndrome (SARS) caused by the closely related SARS-CoV. To date, SARS-CoV-2 is continuing its spread across the world with nearly 460 million confirmed cases in over 200 countries and more than six million deaths. While current vaccines still provide some protection against circulating SARS-CoV-2 variants, the ongoing emergence of increasingly diverse variants and the possibility of future spillovers of novel CoVs make pan-CoV vaccine

development a public health issue of the highest priority.

[0005] In view of the continuing threat to human health, there is an urgent need for preventive and therapeutic antiviral therapies for SARS-CoV-2 control. Because this virus uses its spike glycoprotein for interaction with the cellular receptor ACE2 and the serine protease TMPRSS2 for entry into a target cell, this spike (S) protein represents a target for antibody therapeutics. In particular, the immunogenic property of the S protein, including its ability to induce neutralizing antibodies and its essential role in viral attachment and fusion, make it a promising target for developing effective immunotherapy against SARS-CoV infection. For example, fully human antibodies that specifically bind to the SARS-CoV-2 spike protein with high affinity and that inhibit virus infectivity could be important in the prevention and treatment of coronavirus infection.

[0006] It has been reported that during an outbreak, the SARS-CoV can mutate and exhibit antigenic variation. In fact, sequence analysis indicated that the clinical isolates could be divided into early, middle, and late isolates. The significance of this is demonstrated in the ability of later isolates to escape neutralization by a monoclonal antibody that effectively neutralized an earlier isolate. Therefore, it is important to produce neutralizing antibodies that are effective against a wide range of clinical isolates with antigenic diversity. Because of the potential evolution of antigenic variants, an effective passive therapy against SARS-CoV will likely contain a cocktail of neutralizing antibodies that target different epitopes and/or steps in the entry process, such as blocking receptor binding and fusion.

[0007] Accordingly, there remains an urgent need for potent, broad-spectrum antibody therapeutics for use in preventing and/or treating SARS- CoV infection. In particular, there is a need for antibodies with specific binding affinity to the SARS-CoV-2 spike protein, including neutralizing therapeutic antibodies and their use for treating or preventing coronavirus infection. Furthermore, there is a continuing need for formulations and methods for delivering a functional antibody therapeutic or for expressing a functional form of an antibody therapeutic within a subject who suffers from coronavirus infection. The present disclosure addresses this need, in part, by providing anti-SARS-CoV-2 S antibodies and methods of using the same in the prevention, diagnosis, prognosis, monitoring, evaluation, and/or treatment of viral infections.

SUMMARY

[0008] This present disclosure relates generally to compositions, including without limitation lipid-based nanoparticle (LNP) formulations, comprising an antigen-binding molecule or a combination of two, three, four, or more antigen-binding molecules, *e.g.*, antigen-binding polypeptides, antibodies, and antigen-binding fragments that specifically bind to a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), nucleic acids encoding such antigen-binding molecules, and/or combinations thereof. Also provided are methods for manufacturing such LNP compositions, therapeutic and diagnostic methods using the compositions described herein, as well as kits for preventing, treating, diagnosing, or imaging a virus, a disease, a disorder, and/or a health condition using the compositions described herein.

[0009] In one aspect of the disclosure, provided herein are compositions including a nucleic acid encoding an antigen-binding molecule, or an antigen-binding fragment thereof, that binds to a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), wherein the antigen-binding molecule or antigen-binding fragment thereof includes all six complementary determining regions (CDRs) from an antibody of the disclosure. In certain embodiments, the compositions of the invention are formulated in any formulation suitable for a therapeutic delivery of compositions comprising nucleic acids and/or proteins. In certain embodiments, the composition is formulated in a lipid-based nanoparticle (LNP). In some embodiments, the antigen-binding molecule, an antigen-binding fragment includes all six CDRs from an antibody identified in Tables 1A-1B. In some embodiments, the antigen-binding molecule or antigen-binding fragment is any one of TXG-0001, TXG-0002, TXG-0004, TXG-0005, TXG-0006, TXG-0008, TXG-0009, TXG-0048, TXG-0057, TXG-0060, TXG-0063, TXG-0066, TXG-0070, TXG-0072, TXG-0074, TXG-0076, TXG-0078, TXG-0080, TXG-0081, TXG-0087, TXG-0088, TXG-0091, TXG-0094, TXG-0098, TXG-0099, TXG-0100, TXG-0104, TXG-0109, TXG-0112, TXG-0114, TXG-0115, TXG-0120, TXG-0129, TXG-0136, TXG-0141, TXG-0144, TXG-0153, TXG-0154, TXG-0170, TXG-0173, TXG-0174, TXG-0175, TXG-0180, TXG-0181, TXG-0183, TXG-0187, TXG-0189, TXG-0192, TXG-0197, TXG-0198, TXG-0200, TXG-0201, TXG-0202, TXG-0203, TXG-0204, TXG-0209, TXG-0210, TXG-0228, or TXG-0230, and wherein optionally the composition is formulated in a lipid-based nanoparticle (LNP).

[0010] In one aspect, provided herein are compositions including an antigen-binding molecule, or an antigen-binding fragment thereof, that binds to a SARS-CoV-2, wherein the

antigen-binding molecule or antigen-binding fragment thereof includes all six CDRs from an antibody of the disclosure. In certain embodiments, the compositions of the invention are formulated in any formulation suitable for a therapeutic delivery of compositions comprising nucleic acids and/or proteins. In certain embodiments, the composition is formulated in a lipid-based nanoparticle (LNP). In some embodiments, the antigen-binding molecule, an antigen-binding fragment includes all six CDRs from an antibody identified in Tables 1A-1B. In some embodiments, the antigen-binding molecule, an antigen-binding fragment is any one of TXG-0001, TXG-0002, TXG-0004, TXG-0005, TXG-0006, TXG-0008, TXG-0009, TXG-0048, TXG-0057, TXG-0060, TXG-0063, TXG-0066, TXG-0070, TXG-0072, TXG-0074, TXG-0076, TXG-0078, TXG-0080, TXG-0081, TXG-0087, TXG-0088, TXG-0091, TXG-0094, TXG-0098, TXG-0099, TXG-0100, TXG-0104, TXG-0109, TXG-0112, TXG-0114, TXG-0115, TXG-0120, TXG-0129, TXG-0136, TXG-0141, TXG-0144, TXG-0153, TXG-0154, TXG-0170, TXG-0173, TXG-0174, TXG-0175, TXG-0180, TXG-0181, TXG-0183, TXG-0187, TXG-0189, TXG-0192, TXG-0197, TXG-0198, TXG-0200, TXG-0201, TXG-0202, TXG-0203, TXG-0204, TXG-0209, TXG-0210, TXG-0228, or TXG-0230, and wherein optionally the composition is formulated in a lipid-based nanoparticle (LNP).

[0011] Non-limiting exemplary embodiments of the compositions the disclosure can include one or more of the following features. In some embodiments, the antigen-binding molecule or antigen-binding fragment thereof includes all six complementary determining regions (CDRs) from an antibody being any one of TXG-0001, TXG-0002, TXG-0004, TXG-0005, TXG-0006, TXG-0008, TXG-0009, TXG-0048, TXG-0070, TXG-0078, TXG-0081, TXG-0087, TXG-0114, TXG-0115, TXG-0154, TXG-0174, TXG-0175, TXG-0180, TXG-0192, or TXG-0203. In some embodiments, the antigen-binding molecule or antigen-binding fragment thereof has a binding affinity for a spike (S) protein of SARS-CoV-2.

[0012] In some embodiments, the nucleic acid encoding an antigen-binding molecule, or an antigen-binding fragment thereof, is a DNA molecule or an RNA molecule. In some embodiments, the RNA molecule is a messenger RNA (mRNA) molecule. In some embodiments, the nucleic acid includes one or more modified nucleosides. In some embodiments, the one or more modified nucleosides includes pyridin-4-one ribonucleoside, 5-aza-uridine, 2-thio- 5-aza-uridine, 2-thiouridine, 4-thio-pseudouridine, 2-thio-pseudouridine, 5-hydroxyuridine, 3-methyluridine, 5-carboxymethyl-uridine, 1-carboxymethyl- pseudouridine, 5-

propynyl-uridine, 1-propynyl-pseudouridine, 5-aurinomethyluridine, 1-aurinomethyl-pseudouridine, 5-aurinomethyl-2-thio-uridine, 1-aurinomethyl-4-thio-uridine, 5-methyl-uridine, 1-methyl-pseudouridine, 4-thio-1-methyl-pseudouridine, 2-thio-1-methyl-pseudouridine, 1-methyl-1-deaza-pseudouridine, 2-thio-1-methyl-1-deaza-pseudouridine, dihydrouridine, dihydropseudouridine, 2-thio-dihydrouridine, 2-thio-dihydropseudouridine, 2-methoxyuridine, 2-methoxy-4-thio-uridine, 4-methoxy-pseudouridine, 4-methoxy-2-thio-pseudouridine, 5-aza-cytidine, pseudoisocytidine, 3-methyl-cytidine, N4-acetylcytidine, 5-formylcytidine, N4-methylcytidine, 5-hydroxymethylcytidine, 1-methyl-pseudoisocytidine, pyrrolo-cytidine, pyrrolo-pseudoisocytidine, 2-thio-cytidine, 2-thio-5-methyl-cytidine, 4-thio-pseudoisocytidine, 4-thio-1-methyl-pseudoisocytidine, 4-thio-1-methyl-1-deaza-pseudoisocytidine, 1-methyl-1-deaza-pseudoisocytidine, zebularine, 5-aza-zebularine, 5-methyl-zebularine, 5-aza-2-thio-zebularine, 2-thio-zebularine, 2-methoxy-cytidine, 2-methoxy-5-methyl-cytidine, 4-methoxy-pseudoisocytidine, 4-methoxy-1-methyl-pseudoisocytidine, 2-aminopurine, 2,6-diaminopurine, 7-deaza-adenine, 7-deaza-8-aza-adenine, 7-deaza-2-aminopurine, 7-deaza-8-aza-2-aminopurine, 7-deaza-2,6-diaminopurine, 7-deaza-8-aza-2,6-diaminopurine, 1-methyladenosine, N6-methyladenosine, N6-isopentenyladenosine, N6-(cis-hydroxyisopentenyl)adenosine, 2-methylthio-N6-(cis-hydroxyisopentenyl)adenosine, N6-glycinylicarbamoyladenosine, N6-threonylicarbamoyladenosine, 2-methylthio-N6-threonylicarbamoyladenosine, N6,N6-dimethyladenosine, 7-methyladenine, 2-methylthio-adenine, and 2-methoxy-adenine, inosine, 1-methyl-inosine, wyosine, wybutosine, 7-deaza-guanosine, 7-deaza-8-aza-guanosine, 6-thio-guanosine, 6-thio-7-deaza-guanosine, 6-thio-7-deaza-8-aza-guanosine, 7-methyl-guanosine, 6-thio-7-methyl-guanosine, 7-methylinosine, 6-methoxy-guanosine, 1-methyl-guanosine, N2-methyl-guanosine, N2,N2-dimethyl-guanosine, 8-oxo-guanosine, 7-methyl-8-oxo-guanosine, 1-methyl-6-thio-guanosine, N2-methyl-6-thio-guanosine, and N2,N2-dimethyl-6-thio-guanosine, and combinations thereof.

[0013] In some embodiments, the lipid nanoparticle includes an ionizable cationic lipid, a cationic lipid, an anionic lipid, a neutral lipid, a sterol, a PEG-modified lipid, or a combination of any thereof. In some embodiments, the lipid nanoparticle further includes phosphatidyl choline. In some embodiments, the sterol is cholesterol. In some embodiments, the mean ratio of lipid to nucleic acid (wt/wt) ranges from about 2:1 to about 100:1. In some embodiments, the LNP has a mean diameter ranging from about 10 nm to about 200 nm.

[0014] In some embodiments, the antigen-binding molecule or antigen-binding fragment has a binding affinity for the spike (S) protein of two, three, four, five or more variants of SARS-CoV-2. In some embodiments, the SARS-CoV-2 variants are any one of alpha, beta, delta, gamma, kappa, omicron, or a combination thereof. In some embodiments, at least one of the SARS-CoV-2 variants is omicron. In some embodiments, the antigen-binding molecule or antigen-binding fragment further has a binding affinity for one or more human coronaviruses (HCoVs) that is any one of HCoV-229E, HCoV-OC43, HCoV-HKU1, or a combination thereof, or a variant of any thereof. In some embodiments, the one or more HCoVs is HCoV-229E, HCoV-OC43, or a combination thereof.

[0015] In some embodiments, the antigen-binding molecule or antigen-binding fragment has a sub-nanomolar binding affinity for a spike (S) protein of SARS-CoV-2, a fragment thereof, or a multimeric form thereof. In some embodiments, the antigen-binding molecule or antigen-binding fragment has a sub-picomolar binding affinity for a SARS-CoV-2 S protein, a fragment thereof, or a multimeric form thereof. In some embodiments, the antigen-binding molecule or antigen-binding fragment thereof has a binding affinity for S1 subunit of the SARS-CoV-2 S protein. In some embodiments, the antigen-binding molecule or antigen-binding fragment thereof has a binding affinity for a receptor binding domain (RBD) and/or a N-terminal domain (NTD) of the S1 subunit. In some embodiments, the antigen-binding molecule or antigen-binding fragment has a binding affinity to the NTD of the S1 subunit. In some embodiments, the antigen-binding molecule or antigen-binding fragment thereof has binding affinity for a trimeric form of the SARS-CoV-2 S protein.

[0016] In some embodiments, the antigen-binding molecule or antigen-binding fragment thereof comprises all framework regions (FWRs) from the antibody being any one identified in Tables 1A-1B. In some embodiments, the antigen-binding molecule or antigen-binding fragment thereof includes all FWRs from the antibody being any one of TXG-0001, TXG-0002, TXG-0004, TXG-0005, TXG-0006, TXG-0008, TXG-0009, TXG-0048, TXG-0057, TXG-0060, TXG-0063, TXG-0066, TXG-0070, TXG-0072, TXG-0074, TXG-0076, TXG-0078, TXG-0080, TXG-0081, TXG-0087, TXG-0088, TXG-0091, TXG-0094, TXG-0098, TXG-0099, TXG-0100, TXG-0104, TXG-0109, TXG-0112, TXG-0114, TXG-0115, TXG-0120, TXG-0129, TXG-0136, TXG-0141, TXG-0144, TXG-0153, TXG-0154, TXG-0170, TXG-0173, TXG-0174, TXG-0175, TXG-0180, TXG-0181, TXG-0183, TXG-0187, TXG-0189, TXG-0192, TXG-0197, TXG-0198,

TXG-0200, TXG-0201, TXG-0202, TXG-0203, TXG-0204, TXG-0209, TXG-0210, TXG-0228, or TXG-0230.

[0017] In some embodiments, the antigen-binding molecule or antigen-binding fragment further includes a heavy chain constant region. In some embodiments, the heavy chain constant region is an IgA, IgD, IgE, IgG, or IgM heavy chain constant region. In some embodiments, the heavy chain constant region is of the same isotype and subclass as the antibody identified in Tables 1A-1B. In some embodiments, the heavy chain constant region is of the same isotype and subclass as the antibody being any one of TXG-0001, TXG-0002, TXG-0004, TXG-0005, TXG-0006, TXG-0008, TXG-0009, TXG-0048, TXG-0057, TXG-0060, TXG-0063, TXG-0066, TXG-0070, TXG-0072, TXG-0074, TXG-0076, TXG-0078, TXG-0080, TXG-0081, TXG-0087, TXG-0088, TXG-0091, TXG-0094, TXG-0098, TXG-0099, TXG-0100, TXG-0104, TXG-0109, TXG-0112, TXG-0114, TXG-0115, TXG-0120, TXG-0129, TXG-0136, TXG-0141, TXG-0144, TXG-0153, TXG-0154, TXG-0170, TXG-0173, TXG-0174, TXG-0175, TXG-0180, TXG-0181, TXG-0183, TXG-0187, TXG-0189, TXG-0192, TXG-0197, TXG-0198, TXG-0200, TXG-0201, TXG-0202, TXG-0203, TXG-0204, TXG-0209, TXG-0210, TXG-0228, or TXG-0230. In some embodiments, the antigen-binding molecule or antigen-binding fragment further includes a light chain constant region. In some embodiments, the light chain constant region is a kappa type or lambda type light chain constant region. In some embodiments, the light chain constant region is the same light chain constant region of the antibody identified in Tables 1A-1B. In some embodiments, the light chain constant region is the same light chain constant region of the antibody being any one of TXG-0001, TXG-0002, TXG-0004, TXG-0005, TXG-0006, TXG-0008, TXG-0009, TXG-0048, TXG-0057, TXG-0060, TXG-0063, TXG-0066, TXG-0070, TXG-0072, TXG-0074, TXG-0076, TXG-0078, TXG-0080, TXG-0081, TXG-0087, TXG-0088, TXG-0091, TXG-0094, TXG-0098, TXG-0099, TXG-0100, TXG-0104, TXG-0109, TXG-0112, TXG-0114, TXG-0115, TXG-0120, TXG-0129, TXG-0136, TXG-0141, TXG-0144, TXG-0153, TXG-0154, TXG-0170, TXG-0173, TXG-0174, TXG-0175, TXG-0180, TXG-0181, TXG-0183, TXG-0187, TXG-0189, TXG-0192, TXG-0197, TXG-0198, TXG-0200, TXG-0201, TXG-0202, TXG-0203, TXG-0204, TXG-0209, TXG-0210, TXG-0228, or TXG-0230.

[0018] In one aspect, provided herein are methods for reducing binding of a spike (S) protein of a coronavirus (CoV-S) to a cell in a subject and/or reducing entry of the coronavirus into a cell of a subject, wherein the methods include administering (e.g., therapeutically or

prophylactically) to the subject: (a) an antigen-binding molecule, or an antigen-binding fragment thereof, that binds to a spike (S) protein of SARS-CoV-2, wherein the antigen-binding molecule or antigen-binding fragment thereof includes all six CDRs from an antibody being any one of TXG-0001, TXG-0002, TXG-0004, TXG-0005, TXG-0006, TXG-0008, TXG-0009, TXG-0048, TXG-0057, TXG-0060, TXG-0063, TXG-0066, TXG-0070, TXG-0072, TXG-0074, TXG-0076, TXG-0078, TXG-0080, TXG-0081, TXG-0087, TXG-0088, TXG-0091, TXG-0094, TXG-0098, TXG-0099, TXG-0100, TXG-0104, TXG-0109, TXG-0112, TXG-0114, TXG-0115, TXG-0120, TXG-0129, TXG-0136, TXG-0141, TXG-0144, TXG-0153, TXG-0154, TXG-0170, TXG-0173, TXG-0174, TXG-0175, TXG-0180, TXG-0181, TXG-0183, TXG-0187, TXG-0189, TXG-0192, TXG-0197, TXG-0198, TXG-0200, TXG-0201, TXG-0202, TXG-0203, TXG-0204, TXG-0209, TXG-0210, TXG-0228, or TXG-0230, and wherein optionally the antigen-binding molecule or antigen-binding fragment thereof has a binding affinity for the spike (S) protein of two, three, four, five or more variants of SARS-CoV-2, and/or for one or more human coronaviruses (HCoVs) that is any one of HCoV-229E, HCoV-OC43, HCoV-HKU1, or a combination thereof, or a variant of any thereof; and/or (b) a nucleic acid encoding the antigen-binding molecule or antigen-binding fragment thereof of (a). In some embodiments, the one or more HCoVs is HCoV-229E, HCoV-OC43, or a combination thereof.

[0019] In another aspect, provided herein are methods for inducing an immune response in a subject, wherein the methods include administering (e.g., therapeutically or prophylactically) to the subject a composition as disclosed herein.

[0020] In another aspect, provided herein are methods for aiding in the neutralization of two, three, four, five or more variants of SARS-CoV-2, wherein said aiding includes providing: (a) an antigen-binding molecule, or an antigen-binding fragment thereof, that binds to a spike (S) protein of SARS-CoV-2, wherein the antigen-binding molecule or antigen-binding fragment thereof includes all six CDRs from an antibody being any one of TXG-0001, TXG-0002, TXG-0004, TXG-0005, TXG-0006, TXG-0008, TXG-0009, TXG-0048, TXG-0057, TXG-0060, TXG-0063, TXG-0066, TXG-0070, TXG-0072, TXG-0074, TXG-0076, TXG-0078, TXG-0080, TXG-0081, TXG-0087, TXG-0088, TXG-0091, TXG-0094, TXG-0098, TXG-0099, TXG-0100, TXG-0104, TXG-0109, TXG-0112, TXG-0114, TXG-0115, TXG-0120, TXG-0129, TXG-0136, TXG-0141, TXG-0144, TXG-0153, TXG-0154, TXG-0170, TXG-0173, TXG-0174, TXG-0175, TXG-0180, TXG-0181, TXG-0183, TXG-0187, TXG-0189, TXG-0192, TXG-0197, TXG-0198,

TXG-0200, TXG-0201, TXG-0202, TXG-0203, TXG-0204, TXG-0209, TXG-0210, TXG-0228, or TXG-0230; and/or (b) a nucleic acid encoding the antigen-binding molecule or antigen-binding fragment thereof of (a).

[0021] In another aspect, provided herein are methods for aiding in the neutralization of two, three, four, five or more variants of SARS-CoV-2, wherein said aiding includes providing a composition comprising a nucleic acid encoding an antigen-binding molecule, or an antigen-binding fragment thereof, that binds to a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), wherein the antigen-binding molecule is any one of TXG-0001, TXG-0002, TXG-0004, TXG-0005, TXG-0006, TXG-0008, TXG-0009, TXG-0048, TXG-0057, TXG-0060, TXG-0063, TXG-0066, TXG-0070, TXG-0072, TXG-0074, TXG-0076, TXG-0078, TXG-0080, TXG-0081, TXG-0087, TXG-0088, TXG-0091, TXG-0094, TXG-0098, TXG-0099, TXG-0100, TXG-0104, TXG-0109, TXG-0112, TXG-0114, TXG-0115, TXG-0120, TXG-0129, TXG-0136, TXG-0141, TXG-0144, TXG-0153, TXG-0154, TXG-0170, TXG-0173, TXG-0174, TXG-0175, TXG-0180, TXG-0181, TXG-0183, TXG-0187, TXG-0189, TXG-0192, TXG-0197, TXG-0198, TXG-0200, TXG-0201, TXG-0202, TXG-0203, TXG-0204, TXG-0209, TXG-0210, TXG-0228, or TXG-0230.

[0022] In yet another aspect, provided herein are methods for reducing a viral load of two, three, four, five or more variants of SARS-CoV-2, wherein the method includes providing: (a) an antigen-binding molecule, or an antigen-binding fragment thereof, that binds to a spike (S) protein of SARS-CoV-2, wherein the antigen-binding molecule or antigen-binding fragment thereof includes all six CDRs from an antibody being any one of TXG-0001, TXG-0002, TXG-0004, TXG-0005, TXG-0006, TXG-0008, TXG-0009, TXG-0048, TXG-0057, TXG-0060, TXG-0063, TXG-0066, TXG-0070, TXG-0072, TXG-0074, TXG-0076, TXG-0078, TXG-0080, TXG-0081, TXG-0087, TXG-0088, TXG-0091, TXG-0094, TXG-0098, TXG-0099, TXG-0100, TXG-0104, TXG-0109, TXG-0112, TXG-0114, TXG-0115, TXG-0120, TXG-0129, TXG-0136, TXG-0141, TXG-0144, TXG-0153, TXG-0154, TXG-0170, TXG-0173, TXG-0174, TXG-0175, TXG-0180, TXG-0181, TXG-0183, TXG-0187, TXG-0189, TXG-0192, TXG-0197, TXG-0198, TXG-0200, TXG-0201, TXG-0202, TXG-0203, TXG-0204, TXG-0209, TXG-0210, TXG-0228, or TXG-0230; and/or (b) a nucleic acid encoding the antigen-binding molecule or antigen-binding fragment thereof of (a).

[0023] In another aspect, provided herein are methods for aiding in the neutralization of

two, three, four, five or more variants of SARS-CoV-2, wherein said aiding includes providing a composition as disclosed herein. In another aspect, provided herein are methods for reducing the viral load of two, three, four, five or more variants of SARS-CoV-2, wherein the method includes providing a composition as disclosed herein.

[0024] Non-limiting exemplary embodiments of the methods as described herein can include one or more of the following features. In some embodiments, the antigen-binding molecule or antigen-binding fragment thereof includes all six complementary determining regions (CDRs) from an antibody being any one of TXG-0001, TXG-0002, TXG-0004, TXG-0005, TXG-0006, TXG-0008, TXG-0009, TXG-0048, TXG-0070, TXG-0078, TXG-0081, TXG-0087, TXG-0114, TXG-0115, TXG-0154, TXG-0174, TXG-0175, TXG-0180, TXG-0192, or TXG-0203. In some embodiments, the subject is suspected of being infected with a coronavirus, has been diagnosed of having or at risk of having a coronavirus infection, has been infected with a coronavirus, has been vaccinated, or has been recovered from a coronavirus infection. In some embodiments, the subject is an immunocompromised subject or has been previously treated for coronavirus infection. In some embodiments, the subject is a mammalian subject. In some embodiments, the mammalian subject is a human subject. In some embodiments, the coronavirus belongs to a genus being any one of alphacoronavirus, betacoronavirus, gammacoronavirus, or deltacoronavirus. In some embodiments, the coronavirus belongs to a betacoronavirus lineage is any one of lineage A, lineage B, lineage C, or lineage D. In some embodiments, the coronavirus is human coronavirus 229E, OC43, HKU1, NL63, SARS-CoV-1, SARS-CoV-2, MERS-CoV, or a variant of any thereof. In some embodiments, the coronavirus is SARS-CoV-2 or a variant thereof being any one of alpha, beta, delta, gamma, kappa, omicron, or a combination thereof. In some embodiments, one of the two, three, four, five or more variants of SARS-CoV-2 is omicron. In some embodiments, one of the one or more of the HCoV is HCoV-229E or HCoV-OC43; and HCoV-HKU1 is HCoV-229E or HCoV-OC43.

[0025] In some embodiments of the methods disclosed herein, the composition is therapeutically or prophylactically administered at a total dose of about 0.1 mg/kg to about 40 mg/kg. Dosing can be single dosage or cumulative (serial dosing), and can be readily determined by one skilled in the art. For example, treatment of a viral infection can comprise a one-time administration of an effective dose of a pharmaceutical composition disclosed herein. Alternatively, treatment of viral infection may include multiple administrations of an effective

dose of a pharmaceutical composition carried out over a range of time periods, such as, e.g., once daily, twice daily, trice daily, once every few days, or once weekly. The timing of administration can vary from individual to individual, depending upon such factors as the severity of an individual's symptoms and/or viral load. For example, an effective dose of a pharmaceutical composition disclosed herein can be administered to an individual once daily for an indefinite period of time, or until the individual no longer requires therapy. A person of ordinary skill in the art will recognize that the condition of the individual can be monitored throughout the course of treatment and that the effective amount of a pharmaceutical composition disclosed herein that is administered can be adjusted accordingly.

[0026] In some embodiments, the composition is therapeutically or prophylactically administered on a defined schedule such as three times a day, twice a day, once a day, every other day, every third day, weekly, biweekly, every three weeks, every four weeks, and monthly. In some embodiments, the total dose is administered by multiple administrations. In some embodiments, the multiple administrations occur on a defined schedule such as three times a day, twice a day, once a day, every other day, every third day, weekly, biweekly, every three weeks, every four weeks, and monthly. The compositions of the disclosure may be administered parenterally. The compositions may be administered directly into the blood stream, into tissue, into muscle, or into an internal organ. In some embodiments, administration may be systemic, e.g., to injection or infusion. In some embodiments, administration may be local. Suitable means for administration include intravenous, intraarterial, intrathecal, intraventricular, intraurethral, intrasternal, intracranial, subretinal, intravitreal, intra-anterior chamber, intramuscular, intrasynovial and subcutaneous. Suitable devices for administration include needle (including microneedle) injectors, needle-free injectors and infusion techniques. In some embodiments, the composition is administered by intradermal, intravenous, intramuscular, subcutaneous injection, and/or local administration. In some embodiments, the composition is administered intradermal or intramuscular injection.

[0027] In some embodiments, the administered composition reduces binding of the CoV-S protein to and/or reduces coronavirus entry into a cell of the subject. In some embodiments, the administered composition neutralizes against the coronavirus. In some embodiments, the administered composition treats, prevents, or ameliorates a health condition associated with a coronavirus infection in the subject. In some embodiments, the administered composition

reduces the viral load in the subject as compared to a reference subject who has not been administered with the composition. In some embodiments, the methods further include administering to the subject an additional therapy. In some embodiments, the additional therapy includes an anti-viral agent being any one of interferon, Remdesivir, Baricitinib, Azithromycin, Nirmatrelvir, Ritonavir, Molnupiravir, Casirivimab, Imdevimab, Bamlanivimab, Etesevimab, Sotrovimab, Cilgavimab, Bebtelovimab, Tocilizumab, Tixagevimab, or a combination thereof.

[0028] In another aspect, provided herein are methods for detecting the presence of SARS-CoV-2 S protein and/or SARS-CoV-2 in a biological sample, the method comprising contacting a biological sample with an antigen-binding molecule having an amino acid sequence being any one of TXG-0001, TXG-0002, TXG-0004, TXG-0005, TXG-0006, TXG-0008, TXG-0009, TXG-0048, TXG-0057, TXG-0060, TXG-0063, TXG-0066, TXG-0070, TXG-0072, TXG-0074, TXG-0076, TXG-0078, TXG-0080, TXG-0081, TXG-0087, TXG-0088, TXG-0091, TXG-0094, TXG-0098, TXG-0099, TXG-0100, TXG-0104, TXG-0109, TXG-0112, TXG-0114, TXG-0115, TXG-0120, TXG-0129, TXG-0136, TXG-0141, TXG-0144, TXG-0153, TXG-0154, TXG-0170, TXG-0173, TXG-0174, TXG-0175, TXG-0180, TXG-0181, TXG-0183, TXG-0187, TXG-0189, TXG-0192, TXG-0197, TXG-0198, TXG-0200, TXG-0201, TXG-0202, TXG-0203, TXG-0204, TXG-0209, TXG-0210, TXG-0228, or TXG-0230, or an antigen-binding fragment of any thereof, wherein optionally the antigen-binding molecule or antigen-binding fragment has a binding affinity for the omicron variant of SARS-CoV-2 or one or more endemic HCoV-229E, HCoV-OC43, HCoV-NL63, HCoV-HKU1, or a combination thereof. In some embodiments, the antigen-binding molecule or antigen-binding fragment thereof includes all six complementary determining regions (CDRs) from an antibody being any one of TXG-0001, TXG-0002, TXG-0004, TXG-0005, TXG-0006, TXG-0008, TXG-0009, TXG-0048, TXG-0070, TXG-0078, TXG-0081, TXG-0087, TXG-0114, TXG-0115, TXG-0154, TXG-0174, TXG-0175, TXG-0180, TXG-0192, or TXG-0203.

[0029] Non-limiting exemplary embodiments of the detection methods as described herein can include one or more of the following features. In some embodiments, the biological sample is from a subject suspected of being infected with a coronavirus, has been diagnosed of having or at risk of having a coronavirus infection, has been infected with a coronavirus, has been vaccinated, or has been recovered from a coronavirus infection. In some embodiments, the methods further include detecting a complex formed between the antigen-binding molecule or

antigen-binding fragment thereof with a SARS-CoV-2 S antigen. In some embodiments, said detecting includes visualizing the complex by using an enzyme, a secondary antibody, a colored dye, a fluorescent dye, a chemiluminescent molecule, a molecule containing a radioactive atom, or a molecule containing a heavy metal.

[0030] In another aspect, provided herein are methods for aiding in the diagnosis, prognosis, monitoring, and/or evaluation of a coronavirus infection and/or treatment thereof in a subject, wherein said aiding includes providing: (a) an antigen-binding molecule having an amino acid sequence being any one of TXG-0001, TXG-0002, TXG-0004, TXG-0005, TXG-0006, TXG-0008, TXG-0009, TXG-0048, TXG-0057, TXG-0060, TXG-0063, TXG-0066, TXG-0070, TXG-0072, TXG-0074, TXG-0076, TXG-0078, TXG-0080, TXG-0081, TXG-0087, TXG-0088, TXG-0091, TXG-0094, TXG-0098, TXG-0099, TXG-0100, TXG-0104, TXG-0109, TXG-0112, TXG-0114, TXG-0115, TXG-0120, TXG-0129, TXG-0136, TXG-0141, TXG-0144, TXG-0153, TXG-0154, TXG-0170, TXG-0173, TXG-0174, TXG-0175, TXG-0180, TXG-0181, TXG-0183, TXG-0187, TXG-0189, TXG-0192, TXG-0197, TXG-0198, TXG-0200, TXG-0201, TXG-0202, TXG-0203, TXG-0204, TXG-0209, TXG-0210, TXG-0228, or TXG-0230, or an antigen-binding fragment of any thereof, wherein optionally the antigen-binding molecule or antigen-binding fragment thereof has a binding affinity for the omicron variant of SARS-CoV-2 or one or more common HCoVs that is any one of 229E, OC43, HKU1, or a combination thereof.

[0031] In another aspect, provided herein are kits for preventing, treating, diagnosing, or imaging a virus, a disease, a disorder, and/or health condition, the kits include (a) an antigen-binding molecule, or an antigen-binding fragment of any thereof, including all 6 CDRs from an antibody being any one of TXG-0001, TXG-0002, TXG-0004, TXG-0005, TXG-0006, TXG-0008, TXG-0009, TXG-0048, TXG-0057, TXG-0060, TXG-0063, TXG-0066, TXG-0070, TXG-0072, TXG-0074, TXG-0076, TXG-0078, TXG-0080, TXG-0081, TXG-0087, TXG-0088, TXG-0091, TXG-0094, TXG-0098, TXG-0099, TXG-0100, TXG-0104, TXG-0109, TXG-0112, TXG-0114, TXG-0115, TXG-0120, TXG-0129, TXG-0136, TXG-0141, TXG-0144, TXG-0153, TXG-0154, TXG-0170, TXG-0173, TXG-0174, TXG-0175, TXG-0180, TXG-0181, TXG-0183, TXG-0187, TXG-0189, TXG-0192, TXG-0197, TXG-0198, TXG-0200, TXG-0201, TXG-0202, TXG-0203, TXG-0204, TXG-0209, TXG-0210, TXG-0228, or TXG-0230, wherein optionally the antigen-binding molecule or antigen-binding fragment thereof has a binding affinity for the

omicron variant of SARS-CoV-2 or one or more common HCoV-229E, OC43, HKU1, or a combination thereof; and/or (b) a nucleic acid encoding the antigen-binding molecule or antigen-binding fragment thereof of (a); and instructions for performing a method of preventing, treating, diagnosing, or imaging a virus, a disease, a disorder, and/or health condition as disclosed herein.

[0032] In another aspect, provided herein are methods of manufacturing a pharmaceutical composition, the methods including: (a) admixing a lipid solution with an aqueous buffer solution including a buffer agent thereby forming a lipid nanoparticle solution including a lipid nanoparticle (LNP); and (b) adding to the lipid nanoparticle: (i) an antigen-binding molecule, or an antigen-binding fragment include any thereof, including all 6 CDRs from an antibody being any one of TXG-0001, TXG-0002, TXG-0004, TXG-0005, TXG-0006, TXG-0008, TXG-0009, TXG-0048, TXG-0057, TXG-0060, TXG-0063, TXG-0066, TXG-0070, TXG-0072, TXG-0074, TXG-0076, TXG-0078, TXG-0080, TXG-0081, TXG-0087, TXG-0088, TXG-0091, TXG-0094, TXG-0098, TXG-0099, TXG-0100, TXG-0104, TXG-0109, TXG-0112, TXG-0114, TXG-0115, TXG-0120, TXG-0129, TXG-0136, TXG-0141, TXG-0144, TXG-0153, TXG-0154, TXG-0170, TXG-0173, TXG-0174, TXG-0175, TXG-0180, TXG-0181, TXG-0183, TXG-0187, TXG-0189, TXG-0192, TXG-0197, TXG-0198, TXG-0200, TXG-0201, TXG-0202, TXG-0203, TXG-0204, TXG-0209, TXG-0210, TXG-0228, or TXG-0230, wherein optionally the antigen-binding molecule or antigen-binding fragment thereof has a binding affinity for the omicron variant of SARS-CoV-2 or one or more common HCoV-229E, OC43, HKU1, or a combination thereof; and/or (ii) a nucleic acid encoding the antigen-binding molecule or antigen-binding fragment thereof of (a), thereby forming a LNP formulation including the LNP associated with the antigen-binding molecule or antigen-binding fragment thereof, and/or with the nucleic acid encoding the antigen-binding molecule or antigen-binding fragment thereof.

[0033] The foregoing summary is illustrative only and is not intended to be in any way limiting. In addition to the illustrative embodiments and features described herein, further aspects, embodiments, objects and features of the disclosure will become fully apparent from the drawings and the detailed description and the claims.

BRIEF DESCRIPTION OF THE DRAWINGS

[0034] **FIG. 1** shows an exemplary scheme for antigen-specific enrichment of B cells by

using fluorescence-activated cell sorting (FACS) technique. In these experiments, cells were initially gated on being single, live (7AAD^{negative}) and PE-Cy7-CD19+ and then sorted on their PE and/or APC status directly into master mix and water. In this figure, Y axis represents PE signal (pre-fusion trimerized SARS-2 glycoprotein S antigen+ and/or HSA+ control antigen-binding cells). X axis represents APC signal (trimerized SARS-2 S glycoprotein D614G antigen+ and/or HSA+ control antigen-binding cells). Numbers adjacent to each gate name represent the fraction of events relative to the parent population (single, live, CD19+ cells) for that gate.

[0035] **FIG. 2** schematically illustrates that the new scoring system described herein allowed for determining relative K_D values which in turn facilitate identification of binding antibodies with good dynamic range of reporter oligonucleotides.

[0036] **FIGS. 3A-3B** schematically depict the results of representative analysis performed to illustrate that the new scoring system described herein allow for selection of high-affinity antibodies with a data set. In this analysis, BEAM scores are approximately normally distributed, increase exponentially as target antigen-binding relative to expressed antibody and control antigen increases, are correlated with generation probability of the HCDR3 junction, *e.g.*, following the known general relationship of somatic hypermutation (SHM) and increasing affinity, and also reveal that class switching increases predicted relative affinity in concordance with the literature.

[0037] **FIG. 4** schematically summarizes the results of representative analysis performed to illustrate clonotype enrichment based on relative K_D . BEAM scores were found to be also generally higher within sublineages that contain more daughter antibodies than narrow sublineages.

[0038] **FIG. 5** shows an exemplary microfluidic channel structure for partitioning individual biological particles in accordance with some embodiments of the disclosure.

[0039] **FIG. 6** shows an exemplary microfluidic channel structure for the controlled partitioning of beads into discrete droplets.

[0040] **FIG. 7** shows an exemplary barcode carrying bead.

[0041] **FIG. 8** illustrates another example of a barcode carrying bead.

[0042] **FIG. 9** schematically illustrates an example microwell array.

[0043] **FIG. 10** schematically illustrates an example workflow for processing nucleic acid

molecules.

[0044] **FIG. 11** schematically illustrates examples of labelling agents.

[0045] **FIG. 12** depicts an example of a barcode carrying bead.

[0046] **FIGS. 13A, 13B and 13C** schematically depict an example workflow for processing nucleic acid molecules.

[0047] **FIG. 14** shows an exemplary microfluidic channel structure for delivering barcode carrying beads to droplets.

[0048] **FIGS. 15A and 15B** depict the amino acid sequences of a wild-type SARS-CoV spike protein (**FIG. 15A**) and a variant SARS-CoV spike protein (**FIG. 15B**). Various mutations have been introduced and indicated by the original amino acids above the mutated amino acids. These mutations fall in 3 classes: 1) proline stabilization/S2P mutations (F817P, A892P, A899P, A942P, K986P, V987P), 2) alanine stabilization mutations (R683A, R685A), and 3) viral variant mutations (D614G). The asterisks in the sequences indicate the start and end of the sequences used to produce the antigens used in the experiments described in the Examples below. The C-terminal end of the antigens (ending at the 2nd asterisk) is fused to the T4 trimerization domain and the His tag.

[0049] **FIGS. 16A-16B** schematically summarize the results of representative SPR analyses performed to evaluate binding affinity of exemplary antibodies of the disclosure to the following antigens: (1) a trimerized wild-type SARS-CoV-2 S protein (**FIG. 16A**), (2) a SARS-CoV-2 S protein variant with D614G substitution (**FIG. 16B**).

[0050] **FIG. 17A** summarizes the results of experiments performed to assess RBD binding kinetics. A triple mutant RBD containing triple amino acid substitutions K417N, E484K, and N501Y was used. **FIG. 17B**: RBD kinetics in comparison to FDA-approved therapeutic antibodies.

[0051] **FIG. 18A** depicts binding kinetics of hypothetical antibodies having the same K_D value 10 nM, with varying k_{on} and k_{off} rates. Red and yellow curves depict optimal binding kinetics of antibodies having high therapeutic potential due to binding stability, while green and blue curves depict less optimal binding kinetics.

[0052] **FIG. 18B** depicts binding kinetics of exemplary TXG antibodies and FDA-approved or late clinical development stage spike antibodies (data from each antibody shown in triplicate). Antibodies having optimal binding kinetics are depicted in **FIG. 18B** as boxes with

asterisk symbols (*). Antibodies having less optimal binding kinetics are depicted in **FIG. 18B** as boxes with solid circle (●). FDA-approved or late clinical development stage spike antibodies used as positive controls are depicted as boxes with solid triangle (▲).

[0053] **FIG. 18C** depicts the relationship between K_{off} of a given TXG antibody to the pre-fusion trimeric spike and its binding kinetics. K_{off} is shown here for the purpose of brevity as half-life and mean-life kinetics of a receptor-ligand pair are determined by the K_{off} of the interaction and not the K_{on} or the ratio of K_{off} to K_{on} (K_D). Box plots are shown for each kinetic profile described above and shown in **FIG. 18C**. Twenty-seven (27) antibodies are shown as having a K_{off} rate of $1e-05$, indicating they have surpassed the lower limit of detection from the SPR data and therefore have lower estimated K_D values than those reported in the provided data.

[0054] **FIG. 18D** depicts the relationship between K_{off} and K_{on} of given TBS-antibodies to the pre-fusion trimeric spike, color coded by kinetic profile.

[0055] **FIG. 19** schematically depicts binding affinity of exemplary antibodies to wild-type SARS-CoV-2 S protein, illustrating that the majority of tested antibodies could bind to wild-type S protein in picomolar and nanomolar range. Remarkably, several antibodies described herein were found to have binding affinities as good as or superior to FDA-approved antibodies or antibodies in late clinical development.

[0056] **FIG. 20** schematically depicts the general procedure of live virus neutralization assay employed to determine the anti-SARS-CoV-2 activity of various antibodies described herein.

[0057] **FIG. 21** depicts representative raw data from neutralization assay described in **FIG. 20**. CTRL-0004: Casirivimab; CTRL-0006: Bamlanivimab; CTRL-0007: Etesevimab; CTRL-0008: Sotrovimab; CS478 pi_vac_pf1, positive plasma control of Pfizer vaccine.

[0058] **FIG. 22** depicts representative neutralization percentage from neutralization assay described in **FIG. 20**. CTRL-0004: Casirivimab; CTRL-0006: Bamlanivimab; CTRL-0007: Etesevimab; CTRL-0008: Sotrovimab; CS478 pi_vac_pf1, positive plasma control of Pfizer vaccine.

[0059] **FIG. 23** schematically depicts representative neutralization curves (ID_{50}) of four FDA-approved antibodies or antibodies in late clinical development (controls). CTRL-0004: Casirivimab; CTRL-0006: Bamlanivimab; CTRL-0007: Etesevimab; CTRL-0008: Sotrovimab;

CS478 pi_vac_pf1, positive plasma control of Pfizer vaccine.

[0060] **FIG. 24** schematically depicts representative neutralization curves (ID50) of six exemplary antibodies in accordance with some embodiments of the disclosure.

[0061] **FIG. 25** schematically depicts an UpSet plot wherein antibodies are binned into antigen bins based on two rounds of SPR binding affinity data. For an antibody to be placed into a bin a detectable kinetic fit at all concentrations of antigen was required from at least one of the SPR experiments described in Examples 9 and 12, or orthogonal neutralization data.

[0062] **FIG. 26** schematically depicts an UpSet plot of antibodies identified as having neutralization activity against live SARS-CoV-2, wherein the antibodies are binned into antigen bins as described in **FIG. 25**.

[0063] **FIGS. 27A and 27B** depict UpSet plots of the potentially ($IC_{50} \leq 1000$ ng / ml) neutralizing antibodies retrieved in this BEAM-seq workflow. **FIG. 27A** is an Upset plot of the potentially neutralizing antibodies selected from 239 antibodies identified in Example 6. **FIG. 27B** is an Upset plot of the potentially neutralizing antibodies selected from the antibodies of Table 4. In these figures, rows represent the binding of these neutralizing antibodies to pre-fusion spike trimers from major SARS-CoV-2 variants of concern, and the endemic HKU1 coronavirus spike protein as well as the SARS-CoV-2 N terminal domain.

[0064] **FIG. 28** schematically summarizes of the neutralization potency of the antibodies described in Table 10 as determined in testing against SARS-CoV-2. The neutralization potency of an antibody is generally quantified by the inhibitory concentration (IC) values (e.g., IC_{50}) in live SARS-CoV-2 assays (see also, Table 11)

[0065] **FIG. 29** is a heat map summarizing results of the epitope binning assays described in Example 14, wherein antibodies were tested against one another in a pairwise and combinatorial fashion for binding to a specific target antigen, *i.e.*, pre-fusion trimerized spike protein from SARS-CoV-2 USA-WA1/2020 isolate.

[0066] **FIG. 30** is a heat map summarizing results of the epitope binning assays described in Example 14, wherein antibodies were tested against one another in a pairwise and combinatorial fashion for binding to spike protein from SARS-CoV-2 delta variant.

[0067] **FIG. 31** schematically depicts an UpSet plot wherein antibodies are binned into antigen bins based on multiple rounds of SPR binding affinity data. For an antibody to be placed into a bin a detectable kinetic fit at all concentrations of antigen was required from at least one of

the SPR experiments described in Examples 9 and 12. As illustrated in **FIG. 31**, the recovered antibodies have a range of binding breadths including binding to multiple endemic coronaviruses and SARS-CoV-2 variants, and that most of the antibodies recovered successfully bind multiple SARS-CoV-2 variants.

[0068] **FIGS. 32A-32D** summarize the results of experiments demonstrating that TXG-0078 is an NTD supersite-targeting mAb that can bind alpha- and betacoronaviruses. **FIG. 32A**: 3.9Å cryo-electron microscopy image of the digested Fab of TXG-0078 in complex with the spike trimer from the SARS-CoV-2 Wuhan entry strain (WT). **FIG. 32B**: 4A8 sequence threading into the TXG-0078:spike structure, revealing that TXG-0078 targets the NTD supersite as has been described for other antibodies. **FIG. 32C**: the N3 and N5 loops comprise the epitope of TXG-0078; the longer CDRH3 of TXG-0078 reaches into a pocket in the N5 loop and the light chain is only minimally engaged in binding. **FIG. 32D**: A 3Å negative stain EM image of TXG-0078 in complex with the Wuhan spike trimer.

[0069] **FIGS. 33A-33B** summarize the results of experiments illustrating that TXG-0078 protects transgenic ACE2 mice from live SARS-CoV-2 challenge. **FIG. 33A**: Mice were administered 20 µg of (i) TXG-0078, (ii) a reference RBD-targeting antibody, or (iii) Control 1 (antibody targeting Zika virus (ZIKV)). Mean percent change in baseline weight is shown for each group ± SEM. **FIG. 33A**: Percent baseline weight at Day 5 is shown for all mice (n=15), with mean and SEM shown for each group.

DETAILED DESCRIPTION OF THE DISCLOSURE

[0070] In the following detailed description, reference is made to the accompanying drawings, which form a part hereof. In the drawings, similar symbols generally identify similar components, unless context dictates otherwise. The illustrative alternatives described in the detailed description, drawings, and claims are not meant to be limiting. Other alternatives may be used and other changes may be made without departing from the spirit or scope of the subject matter presented here. It will be readily understood that the aspects, as generally described herein, and illustrated in the Figures, can be arranged, substituted, combined, and designed in a wide variety of different configurations, all of which are explicitly contemplated and make part of this application.

[0071] Unless otherwise defined, all terms of art, notations, and other scientific terms or

terminology used herein are intended to have the meanings commonly understood by those of skill in the art to which this application pertains. In some cases, terms with commonly understood meanings are defined herein for clarity and/or for ready reference, and the inclusion of such definitions herein should not necessarily be construed to represent a substantial difference over what is generally understood in the art. Many of the techniques and procedures described or referenced herein are well understood and commonly employed using conventional methodology by those skilled in the art.

DEFINITIONS

[0072] Unless otherwise defined, all terms of art, notations and other scientific terms or terminology used herein are intended to have the meanings commonly understood by those of skill in the art to which this disclosure pertains. In some cases, terms with commonly understood meanings are defined herein for clarity and/or for ready reference, and the inclusion of such definitions herein should not necessarily be construed to represent a substantial difference over what is generally understood in the art. Many of the techniques and procedures described or referenced herein are well understood and commonly employed using conventional methodology by those skilled in the art.

[0073] The singular form “a,” “an,” and “the” include plural references unless the context clearly dictates otherwise. For example, the term “a cell” includes one or more cells, including mixtures thereof. “A and/or B” is used herein to include all of the following alternatives: “A,” “B,” “A or B,” and “A and B.”

[0074] As used herein, a “subject” or an “individual” includes animals, such as human (*e.g.*, human individuals) and non-human animals. The term “non-human animals” includes all vertebrates, *e.g.*, mammals, *e.g.*, rodents, *e.g.*, mice, non-human primates, and other mammals, such as *e.g.*, rat, mouse, cat, dog, cow, pig, sheep, horse, goat, rabbit; and non-mammals, such as amphibians, reptiles, *etc.* A subject can be a mammal, preferably a human or humanized animal, *e.g.*, an animal with humanized or human VDJC loci. The subject may be a non-human animal (*e.g.*, a non-human mammal) with human VDJ loci and non-human C loci. The subject may be non-human animals with humanized or human VDJC loci and knockouts of a target of interest. The subject may be in need of prevention and/or treatment of a disease or disorder such as viral infection or cancer. The subject may have a viral infection, *e.g.*, a coronavirus infection, or be predisposed to developing an infection. Subjects predisposed to developing an infection, or

subjects who may be at elevated risk for contracting an infection (*e.g.*, of coronavirus), include subjects with compromised immune systems because of autoimmune disease, subjects receiving immunosuppressive therapy (for example, following organ transplant), subjects afflicted with human immunodeficiency syndrome (HIV) or acquired immune deficiency syndrome (AIDS), subjects with forms of anemia that deplete or destroy white blood cells, subjects receiving radiation or chemotherapy, or subjects afflicted with an inflammatory disorder. Additionally, subjects of very young (*e.g.*, 5 years of age or younger) or old age (*e.g.*, 65 years of age or older) are at increased risk. Moreover, a subject may be at risk of contracting a viral infection due to proximity to an outbreak of the disease, *e.g.*, subject resides in a densely-populated city or in close proximity to subjects having confirmed or suspected infections of a virus, or choice of employment, *e.g.* hospital worker, pharmaceutical researcher, traveler to infected area, or frequent flier. In some embodiments, a “subject” or “individual” is a patient under the care of a physician.

[0075] The term “viral load,” “viral burden” or “viral titer” refers to a numerical expression of the quantity of virus in a given volume of body fluid, usually blood plasma. It is often expressed as viral particles, or infectious particles per mL depending on the type of assay. A higher viral burden, titer, or viral load often correlates with the severity of an active viral infection.

[0076] 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 disclosure. The upper and lower limits of these smaller ranges may independently be included in the smaller ranges, and are also encompassed within the disclosure, 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 disclosure.

[0077] 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 in

which it is presented, provides the substantial equivalent of the specifically recited number. If the degree of approximation is not otherwise clear from the context, “about” means either within plus or minus 10% of the provided value, or rounded to the nearest significant figure, in all cases inclusive of the provided value. In some embodiments, the term “about” indicates the designated value $\pm$ up to 10%, up to $\pm$ 5%, or up to $\pm$ 1%.

[0078] It is appreciated that certain features of the disclosure, which are, for clarity, described in the context of separate embodiments, may also be provided in combination in a single embodiment. Conversely, various features of the disclosure, which are, for brevity, described in the context of a single embodiment, may also be provided separately or in any suitable sub-combination. All combinations of the embodiments pertaining to the disclosure are specifically embraced by the present disclosure and are disclosed herein just as if each and every combination was individually and explicitly disclosed. In addition, all sub-combinations of the various embodiments and elements thereof are also specifically embraced by the present disclosure and are disclosed herein just as if each and every such sub-combination was individually and explicitly disclosed herein.

CORONAVIRUSES

[0079] Coronaviruses are a family of large, enveloped, positive-sense single-stranded RNA viruses. They infect humans, other mammals and avian species, including livestock and companion animals (such as dogs, cats, chicken, cattle, pigs, and birds), and are therefore not only a challenge for public health but also a veterinary and economic concern. Coronaviruses include the genera of alphacoronaviruses, betacoronaviruses, gammacoronaviruses, and deltacoronaviruses. Whereas alphacoronaviruses and betacoronaviruses exclusively infect mammalian species, gammacoronaviruses and deltacoronaviruses have a wider host range that includes avian species. Coronaviruses cause respiratory, gastrointestinal, and neurological disease. The most common coronaviruses in clinical practice are 229E, OC43, NL63, and HKU1, which typically cause common cold symptoms in immunocompetent individuals. Other coronaviruses include severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus (MERS-CoV) and SARS-CoV-2, which have emerged in the human population over the past 20 years and are highly pathogenic.

[0080] The initial steps of coronavirus infection involve the specific binding of the coronavirus spike (S) protein to the cellular entry receptors, which have been identified for

several coronaviruses and include human aminopeptidase N (APN; HCoV-229E), angiotensin-converting enzyme 2 (ACE2; HCoV-NL63, SARS-CoV and SARS-CoV-2) and dipeptidyl peptidase 4 (DPP4; MERS-CoV).

[0081] The sites of receptor binding domains (RBD) within the S1 region (often referred to as S1 subunit) of a coronavirus S protein vary depending on the virus, with some having the RBD at the C-terminus of S1. The S-protein/receptor interaction is the primary determinant for a coronavirus to infect a host species and also governs the tissue tropism of the virus. Additional information regarding coronavirus biology, pathophysiology, diagnosis, and treatment can be found in recent reviews by V'kovski P. *et al.* (Nature Rev. Microbiol. Oct. 28, 2020) and Wiersinga WJ *et al.* (JAMA. 2020;324(8):782-793).

[0082] Coronavirus spike (S) proteins are class I fusion glycoproteins which assemble into trimers that constitute the spikes or peplomers on the surface of the enveloped coronavirus particle. The proteins are divided into two parts (region or subunit) with distinct functions, host receptor binding and membrane fusion, which are attributed to the N-terminal (S1) and C-terminal (S2) halves of the S proteins. The surface-exposed S1 includes the NTD and RBD that specifically engages the host cell receptor, thereby determining virus cell tropism and pathogenicity. The transmembrane S2 domain contains heptad repeat regions, *e.g.*, heptad repeat 1 (HR1) and heptad repeat 2 (HR2), central helix (CH), connector domain (CD), transmembrane domain (TM), and cytoplasmic tail (CT), the fusion peptide (FP), which mediate the fusion of viral and cellular membranes upon extensive conformational rearrangements. The function of S2 subunit is to fuse the membranes of viruses and host cells. The cleavage site at the border between the S1 and S2 subunits is called S1/S2 protease cleavage site. For all the coronaviruses, host proteases cleave the spike glycoprotein at the S2' cleavage site to activate the proteins which allows subsequent fusion of the membranes of viruses and host cells through irreversible conformational changes. CoV-S binds to its cognate receptor, angiotensin-converting enzyme 2 (ACE2), via a receptor binding domain (RBD) present in the S1 subunit.

[0083] The amino acid sequence of full-length SARS-CoV-2 spike protein is exemplified by the amino acid sequence provided in SEQ ID NO: 3045 and **FIG. 15A**. The term "CoV-S" as used herein includes protein variants of CoV spike protein isolated from different CoV isolates as well as recombinant CoV spike protein or a fragment thereof. CoV spike protein variants include CoV spike proteins with one or more substitutions, as exemplified by the amino acid

sequence provided in SEQ ID NO: 3046 and **FIG. 15B**.

COMPOSITIONS OF THE DISCLOSURE

[0084] As described in greater detail below, one aspect of the present disclosure relates to compositions including (a) antigen-binding molecules, *e.g.*, antibodies and antigen-binding fragments that bind to a SARS-CoV-2; and/or (b) nucleic acids encoding the antigen-binding molecules (*e.g.*, antibodies and antigen-binding fragments) of (a), wherein the composition is formulated in a lipid-based nanoparticle (LNP). Compositions of the disclosure are useful for preventing, treating, diagnosing, or imaging a virus (*e.g.*, coronavirus), a disease, a disorder, and/or a health condition associated with virus infection. Compositions of the disclosure are also useful for methods of aiding the detection and/or treatment of a disease, a disorder, and/or a health condition associated with virus infection, such as a coronavirus infection. As used herein, a “method of aiding” generally refers to methods of assisting in performing or practicing a method disclosed herein, for example, methods of assisting in (i) performing, (ii) practicing, and/or (iii) making a determination concerning the detection, classification, treatment regimen, or nature, of a virus infection (*e.g.*, a coronavirus infection), a disease, a disorder, and/or a health condition.

Antigen-binding molecules

[0085] Generally, the antigen-binding molecules, *e.g.*, antigen-binding polypeptides, antibodies, and antigen-binding fragments, that are formulated into LNP compositions of the disclosure, have a binding affinity for an epitope in the spike (S) protein of a coronavirus.

[0086] An antibody is generally understood by the skilled artisan in the art to refer to immunoglobulin molecules including four polypeptide chains, two heavy chains (HCs) and two light chains (LCs) inter-connected by disulfide bonds (*i.e.*, “full antibody molecules”), as well as multimers thereof (*e.g.*, IgM). Exemplary antibodies include, for example, those listed in Tables 1A-1B and the Sequence Listing. Each heavy chain includes a heavy chain variable region (“HCVR” or “VH”) and a heavy chain constant region (which is comprised of domains CH1, CH2 and CH3). Each light chain is comprised of a light chain variable region (“LCVR” or “VL”) and a light chain constant region (CL). The VH and VL regions can be further subdivided into regions of hypervariability, termed complementarity determining regions (CDR), interspersed with regions that are more conserved, termed framework regions (FWR). Each VH and VL includes three CDRs and four FWRs, arranged from amino-terminus to carboxy-terminus in the

following order: FWR1, CDR1, FWR2, CDR2, FWR3, CDR3, and FWR4. Heavy chain CDRs can also be referred to as HCDRs, and numbered as described above (*e.g.*, HCDR1, HCDR2, and HCDR3). Likewise, light chain CDRs can be referred to as LCDRs, and numbered LCDR1, LCDR2, and LCDR3. In some embodiments of the disclosure, the FWRs of the antibodies or antigen-binding fragments thereof are identical to the human germline sequences, or are naturally or artificially modified. Thus, the present disclosure provides LNP compositions comprising anti-CoV-S antibodies or antigen-binding fragments thereof (*e.g.*, anti-SARS-CoV-2-S antibodies or antigen-binding fragments thereof) including HCDR and LCDR sequences of Tables 1A-1B as well as those identified as such in the Sequence Listing within a variable heavy chain or light chain region of human germline immunoglobulin sequences.

[0087] In some embodiments, the assignment of amino acids to each domain is in accordance with the definitions of Sequences of Proteins of Immunological Interest, Kabat, *et al.*; National Institutes of Health, Bethesda, Md.; 5th ed.; NIH Publ. No. 91-3242 (1991). The amino acid sequence boundaries of an antibody CDR can also be determined by one of skill in the art using any of a number of numbering schemes, including those described by Kabat (1978) *Adv. Prot. Chem.* 32:1-75; Kabat, *et al.*, (1977) *J. Biol. Chem.* 252:6609-6616 (“Kabat” numbering scheme, which derives CDR definitions and a residue numbering scheme based purely on antibody sequence information); Chothia, *et al.*, (1987) *J Mol. Biol.* 196:901-917, Chothia, *et al.*, (1989) *Nature* 342:878-883, or Al-Lazikani *et al.*, 1997, *J. Mol. Biol.*, 273:927-948 (“Chothia” numbering scheme, which defines defined CDRs from the earliest structures of antibodies); MacCallum *et al.*, 1996, *J. Mol. Biol.* 262:732-745 (“Contact” numbering scheme); Lefranc *et al.*, *Dev. Comp. Immunol.*, 2003, 27:55-77 (“IMGT” numbering scheme); and Honegge and Plückthun, *J. Mol. Biol.*, 2001, 309:657-70 (“AHO” numbering scheme). In addition or alternatively, the amino acid sequence boundaries of an antibody CDR can also be determined by one of skill in the art using an “enhanced Chothia” scheme as described previously in, *e.g.*, Abhinandan KR and Martin AC, *Mol Immunol* 2008 Aug;45(14):3832-9; or using a more recent methodology of distance-function clustering of antibody CDR loop conformations based on directional statistics and clustering algorithm using affinity propagation (see, *e.g.*, North B. *et al. J Mol Biol.* 2011 Feb 18; 406(2): 228–256.

[0088] In some embodiments, CDR and FWR regions are determined using evolutionarily conserved motifs. See, *e.g.*, PCT Application No. PCT/US2022/015986, which is hereby

incorporated by reference in its entirety.

TABLES 1A and 1B: Exemplary antigen-binding polypeptides, *e.g.*, antibodies, and clonotypes of the disclosure. HCVR(1) and LCVR(1) correspond to the sequences of heavy chain variable region and light chain variable regions, respectively, without a leader peptide sequence. HCVR(2) and LCVR(2) correspond to the sequences of heavy chain variable region and light chain variable regions, respectively, including a leader peptide sequence.

TABLE 1A

Antibody	Clonotype Family	Amino acid sequence identifiers (SEQ ID NOs)									
		HCVR (1)	HCVR (2)	HCDR 1	HCDR 2	HCDR 3	LCVR (1)	LCVR (2)	LCDR 1	LCDR 2	LCDR 3
TXG-0001	A	2409	2568	183	342	501	2727	2886	660	819	978
TXG-0002	A	2410	2569	184	343	502	2728	2887	661	820	979
TXG-0003	A	2411	2570	185	344	503	2729	2888	662	821	980
TXG-0004	A	2412	2571	186	345	504	2730	2889	663	822	981
TXG-0005	A	2413	2572	187	346	505	2731	2890	664	823	982
TXG-0006	A	2414	2573	188	347	506	2732	2891	665	824	983
TXG-0007	A	2415	2574	189	348	507	2733	2892	666	825	984
TXG-0008	A	2416	2575	190	349	508	2734	2893	667	826	985
TXG-0009	A	2417	2576	191	350	509	2735	2894	668	827	986
TXG-0010	B	2418	2577	192	351	510	2736	2895	669	828	987
TXG-0011	B	2419	2578	193	352	511	2737	2896	670	829	988
TXG-0012	B	2420	2579	194	353	512	2738	2897	671	830	989
TXG-0013	B	2421	2580	195	354	513	2739	2898	672	831	990
TXG-0014	B	2422	2581	196	355	514	2740	2899	673	832	991
TXG-0015	B	2423	2582	197	356	515	2741	2900	674	833	992
TXG-0016	B	2424	2583	198	357	516	2742	2901	675	834	993
TXG-0017	B	2425	2584	199	358	517	2743	2902	676	835	994
TXG-0018	C	2426	2585	200	359	518	2744	2903	677	836	995
TXG-0019	C	2427	2586	201	360	519	2745	2904	678	837	996
TXG-0020	C	2428	2587	202	361	520	2746	2905	679	838	997
TXG-0023		3077	3079	3049	3051	3053	3081	3083	3055	3057	3059
TXG-0024	D	2429	2588	203	362	521	2747	2906	680	839	998
TXG-0025	D	2430	2589	204	363	522	2748	2907	681	840	999
TXG-0026	D	2431	2590	205	364	523	2749	2908	682	841	1000
TXG-0027		3078	3080	3050	3052	3054	3082	3084	3056	3058	3060
TXG-0029	E	2432	2591	206	365	524	2750	2909	683	842	1001
TXG-0030	E	2433	2592	207	366	525	2751	2910	684	843	1002
TXG-0031	F	2434	2593	208	367	526	2752	2911	685	844	1003
TXG-0032	F	2435	2594	209	368	527	2753	2912	686	845	1004

TXG-0033	F	2436	2595	210	369	528	2754	2913	687	846	1005
TXG-0034	G	2437	2596	211	370	529	2755	2914	688	847	1006
TXG-0035	G	2438	2597	212	371	530	2756	2915	689	848	1007
TXG-0036	G	2439	2598	213	372	531	2757	2916	690	849	1008
TXG-0037		2440	2599	214	373	532	2758	2917	691	850	1009
TXG-0038		2441	2600	215	374	533	2759	2918	692	851	1010
TXG-0039	H	2442	2601	216	375	534	2760	2919	693	852	1011
TXG-0040	H	2443	2602	217	376	535	2761	2920	694	853	1012
TXG-0041	H	2444	2603	218	377	536	2762	2921	695	854	1013
TXG-0042		2445	2604	219	378	537	2763	2922	696	855	1014
TXG-0044	I	2446	2605	220	379	538	2764	2923	697	856	1015
TXG-0045	I	2447	2606	221	380	539	2765	2924	698	857	1016
TXG-0046	J	2448	2607	222	381	540	2766	2925	699	858	1017
TXG-0047	J	2449	2608	223	382	541	2767	2926	700	859	1018
TXG-0048		2450	2609	224	383	542	2768	2927	701	860	1019
TXG-0050		2451	2610	225	384	543	2769	2928	702	861	1020
TXG-0052		2452	2611	226	385	544	2770	2929	703	862	1021
TXG-0053		2453	2612	227	386	545	2771	2930	704	863	1022
TXG-0054		2454	2613	228	387	546	2772	2931	705	864	1023
TXG-0055		2455	2614	229	388	547	2773	2932	706	865	1024
TXG-0057		2456	2615	230	389	548	2774	2933	707	866	1025
TXG-0058		2457	2616	231	390	549	2775	2934	708	867	1026
TXG-0059		2458	2617	232	391	550	2776	2935	709	868	1027
TXG-0060		2459	2618	233	392	551	2777	2936	710	869	1028
TXG-0063		2460	2619	234	393	552	2778	2937	711	870	1029
TXG-0064		2461	2620	235	394	553	2779	2938	712	871	1030
TXG-0065		2462	2621	236	395	554	2780	2939	713	872	1031
TXG-0066		2463	2622	237	396	555	2781	2940	714	873	1032
TXG-0069		2464	2623	238	397	556	2782	2941	715	874	1033
TXG-0070		2465	2624	239	398	557	2783	2942	716	875	1034
TXG-0071		2466	2625	240	399	558	2784	2943	717	876	1035
TXG-0073		2467	2626	241	400	559	2785	2944	718	877	1036
TXG-0074		2468	2627	242	401	560	2786	2945	719	878	1037
TXG-0075		2469	2628	243	402	561	2787	2946	720	879	1038
TXG-0076		2470	2629	244	403	562	2788	2947	721	880	1039
TXG-0077		2471	2630	245	404	563	2789	2948	722	881	1040
TXG-0078		2472	2631	246	405	564	2790	2949	723	882	1041
TXG-0079		2473	2632	247	406	565	2791	2950	724	883	1042
TXG-0080		2474	2633	248	407	566	2792	2951	725	884	1043
TXG-0081		2475	2634	249	408	567	2793	2952	726	885	1044
TXG-0082		2476	2635	250	409	568	2794	2953	727	886	1045

TXG-0084		2477	2636	251	410	569	2795	2954	728	887	1046
TXG-0086		2478	2637	252	411	570	2796	2955	729	888	1047
TXG-0087		2479	2638	253	412	571	2797	2956	730	889	1048
TXG-0088		2480	2639	254	413	572	2798	2957	731	890	1049
TXG-0091		2481	2640	255	414	573	2799	2958	732	891	1050
TXG-0093		2482	2641	256	415	574	2800	2959	733	892	1051
TXG-0094		2483	2642	257	416	575	2801	2960	734	893	1052
TXG-0097		2484	2643	258	417	576	2802	2961	735	894	1053
TXG-0099		2485	2644	259	418	577	2803	2962	736	895	1054
TXG-0100		2486	2645	260	419	578	2804	2963	737	896	1055
TXG-0101		2487	2646	261	420	579	2805	2964	738	897	1056
TXG-0102		2488	2647	262	421	580	2806	2965	739	898	1057
TXG-0103		2489	2648	263	422	581	2807	2966	740	899	1058
TXG-0104		2490	2649	264	423	582	2808	2967	741	900	1059
TXG-0107		2491	2650	265	424	583	2809	2968	742	901	1060
TXG-0109		2492	2651	266	425	584	2810	2969	743	902	1061
TXG-0114		2493	2652	267	426	585	2811	2970	744	903	1062
TXG-0116		2494	2653	268	427	586	2812	2971	745	904	1063
TXG-0117		2495	2654	269	428	587	2813	2972	746	905	1064
TXG-0119		2496	2655	270	429	588	2814	2973	747	906	1065
TXG-0120		2497	2656	271	430	589	2815	2974	748	907	1066
TXG-0122		2498	2657	272	431	590	2816	2975	749	908	1067
TXG-0125		2499	2658	273	432	591	2817	2976	750	909	1068
TXG-0126		2500	2659	274	433	592	2818	2977	751	910	1069
TXG-0127		2501	2660	275	434	593	2819	2978	752	911	1070
TXG-0128		2502	2661	276	435	594	2820	2979	753	912	1071
TXG-0129		2503	2662	277	436	595	2821	2980	754	913	1072
TXG-0131		2504	2663	278	437	596	2822	2981	755	914	1073
TXG-0132		2505	2664	279	438	597	2823	2982	756	915	1074
TXG-0133		2506	2665	280	439	598	2824	2983	757	916	1075
TXG-0139		2507	2666	281	440	599	2825	2984	758	917	1076
TXG-0141		2508	2667	282	441	600	2826	2985	759	918	1077
TXG-0142		2509	2668	283	442	601	2827	2986	760	919	1078
TXG-0143		2510	2669	284	443	602	2828	2987	761	920	1079
TXG-0144		2511	2670	285	444	603	2829	2988	762	921	1080
TXG-0146		2512	2671	286	445	604	2830	2989	763	922	1081
TXG-0148		2513	2672	287	446	605	2831	2990	764	923	1082
TXG-0149		2514	2673	288	447	606	2832	2991	765	924	1083
TXG-0151		2515	2674	289	448	607	2833	2992	766	925	1084
TXG-0155		2516	2675	290	449	608	2834	2993	767	926	1085
TXG-0156		2517	2676	291	450	609	2835	2994	768	927	1086

TXG-0157		2518	2677	292	451	610	2836	2995	769	928	1087
TXG-0158		2519	2678	293	452	611	2837	2996	770	929	1088
TXG-0159		2520	2679	294	453	612	2838	2997	771	930	1089
TXG-0161		2521	2680	295	454	613	2839	2998	772	931	1090
TXG-0162		2522	2681	296	455	614	2840	2999	773	932	1091
TXG-0163		2523	2682	297	456	615	2841	3000	774	933	1092
TXG-0164		2524	2683	298	457	616	2842	3001	775	934	1093
TXG-0166		2525	2684	299	458	617	2843	3002	776	935	1094
TXG-0168		2526	2685	300	459	618	2844	3003	777	936	1095
TXG-0170		2527	2686	301	460	619	2845	3004	778	937	1096
TXG-0175		2528	2687	302	461	620	2846	3005	779	938	1097
TXG-0176		2529	2688	303	462	621	2847	3006	780	939	1098
TXG-0178		2530	2689	304	463	622	2848	3007	781	940	1099
TXG-0180		2531	2690	305	464	623	2849	3008	782	941	1100
TXG-0181		2532	2691	306	465	624	2850	3009	783	942	1101
TXG-0183		2533	2692	307	466	625	2851	3010	784	943	1102
TXG-0184		2534	2693	308	467	626	2852	3011	785	944	1103
TXG-0185		2535	2694	309	468	627	2853	3012	786	945	1104
TXG-0186		2536	2695	310	469	628	2854	3013	787	946	1105
TXG-0187		2537	2696	311	470	629	2855	3014	788	947	1106
TXG-0188		2538	2697	312	471	630	2856	3015	789	948	1107
TXG-0189		2539	2698	313	472	631	2857	3016	790	949	1108
TXG-0190		2540	2699	314	473	632	2858	3017	791	950	1109
TXG-0193		2541	2700	315	474	633	2859	3018	792	951	1110
TXG-0197		2542	2701	316	475	634	2860	3019	793	952	1111
TXG-0198		2543	2702	317	476	635	2861	3020	794	953	1112
TXG-0199		2544	2703	318	477	636	2862	3021	795	954	1113
TXG-0200		2545	2704	319	478	637	2863	3022	796	955	1114
TXG-0201		2546	2705	320	479	638	2864	3023	797	956	1115
TXG-0202		2547	2706	321	480	639	2865	3024	798	957	1116
TXG-0203		2548	2707	322	481	640	2866	3025	799	958	1117
TXG-0204		2549	2708	323	482	641	2867	3026	800	959	1118
TXG-0206		2550	2709	324	483	642	2868	3027	801	960	1119
TXG-0207		2551	2710	325	484	643	2869	3028	802	961	1120
TXG-0209		2552	2711	326	485	644	2870	3029	803	962	1121
TXG-0210		2553	2712	327	486	645	2871	3030	804	963	1122
TXG-0219	K	2554	2713	328	487	646	2872	3031	805	964	1123
TXG-0220	K	2555	2714	329	488	647	2873	3032	806	965	1124
TXG-0221	K	2556	2715	330	489	648	2874	3033	807	966	1125
TXG-0222	L	2557	2716	331	490	649	2875	3034	808	967	1126
TXG-0223	L	2558	2717	332	491	650	2876	3035	809	968	1127

TXG-0224		2559	2718	333	492	651	2877	3036	810	969	1128
TXG-0225		2560	2719	334	493	652	2878	3037	811	970	1129
TXG-0232		2561	2720	335	494	653	2879	3038	812	971	1130
TXG-0233		2562	2721	336	495	654	2880	3039	813	972	1131
TXG-0234	M	2563	2722	337	496	655	2881	3040	814	973	1132
TXG-0235	M	2564	2723	338	497	656	2882	3041	815	974	1133
TXG-0236	M	2565	2724	339	498	657	2883	3042	816	975	1134
TXG-0238		2566	2725	340	499	658	2884	3043	817	976	1135
TXG-0239		2567	2726	341	500	659	2885	3044	818	977	1136

TABLE 1B

Antibody	Clonotype	Amino acid sequence identifiers (SEQ ID NOs)									
		HCVR (1)	HCVR (2)	HCDR 1	HCDR 2	HCDR 3	LCVR (1)	LCVR (2)	LCDR 1	LCDR 2	LCDR 3
TXG-0021	A1	5857	5937	4737	4817	4897	6017	6097	4977	5057	5137
TXG-0022	A1	5858	5938	4738	4818	4898	6018	6098	4978	5058	5138
TXG-0023	A1	5859	5939	4739	4819	4899	6019	6099	4979	5059	5139
TXG-0027	B1	5860	5940	4740	4820	4900	6020	6100	4980	5060	5140
TXG-0028	B1	5861	5941	4741	4821	4901	6021	6101	4981	5061	5141
TXG-0043		5862	5942	4742	4822	4902	6022	6102	4982	5062	5142
TXG-0049		5863	5943	4743	4823	4903	6023	6103	4983	5063	5143
TXG-0051		5864	5944	4744	4824	4904	6024	6104	4984	5064	5144
TXG-0056		5865	5945	4745	4825	4905	6025	6105	4985	5065	5145
TXG-0061		5866	5946	4746	4826	4906	6026	6106	4986	5066	5146
TXG-0062		5867	5947	4747	4827	4907	6027	6107	4987	5067	5147
TXG-0067		5868	5948	4748	4828	4908	6028	6108	4988	5068	5148
TXG-0068		5869	5949	4749	4829	4909	6029	6109	4989	5069	5149
TXG-0072		5870	5950	4750	4830	4910	6030	6110	4990	5070	5150
TXG-0083		5871	5951	4751	4831	4911	6031	6111	4991	5071	5151
TXG-0085		5872	5952	4752	4832	4912	6032	6112	4992	5072	5152
TXG-0089		5873	5953	4753	4833	4913	6033	6113	4993	5073	5153
TXG-0090		5874	5954	4754	4834	4914	6034	6114	4994	5074	5154
TXG-0092		5875	5955	4755	4835	4915	6035	6115	4995	5075	5155
TXG-0095		5876	5956	4756	4836	4916	6036	6116	4996	5076	5156
TXG-0096		5877	5957	4757	4837	4917	6037	6117	4997	5077	5157
TXG-0098		5878	5958	4758	4838	4918	6038	6118	4998	5078	5158
TXG-0105		5879	5959	4759	4839	4919	6039	6119	4999	5079	5159
TXG-0106		5880	5960	4760	4840	4920	6040	6120	5000	5080	5160
TXG-0108		5881	5961	4761	4841	4921	6041	6121	5001	5081	5161
TXG-0110		5882	5962	4762	4842	4922	6042	6122	5002	5082	5162
TXG-0111		5883	5963	4763	4843	4923	6043	6123	5003	5083	5163

TXG-0112		5884	5964	4764	4844	4924	6044	6124	5004	5084	5164
TXG-0113		5885	5965	4765	4845	4925	6045	6125	5005	5085	5165
TXG-0115		5886	5966	4766	4846	4926	6046	6126	5006	5086	5166
TXG-0118		5887	5967	4767	4847	4927	6047	6127	5007	5087	5167
TXG-0121		5888	5968	4768	4848	4928	6048	6128	5008	5088	5168
TXG-0123		5889	5969	4769	4849	4929	6049	6129	5009	5089	5169
TXG-0124		5890	5970	4770	4850	4930	6050	6130	5010	5090	5170
TXG-0130		5891	5971	4771	4851	4931	6051	6131	5011	5091	5171
TXG-0134		5892	5972	4772	4852	4932	6052	6132	5012	5092	5172
TXG-0135		5893	5973	4773	4853	4933	6053	6133	5013	5093	5173
TXG-0136		5894	5974	4774	4854	4934	6054	6134	5014	5094	5174
TXG-0137		5895	5975	4775	4855	4935	6055	6135	5015	5095	5175
TXG-0138		5896	5976	4776	4856	4936	6056	6136	5016	5096	5176
TXG-0140		5897	5977	4777	4857	4937	6057	6137	5017	5097	5177
TXG-0145		5898	5978	4778	4858	4938	6058	6138	5018	5098	5178
TXG-0147		5899	5979	4779	4859	4939	6059	6139	5019	5099	5179
TXG-0150		5900	5980	4780	4860	4940	6060	6140	5020	5100	5180
TXG-0152		5901	5981	4781	4861	4941	6061	6141	5021	5101	5181
TXG-0153		5902	5982	4782	4862	4942	6062	6142	5022	5102	5182
TXG-0154		5903	5983	4783	4863	4943	6063	6143	5023	5103	5183
TXG-0160		5904	5984	4784	4864	4944	6064	6144	5024	5104	5184
TXG-0165		5905	5985	4785	4865	4945	6065	6145	5025	5105	5185
TXG-0167		5906	5986	4786	4866	4946	6066	6146	5026	5106	5186
TXG-0169		5907	5987	4787	4867	4947	6067	6147	5027	5107	5187
TXG-0171		5908	5988	4788	4868	4948	6068	6148	5028	5108	5188
TXG-0172		5909	5989	4789	4869	4949	6069	6149	5029	5109	5189
TXG-0173		5910	5990	4790	4870	4950	6070	6150	5030	5110	5190
TXG-0174		5911	5991	4791	4871	4951	6071	6151	5031	5111	5191
TXG-0177		5912	5992	4792	4872	4952	6072	6152	5032	5112	5192
TXG-0179		5913	5993	4793	4873	4953	6073	6153	5033	5113	5193
TXG-0182		5914	5994	4794	4874	4954	6074	6154	5034	5114	5194
TXG-0191		5915	5995	4795	4875	4955	6075	6155	5035	5115	5195
TXG-0192		5916	5996	4796	4876	4956	6076	6156	5036	5116	5196
TXG-0194		5917	5997	4797	4877	4957	6077	6157	5037	5117	5197
TXG-0195		5918	5998	4798	4878	4958	6078	6158	5038	5118	5198
TXG-0196		5919	5999	4799	4879	4959	6079	6159	5039	5119	5199
TXG-0205		5920	6000	4800	4880	4960	6080	6160	5040	5120	5200
TXG-0208		5921	6001	4801	4881	4961	6081	6161	5041	5121	5201
TXG-0211		5922	6002	4802	4882	4962	6082	6162	5042	5122	5202
TXG-0212		5923	6003	4803	4883	4963	6083	6163	5043	5123	5203
TXG-0213		5924	6004	4804	4884	4964	6084	6164	5044	5124	5204

TXG-0214		5925	6005	4805	4885	4965	6085	6165	5045	5125	5205
TXG-0215		5926	6006	4806	4886	4966	6086	6166	5046	5126	5206
TXG-0216		5927	6007	4807	4887	4967	6087	6167	5047	5127	5207
TXG-0217		5928	6008	4808	4888	4968	6088	6168	5048	5128	5208
TXG-0218		5929	6009	4809	4889	4969	6089	6169	5049	5129	5209
TXG-0226		5930	6010	4810	4890	4970	6090	6170	5050	5130	5210
TXG-0227	C1	5931	6011	4811	4891	4971	6091	6171	5051	5131	5211
TXG-0228	C1	5932	6012	4812	4892	4972	6092	6172	5052	5132	5212
TXG-0229	C1	5933	6013	4813	4893	4973	6093	6173	5053	5133	5213
TXG-0230	C1	5934	6014	4814	4894	4974	6094	6174	5054	5134	5214
TXG-0231		5935	6015	4815	4895	4975	6095	6175	5055	5135	5215
TXG-0237		5936	6016	4816	4896	4976	6096	6176	5056	5136	5216

[0089] The term “antigen-binding fragment” of an antibody or antigen-binding polypeptide, as used herein, include any naturally occurring, enzymatically obtainable, synthetic, or genetically engineered polypeptide or glycoprotein that specifically binds an antigen to form a complex. Non-limiting examples of antigen-binding fragments include (i) Fab fragments; (ii) F(ab')₂ fragments; (iii) Fd fragments; (iv) Fv fragments; (v) single-chain Fv (scFv) molecules; (vi) dAb fragments; and (vii) minimal recognition units consisting of the amino acid residues that mimic the hypervariable region of an antibody (*e.g.*, an isolated complementarity determining region (CDR) such as a CDR3 peptide), or a constrained FWR3-CDR3-FWR4 peptide. Other engineered molecules, such as domain-specific antibodies, single domain antibodies, chimeric antibodies, CDR-grafted antibodies, diabodies, triabodies, tetrabodies, minibodies, nanobodies (*e.g.*, monovalent nanobodies, bivalent nanobodies, *etc.*), small modular immunopharmaceuticals (SMIPs), and shark variable IgNAR domains, are also encompassed within the expression “antigen-binding fragment,” as used herein. In some embodiments of the disclosure, the antigen-binding fragment includes three or more CDRs of an antibody of Tables 1A-1B or of an antibody described in the Sequence Listing (*e.g.*, HCDR1, HCDR2 and HCDR3; or LCDR1, CDR2 and LCDR3).

[0090] An antigen-binding fragment of an antibody, in some embodiment of the disclosure, include at least one variable domain. The variable domain can be of any size or amino acid composition and will generally include at least one CDR, which is adjacent to or in frame with one or more framework sequences. In antigen-binding fragments having a VH domain associated with a VL domain, the VH and VL domains can be situated relative to one another in any

suitable arrangement. For example, the variable region can be dimeric and contain VH-VH, VH-VL or VL-VL dimers. Alternatively, the antigen-binding fragment of an antibody can contain a monomeric VH or VL domain.

[0091] In some embodiments, an antigen-binding fragment of an antibody can contain at least one variable domain covalently linked to at least one constant domain. Non-limiting, exemplary configurations of variable and constant domains that can be found within an antigen-binding fragment of an antibody of the present disclosure include (i) V_H-C_H1; (ii) V_H-C_H2; (iii) V_H-C_H3; (iv) V_H-C_H1-C_H2; (v) V_H-C_H1-C_H2-C_H3; (vi) V_H-C_H2-C_H3; (vii) V_H-C_L; (viii) V_L-C_H1; (ix) V_L-C_H2; (x) V_L-C_H3; (xi) V_L-C_H1-C_H2; (xii) V_L-C_H1-C_H2-C_H3; (xiii) V_L-C_H2-C_H3; and (xiv) V_L-C_L. In any configuration of variable and constant domains, including any of the exemplary configurations listed above, the variable and constant domains can be either directly linked to one another or may be linked by a full or partial hinge or linker region. A hinge region may consist of at least 2 (*e.g.*, 5, 10, 15, 20, 40, 60 or more) amino acids, which result in a flexible or semi-flexible linkage between adjacent variable and/or constant domains in a single polypeptide molecule. Moreover, an antigen-binding fragment of an antibody of the present disclosure may include a homo-dimer or hetero-dimer (or other multimer) of any of the variable and constant domain configurations listed above in non-covalent association with one another and/or with one or more monomeric VH or VL domain (*e.g.*, by disulfide bond(s)). Antigen-binding proteins (*e.g.*, antibodies and antigen-binding fragments) can be mono-specific or multi-specific (*e.g.*, bi-specific).

[0092] In some embodiments, the compositions of the disclosure include a nucleic acid encoding an antigen-binding molecule, or an antigen-binding fragment thereof, that binds to a SARS-CoV-2. In some embodiments, the antigen-binding molecule or antigen-binding fragment thereof comprises all six complementary determining regions (CDRs) from an antibody being any one of TXG-0001, TXG-0002, TXG-0004, TXG-0005, TXG-0006, TXG-0008, TXG-0009, TXG-0048, TXG-0057, TXG-0060, TXG-0063, TXG-0066, TXG-0070, TXG-0072, TXG-0074, TXG-0076, TXG-0078, TXG-0080, TXG-0081, TXG-0087, TXG-0088, TXG-0091, TXG-0094, TXG-0098, TXG-0099, TXG-0100, TXG-0104, TXG-0109, TXG-0112, TXG-0114, TXG-0115, TXG-0120, TXG-0129, TXG-0136, TXG-0141, TXG-0144, TXG-0153, TXG-0154, TXG-0170, TXG-0173, TXG-0174, TXG-0175, TXG-0180, TXG-0181, TXG-0183, TXG-0187, TXG-0189, TXG-0192, TXG-0197, TXG-0198, TXG-0200, TXG-0201, TXG-0202, TXG-0203, TXG-0204,

TXG-0209, TXG-0210, TXG-0228, or TXG-0230, and wherein optionally the composition is formulated in an LNP.

[0093] In some embodiments, the compositions of the disclosure include a nucleic acid encoding an antigen-binding molecule, or an antigen-binding fragment thereof, that includes all six CDRs from TXG-0048. In some embodiments, the compositions of the disclosure include a nucleic acid encoding an antigen-binding molecule, or an antigen-binding fragment thereof, that includes all six CDRs from TXG-0070. In some embodiments, the antigen-binding molecule or an antigen-binding fragment thereof includes all six CDRs from TXG-0087. In some embodiments, the antigen-binding molecule or an antigen-binding fragment thereof includes all six CDRs from TXG-0114. In some embodiments, the antigen-binding molecule or an antigen-binding fragment thereof includes all six CDRs from TXG-0175. In some embodiments, the antigen-binding molecule or an antigen-binding fragment thereof includes all six CDRs from TXG-0192. In some embodiments, the antigen-binding molecule or an antigen-binding fragment thereof includes all six CDRs from TXG-0203. In some embodiments, the antigen-binding molecule or an antigen-binding fragment thereof includes all six CDRs from TXG-0001. In some embodiments, the antigen-binding molecule or an antigen-binding fragment thereof includes all six CDRs from TXG-0002. In some embodiments, the antigen-binding molecule or an antigen-binding fragment thereof includes all six CDRs from TXG-0004. In some embodiments, the antigen-binding molecule or an antigen-binding fragment thereof includes all six CDRs from TXG-0005. In some embodiments, the antigen-binding molecule or an antigen-binding fragment thereof includes all six CDRs from TXG-0006. In some embodiments, the antigen-binding molecule or an antigen-binding fragment thereof includes all six CDRs from TXG-0008. In some embodiments, the antigen-binding molecule or an antigen-binding fragment thereof includes all six CDRs from TXG-0009. In some embodiments, the antigen-binding molecule or an antigen-binding fragment thereof includes all six CDRs from TXG-0009. In some embodiments, the antigen-binding molecule or an antigen-binding fragment thereof includes all six CDRs from TXG-0081. In some embodiments, the antigen-binding molecule or an antigen-binding fragment thereof includes all six CDRs from TXG-0115. In some embodiments, the antigen-binding molecule or an antigen-binding fragment thereof includes all six CDRs from TXG-0154. In some embodiments, the antigen-binding molecule or an antigen-binding fragment thereof includes all six CDRs from TXG-0174. In some embodiments, the antigen-binding molecule or an antigen-

binding fragment thereof includes all six CDRs from TXG-0180.

[0094] In some embodiments, the compositions of the disclosure include an antigen-binding molecule, or an antigen-binding fragment thereof, that binds to a SARS-CoV-2, wherein the antigen-binding molecule or antigen-binding fragment thereof includes all six CDRs from an antibody being any one of TXG-0001, TXG-0002, TXG-0004, TXG-0005, TXG-0006, TXG-0008, TXG-0009, TXG-0048, TXG-0057, TXG-0060, TXG-0063, TXG-0066, TXG-0070, TXG-0072, TXG-0074, TXG-0076, TXG-0078, TXG-0080, TXG-0081, TXG-0087, TXG-0088, TXG-0091, TXG-0094, TXG-0098, TXG-0099, TXG-0100, TXG-0104, TXG-0109, TXG-0112, TXG-0114, TXG-0115, TXG-0120, TXG-0129, TXG-0136, TXG-0141, TXG-0144, TXG-0153, TXG-0154, TXG-0170, TXG-0173, TXG-0174, TXG-0175, TXG-0180, TXG-0181, TXG-0183, TXG-0187, TXG-0189, TXG-0192, TXG-0197, TXG-0198, TXG-0200, TXG-0201, TXG-0202, TXG-0203, TXG-0204, TXG-0209, TXG-0210, TXG-0228, or TXG-0230, and wherein optionally the composition is formulated in an LNP.

[0095] In some embodiments, the compositions of the disclosure include an antigen-binding molecule, or an antigen-binding fragment thereof, that includes all six CDRs from TXG-0048. In some embodiments, the compositions of the disclosure include an antigen-binding molecule, or an antigen-binding fragment thereof, that includes all six CDRs from TXG-0070. In some embodiments, the antigen-binding molecule or an antigen-binding fragment thereof includes all six CDRs from TXG-0087. In some embodiments, the antigen-binding molecule or an antigen-binding fragment thereof includes all six CDRs from TXG-0114. In some embodiments, the antigen-binding molecule or an antigen-binding fragment thereof includes all six CDRs from TXG-0175. In some embodiments, the antigen-binding molecule or an antigen-binding fragment thereof includes all six CDRs from TXG-0192. In some embodiments, the antigen-binding molecule or an antigen-binding fragment thereof includes all six CDRs from TXG-0203. In some embodiments, the antigen-binding molecule or an antigen-binding fragment thereof includes all six CDRs from TXG-0001. In some embodiments, the antigen-binding molecule or an antigen-binding fragment thereof includes all six CDRs from TXG-0002. In some embodiments, the antigen-binding molecule or an antigen-binding fragment thereof includes all six CDRs from TXG-0004. In some embodiments, the antigen-binding molecule or an antigen-binding fragment thereof includes all six CDRs from TXG-0005. In some embodiments, the antigen-binding molecule or an antigen-binding fragment thereof includes all six CDRs from

TXG-0006. In some embodiments, the antigen-binding molecule or an antigen-binding fragment thereof includes all six CDRs from TXG-0008. In some embodiments, the antigen-binding molecule or an antigen-binding fragment thereof includes all six CDRs from TXG-0009. In some embodiments, the antigen-binding molecule or an antigen-binding fragment thereof includes all six CDRs from TXG-0009. In some embodiments, the antigen-binding molecule or an antigen-binding fragment thereof includes all six CDRs from TXG-0081. In some embodiments, the antigen-binding molecule or an antigen-binding fragment thereof includes all six CDRs from TXG-0115. In some embodiments, the antigen-binding molecule or an antigen-binding fragment thereof includes all six CDRs from TXG-0154. In some embodiments, the antigen-binding molecule or an antigen-binding fragment thereof includes all six CDRs from TXG-0174. In some embodiments, the antigen-binding molecule or an antigen-binding fragment thereof includes all six CDRs from TXG-0180.

[0096] In some embodiments, the antibodies and antigen-binding fragments thereof of the disclosure include the heavy chain CDRs (HCDR1, HCDR2, and HCDR3) from the antibodies belonging to the same clonotype family, for example, from any one of the following clonotype families: A, A1, B, B1, C, C1, D, E, F, G, H, I, J, K, L, and M. In some embodiments, the antibodies and antigen-binding fragments thereof of the disclosure include the heavy chain CDRs (HCDR1, HCDR2, and HCDR3) from the antibodies belonging to the same clonotype family that is clonotype family A or C1 (see, *e.g.*, Tables 1A and 1B). In some embodiments, the antibodies and antigen-binding fragments thereof of the disclosure include the heavy chain CDRs (HCDR1, HCDR2, and HCDR3) from an antibody belonging to clonotype family A. In some embodiments, the antibody is TXG-0001, TXG-0002, TXG-0004, TXG-0005, TXG-0006, TXG-0008, or TXG-0009.

[0097] In some embodiments, the antibodies and antigen-binding fragments thereof of the disclosure include the heavy chain CDRs (HCDR1, HCDR2, and HCDR3) from an antibody belonging to clonotype family C1. In some embodiments, the antibody is TXG-0228 or TXG-0230.

[0098] In some embodiments, the antibodies and antigen-binding fragments thereof of the disclosure include the light chain CDRs (LCDR1, LCDR2, and LCDR3) from the antibodies belonging to the same clonotype family, for example, from any one of the following clonotype families A, A1, B, B1, C, C1, D, E, F, G, H, I, J, K, L, and M. In some embodiments, the

antibodies and antigen-binding fragments thereof of the disclosure include the light chain CDRs (LCDR1, LCDR2, and LCDR3) from the antibodies belonging to the same clonotype family that is any one of clonotype families A or C1. In some embodiments, the antibodies and antigen-binding fragments thereof of the disclosure include the CDRs (LCDR1, LCDR2, and LCDR3) from an antibody belonging to clonotype family A. In some embodiments, the antibody is TXG-0001, TXG-0002, TXG-0004, TXG-0005, TXG-0006, TXG-0008, or TXG-0009. In some embodiments, the antibodies and antigen-binding fragments thereof of the disclosure include the CDRs (LCDR1, LCDR2, and LCDR3) from an antibody belonging to clonotype family C1. In some embodiments, the antibody is TXG-0228 or TXG-0230.

[0099] In some embodiments, the antibodies and antigen-binding fragments thereof of the disclosure include (a) the heavy chain CDRs (HCDR1, HCDR2, and HCDR3), and (b) the light chain CDRs (LCDR1, LCDR2, and LCDR3) from the antibodies belonging to the same clonotype family, for example, from a clonotype family being any one of the clonotype families A, A1, B, B1, C, C1, D, E, F, G, H, I, J, K, L, or M. In some embodiments, the antibodies and antigen-binding fragments thereof of the disclosure include (a) the heavy chain CDRs (HCDR1, HCDR2, and HCDR3), and (b) the light chain CDRs (LCDR1, LCDR2, and LCDR3) from the antibodies belonging to the same clonotype family selected from the group consisting of clonotype families A and C1. In some embodiments, the antibodies and antigen-binding fragments thereof of the disclosure include (a) the heavy chain CDRs (HCDR1, HCDR2, and HCDR3), and (b) the light chain CDRs (LCDR1, LCDR2, and LCDR3) from an antibody belonging to clonotype family A. In some embodiments, the antibody is TXG-0001, TXG-0002, TXG-0004, TXG-0005, TXG-0006, TXG-0008, or TXG-0009. In some embodiments, the antibodies and antigen-binding fragments thereof of the disclosure include (a) the heavy chain CDRs (HCDR1, HCDR2, and HCDR3), and (b) the light chain CDRs (LCDR1, LCDR2, and LCDR3) from an antibody belonging to clonotype family C1. In some embodiments, the antibody is TXG-0228 or TXG-0230.

[0100] Non-limiting exemplary embodiments of the antibodies and antigen-binding fragments thereof of the disclosure can include one or more of the following features. In some embodiments, the antibodies and antigen-binding fragments thereof of the disclosure can include a polypeptide including an amino acid sequence that is set forth herein except for one or more (*e.g.*, 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10) mutations such as, for example, missense mutations (*e.g.*,

conservative substitutions), non-sense mutations, deletions, or insertions. For example, the present disclosure includes antigen-binding polypeptides which include an immunoglobulin light chain variant comprising an LCVR amino acid sequence set forth in Tables 1A-1B and Sequence Listing but having one or more of such mutations and/or an immunoglobulin heavy chain variant comprising an HCVR amino acid sequence set forth in Tables 1A-1B and Sequence Listing but having one or more of such mutations. As described in greater detail below, in some embodiments, an antigen-binding molecule or antigen-binding fragment of the disclosure can include an immunoglobulin light chain variant comprising LCDR1, LCDR2 and LCDR3 wherein one or more (*e.g.*, 1 or 2 or 3) of such CDRs has one or more of such mutations (*e.g.*, conservative substitutions) and/or an immunoglobulin heavy chain variant comprising HCDR1, HCDR2 and HCDR3 wherein one or more (*e.g.*, 1 or 2 or 3) of such CDRs has one or more of such mutations (*e.g.*, conservative substitutions). Such substitutions can be in a CDR, framework, and/or constant region of an antibody or antigen-binding fragment.

[0101] Accordingly, in some embodiments, the antibodies and antigen-binding fragments thereof of the disclosure can include one or more variant CDRs (*e.g.*, any one or more of HCDR1, HCDR2, HCDR3, LCDR1, LCDR2 and/or LCDR3) that are set forth herein with at least 90%, *e.g.*, at least 91%, at least 92%, at least 93%, at least 93%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, sequence identity to, *e.g.*, the heavy chain and light chain CDRs of the Sequence Listing.

[0102] In some embodiments, the HCDR1 amino acid sequence is at least 90%, *e.g.*, at least 91%, at least 92%, at least 93%, at least 93%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, identical to an HCDR1 amino acid sequence identified as such in Tables 1A-1B and Sequence Listing. In some embodiments, the HCDR1 amino acid sequence is at least 90%, *e.g.*, at least 91%, at least 92%, at least 93%, at least 93%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, identical to the HCDR1 of an antibody being any one of TXG-0001, TXG-0002, TXG-0004, TXG-0005, TXG-0006, TXG-0008, TXG-0009, TXG-0048, TXG-0057, TXG-0060, TXG-0063, TXG-0066, TXG-0070, TXG-0072, TXG-0074, TXG-0076, TXG-0078, TXG-0080, TXG-0081, TXG-0087, TXG-0088, TXG-0091, TXG-0094, TXG-0098, TXG-0099, TXG-0100, TXG-0104, TXG-0109, TXG-0112, TXG-0114, TXG-0115, TXG-0120, TXG-0129, TXG-0136, TXG-0141, TXG-0144, TXG-0153, TXG-0154, TXG-0170, TXG-0173, TXG-0174, TXG-0175, TXG-0180, TXG-0181, TXG-0183, TXG-0187, TXG-0189,

TXG-0192, TXG-0197, TXG-0198, TXG-0200, TXG-0201, TXG-0202, TXG-0203, TXG-0204, TXG-0209, TXG-0210, TXG-0228, or TXG-0230.

[0103] In some embodiments, the HCDR1 includes an amino acid sequence identical to an HCDR1 amino acid sequence identified as such in Tables 1A-1B and Sequence Listing, and further wherein one, two, or three amino acids in the amino acid sequence is substituted by a different amino acid. In some embodiments, the HCDR1 includes an amino acid sequence identical to the HCDR1 of an antibody any one of TXG-0001, TXG-0002, TXG-0004, TXG-0005, TXG-0006, TXG-0008, TXG-0009, TXG-0048, TXG-0057, TXG-0060, TXG-0063, TXG-0066, TXG-0070, TXG-0072, TXG-0074, TXG-0076, TXG-0078, TXG-0080, TXG-0081, TXG-0087, TXG-0088, TXG-0091, TXG-0094, TXG-0098, TXG-0099, TXG-0100, TXG-0104, TXG-0109, TXG-0112, TXG-0114, TXG-0115, TXG-0120, TXG-0129, TXG-0136, TXG-0141, TXG-0144, TXG-0153, TXG-0154, TXG-0170, TXG-0173, TXG-0174, TXG-0175, TXG-0180, TXG-0181, TXG-0183, TXG-0187, TXG-0189, TXG-0192, TXG-0197, TXG-0198, TXG-0200, TXG-0201, TXG-0202, TXG-0203, TXG-0204, TXG-0209, TXG-0210, TXG-0228, or TXG-0230; and further wherein one, two, or three amino acids in the amino acid sequence is substituted by a different amino acid.

[0104] In some embodiments, the HCDR1 amino acid sequence is 100% identical to an amino acid sequence identical to an HCDR1 amino acid sequence identified as such in Tables 1A-1B and Sequence Listing. In some embodiments, the HCDR1 amino acid sequence is 100% identical to an amino acid sequence identical to the HCDR1 of an antibody being any one of TXG-0001, TXG-0002, TXG-0004, TXG-0005, TXG-0006, TXG-0008, TXG-0009, TXG-0048, TXG-0057, TXG-0060, TXG-0063, TXG-0066, TXG-0070, TXG-0072, TXG-0074, TXG-0076, TXG-0078, TXG-0080, TXG-0081, TXG-0087, TXG-0088, TXG-0091, TXG-0094, TXG-0098, TXG-0099, TXG-0100, TXG-0104, TXG-0109, TXG-0112, TXG-0114, TXG-0115, TXG-0120, TXG-0129, TXG-0136, TXG-0141, TXG-0144, TXG-0153, TXG-0154, TXG-0170, TXG-0173, TXG-0174, TXG-0175, TXG-0180, TXG-0181, TXG-0183, TXG-0187, TXG-0189, TXG-0192, TXG-0197, TXG-0198, TXG-0200, TXG-0201, TXG-0202, TXG-0203, TXG-0204, TXG-0209, TXG-0210, TXG-0228, or TXG-0230.

[0105] In some embodiments, the HCDR2 amino acid sequence is at least 90%, *e.g.*, at least 91%, at least 92%, at least 93%, at least 93%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, identical to an HCDR2 amino acid sequence identified as such in

Tables 1A-1B and Sequence Listing. In some embodiments, the HCDR2 amino acid sequence is at least 90%, *e.g.*, at least 91%, at least 92%, at least 93%, at least 93%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, identical to the HCDR2 of an antibody being any one of TXG-0001, TXG-0002, TXG-0004, TXG-0005, TXG-0006, TXG-0008, TXG-0009, TXG-0048, TXG-0057, TXG-0060, TXG-0063, TXG-0066, TXG-0070, TXG-0072, TXG-0074, TXG-0076, TXG-0078, TXG-0080, TXG-0081, TXG-0087, TXG-0088, TXG-0091, TXG-0094, TXG-0098, TXG-0099, TXG-0100, TXG-0104, TXG-0109, TXG-0112, TXG-0114, TXG-0115, TXG-0120, TXG-0129, TXG-0136, TXG-0141, TXG-0144, TXG-0153, TXG-0154, TXG-0170, TXG-0173, TXG-0174, TXG-0175, TXG-0180, TXG-0181, TXG-0183, TXG-0187, TXG-0189, TXG-0192, TXG-0197, TXG-0198, TXG-0200, TXG-0201, TXG-0202, TXG-0203, TXG-0204, TXG-0209, TXG-0210, TXG-0228, or TXG-0230.

[0106] In some embodiments, the HCDR2 includes an amino acid sequence identical to an HCDR2 amino acid sequence identified as such in Tables 1A-1B and Sequence Listing, and further wherein one, two, or three amino acids in the amino acid sequence is substituted by a different amino acid. In some embodiments, the HCDR2 includes an amino acid sequence identical to the HCDR2 of an antibody being any one of TXG-0001, TXG-0002, TXG-0004, TXG-0005, TXG-0006, TXG-0008, TXG-0009, TXG-0048, TXG-0057, TXG-0060, TXG-0063, TXG-0066, TXG-0070, TXG-0072, TXG-0074, TXG-0076, TXG-0078, TXG-0080, TXG-0081, TXG-0087, TXG-0088, TXG-0091, TXG-0094, TXG-0098, TXG-0099, TXG-0100, TXG-0104, TXG-0109, TXG-0112, TXG-0114, TXG-0115, TXG-0120, TXG-0129, TXG-0136, TXG-0141, TXG-0144, TXG-0153, TXG-0154, TXG-0170, TXG-0173, TXG-0174, TXG-0175, TXG-0180, TXG-0181, TXG-0183, TXG-0187, TXG-0189, TXG-0192, TXG-0197, TXG-0198, TXG-0200, TXG-0201, TXG-0202, TXG-0203, TXG-0204, TXG-0209, TXG-0210, TXG-0228, or TXG-0230; and further wherein one, two, or three amino acids in the amino acid sequence is substituted by a different amino acid.

[0107] In some embodiments, the HCDR2 amino acid sequence is 100% identical to an amino acid sequence identical to an HCDR2 amino acid sequence identified as such in Tables 1A-1B and Sequence Listing. In some embodiments, the HCDR2 amino acid sequence is 100% identical to an amino acid sequence identical to the HCDR2 of an antibody being any one of TXG-0001, TXG-0002, TXG-0004, TXG-0005, TXG-0006, TXG-0008, TXG-0009, TXG-0048, TXG-0057, TXG-0060, TXG-0063, TXG-0066, TXG-0070, TXG-0072, TXG-0074, TXG-0076,

TXG-0078, TXG-0080, TXG-0081, TXG-0087, TXG-0088, TXG-0091, TXG-0094, TXG-0098, TXG-0099, TXG-0100, TXG-0104, TXG-0109, TXG-0112, TXG-0114, TXG-0115, TXG-0120, TXG-0129, TXG-0136, TXG-0141, TXG-0144, TXG-0153, TXG-0154, TXG-0170, TXG-0173, TXG-0174, TXG-0175, TXG-0180, TXG-0181, TXG-0183, TXG-0187, TXG-0189, TXG-0192, TXG-0197, TXG-0198, TXG-0200, TXG-0201, TXG-0202, TXG-0203, TXG-0204, TXG-0209, TXG-0210, TXG-0228, or TXG-0230.

[0108] In some embodiments, the LCDR1 amino acid sequence is at least 90%, *e.g.*, at least 91%, at least 92%, at least 93%, at least 93%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, identical to an LCDR1 amino acid sequence identified as such in Tables 1A-1B and Sequence Listing. In some embodiments, the LCDR1 amino acid sequence is at least 90%, *e.g.*, at least 91%, at least 92%, at least 93%, at least 93%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, identical to the LCDR1 of an antibody being any one of TXG-0001, TXG-0002, TXG-0004, TXG-0005, TXG-0006, TXG-0008, TXG-0009, TXG-0048, TXG-0057, TXG-0060, TXG-0063, TXG-0066, TXG-0070, TXG-0072, TXG-0074, TXG-0076, TXG-0078, TXG-0080, TXG-0081, TXG-0087, TXG-0088, TXG-0091, TXG-0094, TXG-0098, TXG-0099, TXG-0100, TXG-0104, TXG-0109, TXG-0112, TXG-0114, TXG-0115, TXG-0120, TXG-0129, TXG-0136, TXG-0141, TXG-0144, TXG-0153, TXG-0154, TXG-0170, TXG-0173, TXG-0174, TXG-0175, TXG-0180, TXG-0181, TXG-0183, TXG-0187, TXG-0189, TXG-0192, TXG-0197, TXG-0198, TXG-0200, TXG-0201, TXG-0202, TXG-0203, TXG-0204, TXG-0209, TXG-0210, TXG-0228, or TXG-0230.

[0109] In some embodiments, the LCDR1 includes an amino acid sequence identical to an LCDR1 amino acid sequence identified as such in Tables 1A-1B and Sequence Listing, and further wherein one, two, or three amino acids in the amino acid sequence is substituted by a different amino acid. In some embodiments, the LCDR1 includes an amino acid sequence identical to the LCDR1 of an antibody being any one of TXG-0001, TXG-0002, TXG-0004, TXG-0005, TXG-0006, TXG-0008, TXG-0009, TXG-0048, TXG-0057, TXG-0060, TXG-0063, TXG-0066, TXG-0070, TXG-0072, TXG-0074, TXG-0076, TXG-0078, TXG-0080, TXG-0081, TXG-0087, TXG-0088, TXG-0091, TXG-0094, TXG-0098, TXG-0099, TXG-0100, TXG-0104, TXG-0109, TXG-0112, TXG-0114, TXG-0115, TXG-0120, TXG-0129, TXG-0136, TXG-0141, TXG-0144, TXG-0153, TXG-0154, TXG-0170, TXG-0173, TXG-0174, TXG-0175, TXG-0180, TXG-0181, TXG-0183, TXG-0187, TXG-0189, TXG-0192, TXG-0197, TXG-0198, TXG-0200,

TXG-0201, TXG-0202, TXG-0203, TXG-0204, TXG-0209, TXG-0210, TXG-0228, or TXG-0230; and further wherein one, two, or three amino acids in the amino acid sequence is substituted by a different amino acid.

[0110] In some embodiments, the LCDR1 amino acid sequence is 100% identical to an amino acid sequence identical to an LCDR1 amino acid sequence identified as such in Tables 1A-1B and Sequence Listing. In some embodiments, the LCDR1 amino acid sequence is 100% identical to an amino acid sequence identical to the LCDR1 of an antibody being any one of TXG-0001, TXG-0002, TXG-0004, TXG-0005, TXG-0006, TXG-0008, TXG-0009, TXG-0048, TXG-0057, TXG-0060, TXG-0063, TXG-0066, TXG-0070, TXG-0072, TXG-0074, TXG-0076, TXG-0078, TXG-0080, TXG-0081, TXG-0087, TXG-0088, TXG-0091, TXG-0094, TXG-0098, TXG-0099, TXG-0100, TXG-0104, TXG-0109, TXG-0112, TXG-0114, TXG-0115, TXG-0120, TXG-0129, TXG-0136, TXG-0141, TXG-0144, TXG-0153, TXG-0154, TXG-0170, TXG-0173, TXG-0174, TXG-0175, TXG-0180, TXG-0181, TXG-0183, TXG-0187, TXG-0189, TXG-0192, TXG-0197, TXG-0198, TXG-0200, TXG-0201, TXG-0202, TXG-0203, TXG-0204, TXG-0209, TXG-0210, TXG-0228, or TXG-0230.

[0111] In some embodiments, the LCDR2 amino acid sequence is at least 90%, *e.g.*, at least 91%, at least 92%, at least 93%, at least 93%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, identical to an LCDR2 amino acid sequence identified as such in Tables 1A-1B and Sequence Listing. In some embodiments, the LCDR2 amino acid sequence is at least 90%, *e.g.*, at least 91%, at least 92%, at least 93%, at least 93%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, identical to the LCDR2 of an antibody being any one of TXG-0001, TXG-0002, TXG-0004, TXG-0005, TXG-0006, TXG-0008, TXG-0009, TXG-0048, TXG-0057, TXG-0060, TXG-0063, TXG-0066, TXG-0070, TXG-0072, TXG-0074, TXG-0076, TXG-0078, TXG-0080, TXG-0081, TXG-0087, TXG-0088, TXG-0091, TXG-0094, TXG-0098, TXG-0099, TXG-0100, TXG-0104, TXG-0109, TXG-0112, TXG-0114, TXG-0115, TXG-0120, TXG-0129, TXG-0136, TXG-0141, TXG-0144, TXG-0153, TXG-0154, TXG-0170, TXG-0173, TXG-0174, TXG-0175, TXG-0180, TXG-0181, TXG-0183, TXG-0187, TXG-0189, TXG-0192, TXG-0197, TXG-0198, TXG-0200, TXG-0201, TXG-0202, TXG-0203, TXG-0204, TXG-0209, TXG-0210, TXG-0228, or TXG-0230.

[0112] In some embodiments, the LCDR2 includes an amino acid sequence identical to an LCDR2 amino acid sequence identified as such in Tables 1A-1B and Sequence Listing, and

further wherein one, two, or three amino acids in the amino acid sequence is substituted by a different amino acid. In some embodiments, the LCDR2 includes an amino acid sequence identical to the LCDR2 of an antibody being any one of TXG-0001, TXG-0002, TXG-0004, TXG-0005, TXG-0006, TXG-0008, TXG-0009, TXG-0048, TXG-0057, TXG-0060, TXG-0063, TXG-0066, TXG-0070, TXG-0072, TXG-0074, TXG-0076, TXG-0078, TXG-0080, TXG-0081, TXG-0087, TXG-0088, TXG-0091, TXG-0094, TXG-0098, TXG-0099, TXG-0100, TXG-0104, TXG-0109, TXG-0112, TXG-0114, TXG-0115, TXG-0120, TXG-0129, TXG-0136, TXG-0141, TXG-0144, TXG-0153, TXG-0154, TXG-0170, TXG-0173, TXG-0174, TXG-0175, TXG-0180, TXG-0181, TXG-0183, TXG-0187, TXG-0189, TXG-0192, TXG-0197, TXG-0198, TXG-0200, TXG-0201, TXG-0202, TXG-0203, TXG-0204, TXG-0209, TXG-0210, TXG-0228, or TXG-0230; and further wherein one, two, or three amino acids in the amino acid sequence is substituted by a different amino acid.

[0113] In some embodiments, the LCDR2 amino acid sequence is 100% identical to an amino acid sequence identical to an LCDR2 amino acid sequence identified as such in Tables 1A-1B and Sequence Listing. In some embodiments, the LCDR2 amino acid sequence is 100% identical to an amino acid sequence identical to the LCDR2 of an antibody being any one of TXG-0001, TXG-0002, TXG-0004, TXG-0005, TXG-0006, TXG-0008, TXG-0009, TXG-0048, TXG-0057, TXG-0060, TXG-0063, TXG-0066, TXG-0070, TXG-0072, TXG-0074, TXG-0076, TXG-0078, TXG-0080, TXG-0081, TXG-0087, TXG-0088, TXG-0091, TXG-0094, TXG-0098, TXG-0099, TXG-0100, TXG-0104, TXG-0109, TXG-0112, TXG-0114, TXG-0115, TXG-0120, TXG-0129, TXG-0136, TXG-0141, TXG-0144, TXG-0153, TXG-0154, TXG-0170, TXG-0173, TXG-0174, TXG-0175, TXG-0180, TXG-0181, TXG-0183, TXG-0187, TXG-0189, TXG-0192, TXG-0197, TXG-0198, TXG-0200, TXG-0201, TXG-0202, TXG-0203, TXG-0204, TXG-0209, TXG-0210, TXG-0228, or TXG-0230.

[0114] In some embodiments, an antibody or antigen-binding fragment of the disclosure includes: (a) a HCDR1 comprising an amino acid sequence having 100% sequence identity to an HCDR1 amino acid sequence identified as such in Tables 1A-1B and Sequence Listing; (b) a HCDR2 comprising an amino acid sequence having 100% sequence identity to an HCDR2 amino acid sequence identified as such in Tables 1A-1B and Sequence Listing; (c) a HCDR3 comprising an amino acid sequence having 100% sequence identity to an HCDR3 amino acid sequence identified as such in Tables 1A-1B and Sequence Listing; (d) a LCDR1 comprising an

amino acid sequence having 100% sequence identity to an LCDR1 amino acid sequence identified as such in Tables 1A-1B and Sequence Listing; (e) a LCDR2 comprising an amino acid sequence having 100% sequence identity to an LCDR2 amino acid sequence identified as such in Tables 1A-1B and Sequence Listing; and (f) a LCDR3 comprising an amino acid sequence having 100% sequence identity to an LCDR3 amino acid sequence identified as such in Tables 1A-1B and Sequence Listing.

[0115] In some embodiments, the antibody or antigen-binding fragment of the disclosure includes three heavy chain CDRs (HCDR1, HCDR2 and HCDR3), and three light chain CDRs (LCDR1, LCDR2 and LCDR3), wherein the heavy chain CDRs and light chain CDRs are independently selected from the HCDRs and LCDRs of the antibodies belonging to a clonotype family. One skilled in the art will appreciate that when an antibody is said to include a plurality of HCDRs and/or LCDRs that “are independently selected from a group of antibodies,” this can mean that each of the HCDRs and/or LCDRs of the antibody or antigen-binding fragment can be independently selected from the HCDRs and LCDRs of the antibodies belonging to said group of antibodies. As such, in some embodiments, an antibody or antigen-binding fragment as disclosed herein can include three HCDRs and three LCDRs each of which can be independently selected from the HCDRs and LCDRs of different antibodies belonging to the same group of antibodies. As such, in some embodiments, an antibody or antigen-binding fragment as disclosed herein can include the three HCDRs and three LCDRs of any one of the antibodies of the group.

[0116] Some embodiments of the disclosure provide an antibody or antigen-binding fragment including three HCDRs and three LCDRs each of which are independently selected from the HCDRs and LCDRs of the antibodies belonging to a clonotype family. In some embodiments, an antibody or antigen-binding fragment as disclosed herein can include three HCDRs and three LCDRs each of which can be independently selected from the HCDRs and LCDRs of different antibodies belonging to the same clonotype family. In some embodiments, an antibody or antigen-binding fragment as disclosed herein can include the three HCDRs and the three LCDRs of a selected antibody of a clonotype family. As described in greater detail in Examples 6-7 below, antibodies and antigen-binding fragments exhibiting a binding affinity to a target antigen above a cut-off threshold were selected for further analysis using 10x Genomics “Enclone” (available at <https://bit.ly/enclone>), which is a computational tool developed for clonal grouping to study the adaptive immune system. In this computational tool, the 10x Genomics

Chromium Single Cell V(D)J data containing B cell receptor (BCR) and T cell receptor (TCR) RNA sequences are entered as input data to Enclone. Based on the input, Enclone finds and organizes cells arising from the same progenitors into groups (*e.g.*, clonotype families) and compactly displays each clonotype along with its salient features, including mutated amino acids. In some embodiments, the antibodies belong to clonotype family A or clonotype family C1. In some embodiments, the antibody or antigen-binding fragment of the disclosure includes three heavy chain CDRs (HCDR1, HCDR2 and HCDR3), and three light chain CDRs (LCDR1, LCDR2 and LCDR3), wherein the heavy chain CDRs and light chain CDRs are independently selected from the HCDRs and LCDRs of the following clonotype family of antibodies: (a) clonotype family A: or (b) clonotype family C1.

[0117] In some embodiments, the antibody or antigen-binding fragment of the disclosure includes three heavy chain CDRs (HCDR1, HCDR2 and HCDR3), and three light chain CDRs (LCDR1, LCDR2 and LCDR3), wherein the heavy chain CDRs and light chain CDRs are independently selected from the HCDRs and LCDRs of the antibodies belonging to a clonotype family A as identified in Tables 1A and 1B.

[0118] In some embodiments, the antibody or antigen-binding fragment of the disclosure includes three heavy chain CDRs (HCDR1, HCDR2 and HCDR3), and three light chain CDRs (LCDR1, LCDR2 and LCDR3), wherein the heavy chain CDRs and light chain CDRs are independently selected from the HCDRs and LCDRs of the antibodies belonging to a clonotype family C1 as identified in Tables 1A and 1B.

[0119] Variations in amino acid sequences of the CoV-S antibodies and antigen-binding fragments described herein may be naturally occurring, such as splicing variants or allelic variants. In addition or alternatively, variations in amino acid sequences of the CoV-S antibodies and antigen-binding fragments may be introduced by substitution, deletion or insertion of one or more codons into the nucleic acid sequences encoding the antibodies that results in a change in the amino acid sequences of the antibodies. Optionally, the variation may be resulted from substitution of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or more amino acids with any other amino acid in the antibodies. Amino acid substitutions in variants of CoV-S antibodies and antigen-binding fragments may be conservative or non-conservative. Those of skill in the art will understand that a “non-conservative substitution,” when used in reference to a polypeptide, refers to a substitution of an amino acid in a polypeptide with an amino acid with

significantly differing side chain properties. Non-conservative substitutions may use amino acids between, rather than within, the defined groups and affects (a) the structure of the peptide backbone in the area of the substitution (*e.g.*, serine for glycine), (b) the charge or hydrophobicity, or (c) the bulk of the side chain. A non-limiting exemplary non-conservative substitution can be an acidic amino acid substituted with a basic or aliphatic amino acid; an aromatic amino acid substituted with a small amino acid; and a hydrophilic amino acid substituted with a hydrophobic amino acid.

[0120] Conservatively modified variant anti-CoV-S antibodies and antigen-binding fragments thereof are also contemplated as part of the present disclosure. A “conservatively modified variant” or a “conservative substitution” refers to a variant wherein there is one or more substitutions of amino acids in a polypeptide with other amino acids having similar characteristics (*e.g.* charge, side-chain size, hydrophobicity/hydrophilicity, backbone conformation and rigidity, *etc.*). Such changes can frequently be made without significantly disrupting the biological activity of the antibody or fragment. Those of skill in this art recognize that, in general, single amino acid substitutions in non-essential regions of a polypeptide do not substantially alter biological activity. In addition, substitutions of structurally or functionally similar amino acids are less likely to significantly disrupt biological activity.

[0121] Examples of groups of amino acids that have side chains with similar chemical properties include 1) aliphatic side chains: glycine, alanine, valine, leucine and isoleucine; 2) aliphatic-hydroxyl side chains: serine and threonine; 3) amide-containing side chains: asparagine and glutamine; 4) aromatic side chains: phenylalanine, tyrosine, and tryptophan; 5) basic side chains: lysine, arginine, and histidine; 6) acidic side chains: aspartate and glutamate, and 7) sulfur-containing side chains: cysteine and methionine. Exemplary conservative amino acids substitution groups include valine-leucine-isoleucine, phenylalanine-tyrosine, lysine-arginine, alanine-valine, glutamate-aspartate, and asparagine-glutamine. Alternatively, a conservative replacement is any change having a positive value in the PAM250 log-likelihood matrix as disclosed in Gonnet et al. (1992) Science 256: 1443 45.

[0122] In some embodiments, the antibody or antigen-binding fragment of the disclosure includes a framework region having at least 90%, *e.g.*, at least 91%, at least 92%, at least 93%, at least 93%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, sequence identity to the amino acid sequence of a framework region (FWR) identified as such in Tables

2A-2B and Sequence Listing.

[0123] In some embodiments, the antibody or antigen-binding fragment of the disclosure includes: (a) a heavy chain framework region 1 (HFWR1) comprising an amino acid sequence selected from the HFWR1 sequences identified as such in Tables 2A-2B and Sequence Listing; (b) a heavy chain framework region 2 (HFWR2) comprising an amino acid sequence selected from the HFWR2 sequences identified as such in Tables 2A-2B and Sequence Listing; (c) a heavy chain framework region 3 (HFWR3) comprising an amino acid sequence selected from the HFWR3 sequences identified as such in Tables 2A-2B and Sequence Listing; and (d) a heavy chain framework region 4 (HFWR4) comprising an amino acid sequence selected from the HFWR4 sequences identified as such in Tables 2A-2B and Sequence Listing.

[0124] In some embodiments, the antibody or antigen-binding fragment of the disclosure includes: (a) a light chain framework region 1 (LFWR1) comprising an amino acid sequence selected from the LFWR1 sequences of the Sequence Listing; (b) a light chain framework region 2 (LFWR2) comprising an amino acid sequence selected from the LFWR2 sequences of the Sequence Listing; (c) a light chain framework region 3 (LFWR3) comprising an amino acid sequence selected from the LFWR3 sequences of the Sequence Listing; and (d) a light chain framework region 4 (LFWR4) comprising an amino acid sequence selected from the LFWR4 sequences of the Sequence Listing.

[0125] In some embodiments, the antibody or antigen-binding fragment of the disclosure includes the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 of an antibody of Tables 1A 1B. In some embodiments, the antibody or antigen-binding fragment of the disclosure further includes the heavy chain framework regions HFWR1, HFWR2, HFWR3, and HFWR4 of the same antibody or antigen-binding fragment of Tables 1A 1B and as set forth in the Sequence Listing. In some embodiments, the antibody or antigen-binding fragment of the disclosure further includes the light chain framework regions LFWR1, LFWR2, LFWR3, and LFWR4 of the same antibody or antigen-binding fragment as set forth in Table 2 and the Sequence Listing.

TABLE 2A: Exemplary antibodies of the disclosure and corresponding framework regions.

Antibody	Clonotype Family	Amino acid sequence identifiers (SEQ ID NOs)							
		HFWR1	HFWR2	HFWR3	HFWR4	LFWR1	LFWR2	LFWR3	LFWR4
TXG-0001	A	1137	1296	1455	1614	1773	1932	2091	2250
TXG-0002	A	1138	1297	1456	1615	1774	1933	2092	2251
TXG-0003	A	1139	1298	1457	1616	1775	1934	2093	2252

TXG-0004	A	1140	1299	1458	1617	1776	1935	2094	2253
TXG-0005	A	1141	1300	1459	1618	1777	1936	2095	2254
TXG-0006	A	1142	1301	1460	1619	1778	1937	2096	2255
TXG-0007	A	1143	1302	1461	1620	1779	1938	2097	2256
TXG-0008	A	1144	1303	1462	1621	1780	1939	2098	2257
TXG-0009	A	1145	1304	1463	1622	1781	1940	2099	2258
TXG-0010	B	1146	1305	1464	1623	1782	1941	2100	2259
TXG-0011	B	1147	1306	1465	1624	1783	1942	2101	2260
TXG-0012	B	1148	1307	1466	1625	1784	1943	2102	2261
TXG-0013	B	1149	1308	1467	1626	1785	1944	2103	2262
TXG-0014	B	1150	1309	1468	1627	1786	1945	2104	2263
TXG-0015	B	1151	1310	1469	1628	1787	1946	2105	2264
TXG-0016	B	1152	1311	1470	1629	1788	1947	2106	2265
TXG-0017	B	1153	1312	1471	1630	1789	1948	2107	2266
TXG-0018	C	1154	1313	1472	1631	1790	1949	2108	2267
TXG-0019	C	1155	1314	1473	1632	1791	1950	2109	2268
TXG-0020	C	1156	1315	1474	1633	1792	1951	2110	2269
TXG-0023		3061	3063	3065	3067	3069	3071	3073	3075
TXG-0024	D	1157	1316	1475	1634	1793	1952	2111	2270
TXG-0025	D	1158	1317	1476	1635	1794	1953	2112	2271
TXG-0026	D	1159	1318	1477	1636	1795	1954	2113	2272
TXG-0027		3062	3064	3066	3068	3070	3072	3074	3076
TXG-0029	E	1160	1319	1478	1637	1796	1955	2114	2273
TXG-0030	E	1161	1320	1479	1638	1797	1956	2115	2274
TXG-0031	F	1162	1321	1480	1639	1798	1957	2116	2275
TXG-0032	F	1163	1322	1481	1640	1799	1958	2117	2276
TXG-0033	F	1164	1323	1482	1641	1800	1959	2118	2277
TXG-0034	G	1165	1324	1483	1642	1801	1960	2119	2278
TXG-0035	G	1166	1325	1484	1643	1802	1961	2120	2279
TXG-0036	G	1167	1326	1485	1644	1803	1962	2121	2280
TXG-0037		1168	1327	1486	1645	1804	1963	2122	2281
TXG-0038		1169	1328	1487	1646	1805	1964	2123	2282
TXG-0039	H	1170	1329	1488	1647	1806	1965	2124	2283
TXG-0040	H	1171	1330	1489	1648	1807	1966	2125	2284
TXG-0041	H	1172	1331	1490	1649	1808	1967	2126	2285
TXG-0042		1173	1332	1491	1650	1809	1968	2127	2286
TXG-0044	I	1174	1333	1492	1651	1810	1969	2128	2287
TXG-0045	I	1175	1334	1493	1652	1811	1970	2129	2288
TXG-0046	J	1176	1335	1494	1653	1812	1971	2130	2289
TXG-0047	J	1177	1336	1495	1654	1813	1972	2131	2290
TXG-0048		1178	1337	1496	1655	1814	1973	2132	2291

TXG-0050		1179	1338	1497	1656	1815	1974	2133	2292
TXG-0052		1180	1339	1498	1657	1816	1975	2134	2293
TXG-0053		1181	1340	1499	1658	1817	1976	2135	2294
TXG-0054		1182	1341	1500	1659	1818	1977	2136	2295
TXG-0055		1183	1342	1501	1660	1819	1978	2137	2296
TXG-0057		1184	1343	1502	1661	1820	1979	2138	2297
TXG-0058		1185	1344	1503	1662	1821	1980	2139	2298
TXG-0059		1186	1345	1504	1663	1822	1981	2140	2299
TXG-0060		1187	1346	1505	1664	1823	1982	2141	2300
TXG-0063		1188	1347	1506	1665	1824	1983	2142	2301
TXG-0064		1189	1348	1507	1666	1825	1984	2143	2302
TXG-0065		1190	1349	1508	1667	1826	1985	2144	2303
TXG-0066		1191	1350	1509	1668	1827	1986	2145	2304
TXG-0069		1192	1351	1510	1669	1828	1987	2146	2305
TXG-0070		1193	1352	1511	1670	1829	1988	2147	2306
TXG-0071		1194	1353	1512	1671	1830	1989	2148	2307
TXG-0073		1195	1354	1513	1672	1831	1990	2149	2308
TXG-0074		1196	1355	1514	1673	1832	1991	2150	2309
TXG-0075		1197	1356	1515	1674	1833	1992	2151	2310
TXG-0076		1198	1357	1516	1675	1834	1993	2152	2311
TXG-0077		1199	1358	1517	1676	1835	1994	2153	2312
TXG-0078		1200	1359	1518	1677	1836	1995	2154	2313
TXG-0079		1201	1360	1519	1678	1837	1996	2155	2314
TXG-0080		1202	1361	1520	1679	1838	1997	2156	2315
TXG-0081		1203	1362	1521	1680	1839	1998	2157	2316
TXG-0082		1204	1363	1522	1681	1840	1999	2158	2317
TXG-0084		1205	1364	1523	1682	1841	2000	2159	2318
TXG-0086		1206	1365	1524	1683	1842	2001	2160	2319
TXG-0087		1207	1366	1525	1684	1843	2002	2161	2320
TXG-0088		1208	1367	1526	1685	1844	2003	2162	2321
TXG-0091		1209	1368	1527	1686	1845	2004	2163	2322
TXG-0093		1210	1369	1528	1687	1846	2005	2164	2323
TXG-0094		1211	1370	1529	1688	1847	2006	2165	2324
TXG-0097		1212	1371	1530	1689	1848	2007	2166	2325
TXG-0099		1213	1372	1531	1690	1849	2008	2167	2326
TXG-0100		1214	1373	1532	1691	1850	2009	2168	2327
TXG-0101		1215	1374	1533	1692	1851	2010	2169	2328
TXG-0102		1216	1375	1534	1693	1852	2011	2170	2329
TXG-0103		1217	1376	1535	1694	1853	2012	2171	2330
TXG-0104		1218	1377	1536	1695	1854	2013	2172	2331
TXG-0107		1219	1378	1537	1696	1855	2014	2173	2332

TXG-0109		1220	1379	1538	1697	1856	2015	2174	2333
TXG-0114		1221	1380	1539	1698	1857	2016	2175	2334
TXG-0116		1222	1381	1540	1699	1858	2017	2176	2335
TXG-0117		1223	1382	1541	1700	1859	2018	2177	2336
TXG-0119		1224	1383	1542	1701	1860	2019	2178	2337
TXG-0120		1225	1384	1543	1702	1861	2020	2179	2338
TXG-0122		1226	1385	1544	1703	1862	2021	2180	2339
TXG-0125		1227	1386	1545	1704	1863	2022	2181	2340
TXG-0126		1228	1387	1546	1705	1864	2023	2182	2341
TXG-0127		1229	1388	1547	1706	1865	2024	2183	2342
TXG-0128		1230	1389	1548	1707	1866	2025	2184	2343
TXG-0129		1231	1390	1549	1708	1867	2026	2185	2344
TXG-0131		1232	1391	1550	1709	1868	2027	2186	2345
TXG-0132		1233	1392	1551	1710	1869	2028	2187	2346
TXG-0133		1234	1393	1552	1711	1870	2029	2188	2347
TXG-0139		1235	1394	1553	1712	1871	2030	2189	2348
TXG-0141		1236	1395	1554	1713	1872	2031	2190	2349
TXG-0142		1237	1396	1555	1714	1873	2032	2191	2350
TXG-0143		1238	1397	1556	1715	1874	2033	2192	2351
TXG-0144		1239	1398	1557	1716	1875	2034	2193	2352
TXG-0146		1240	1399	1558	1717	1876	2035	2194	2353
TXG-0148		1241	1400	1559	1718	1877	2036	2195	2354
TXG-0149		1242	1401	1560	1719	1878	2037	2196	2355
TXG-0151		1243	1402	1561	1720	1879	2038	2197	2356
TXG-0155		1244	1403	1562	1721	1880	2039	2198	2357
TXG-0156		1245	1404	1563	1722	1881	2040	2199	2358
TXG-0157		1246	1405	1564	1723	1882	2041	2200	2359
TXG-0158		1247	1406	1565	1724	1883	2042	2201	2360
TXG-0159		1248	1407	1566	1725	1884	2043	2202	2361
TXG-0161		1249	1408	1567	1726	1885	2044	2203	2362
TXG-0162		1250	1409	1568	1727	1886	2045	2204	2363
TXG-0163		1251	1410	1569	1728	1887	2046	2205	2364
TXG-0164		1252	1411	1570	1729	1888	2047	2206	2365
TXG-0166		1253	1412	1571	1730	1889	2048	2207	2366
TXG-0168		1254	1413	1572	1731	1890	2049	2208	2367
TXG-0170		1255	1414	1573	1732	1891	2050	2209	2368
TXG-0175		1256	1415	1574	1733	1892	2051	2210	2369
TXG-0176		1257	1416	1575	1734	1893	2052	2211	2370
TXG-0178		1258	1417	1576	1735	1894	2053	2212	2371
TXG-0180		1259	1418	1577	1736	1895	2054	2213	2372
TXG-0181		1260	1419	1578	1737	1896	2055	2214	2373

TXG-0183		1261	1420	1579	1738	1897	2056	2215	2374
TXG-0184		1262	1421	1580	1739	1898	2057	2216	2375
TXG-0185		1263	1422	1581	1740	1899	2058	2217	2376
TXG-0186		1264	1423	1582	1741	1900	2059	2218	2377
TXG-0187		1265	1424	1583	1742	1901	2060	2219	2378
TXG-0188		1266	1425	1584	1743	1902	2061	2220	2379
TXG-0189		1267	1426	1585	1744	1903	2062	2221	2380
TXG-0190		1268	1427	1586	1745	1904	2063	2222	2381
TXG-0193		1269	1428	1587	1746	1905	2064	2223	2382
TXG-0197		1270	1429	1588	1747	1906	2065	2224	2383
TXG-0198		1271	1430	1589	1748	1907	2066	2225	2384
TXG-0199		1272	1431	1590	1749	1908	2067	2226	2385
TXG-0200		1273	1432	1591	1750	1909	2068	2227	2386
TXG-0201		1274	1433	1592	1751	1910	2069	2228	2387
TXG-0202		1275	1434	1593	1752	1911	2070	2229	2388
TXG-0203		1276	1435	1594	1753	1912	2071	2230	2389
TXG-0204		1277	1436	1595	1754	1913	2072	2231	2390
TXG-0206		1278	1437	1596	1755	1914	2073	2232	2391
TXG-0207		1279	1438	1597	1756	1915	2074	2233	2392
TXG-0209		1280	1439	1598	1757	1916	2075	2234	2393
TXG-0210		1281	1440	1599	1758	1917	2076	2235	2394
TXG-0219	K	1282	1441	1600	1759	1918	2077	2236	2395
TXG-0220	K	1283	1442	1601	1760	1919	2078	2237	2396
TXG-0221	K	1284	1443	1602	1761	1920	2079	2238	2397
TXG-0222	L	1285	1444	1603	1762	1921	2080	2239	2398
TXG-0223	L	1286	1445	1604	1763	1922	2081	2240	2399
TXG-0224		1287	1446	1605	1764	1923	2082	2241	2400
TXG-0225		1288	1447	1606	1765	1924	2083	2242	2401
TXG-0232		1289	1448	1607	1766	1925	2084	2243	2402
TXG-0233		1290	1449	1608	1767	1926	2085	2244	2403
TXG-0234	M	1291	1450	1609	1768	1927	2086	2245	2404
TXG-0235	M	1292	1451	1610	1769	1928	2087	2246	2405
TXG-0236	M	1293	1452	1611	1770	1929	2088	2247	2406
TXG-0238		1294	1453	1612	1771	1930	2089	2248	2407
TXG-0239		1295	1454	1613	1772	1931	2090	2249	2408

TABLE 2B: Exemplary antibodies of the disclosure and corresponding framework regions.

Antibody	Clonotype	Amino acid sequence identifiers (SEQ ID NOs)							
		HFWR1	HFWR2	HFWR3	HFWR4	LFWR1	LFWR2	LFWR3	LFWR4

TXG-0021	A1	5217	5297	5377	5457	5537	5617	5697	5777
TXG-0022	A1	5218	5298	5378	5458	5538	5618	5698	5778
TXG-0023	A1	5219	5299	5379	5459	5539	5619	5699	5779
TXG-0027	B1	5220	5300	5380	5460	5540	5620	5700	5780
TXG-0028	B1	5221	5301	5381	5461	5541	5621	5701	5781
TXG-0043		5222	5302	5382	5462	5542	5622	5702	5782
TXG-0049		5223	5303	5383	5463	5543	5623	5703	5783
TXG-0051		5224	5304	5384	5464	5544	5624	5704	5784
TXG-0056		5225	5305	5385	5465	5545	5625	5705	5785
TXG-0061		5226	5306	5386	5466	5546	5626	5706	5786
TXG-0062		5227	5307	5387	5467	5547	5627	5707	5787
TXG-0067		5228	5308	5388	5468	5548	5628	5708	5788
TXG-0068		5229	5309	5389	5469	5549	5629	5709	5789
TXG-0072		5230	5310	5390	5470	5550	5630	5710	5790
TXG-0083		5231	5311	5391	5471	5551	5631	5711	5791
TXG-0085		5232	5312	5392	5472	5552	5632	5712	5792
TXG-0089		5233	5313	5393	5473	5553	5633	5713	5793
TXG-0090		5234	5314	5394	5474	5554	5634	5714	5794
TXG-0092		5235	5315	5395	5475	5555	5635	5715	5795
TXG-0095		5236	5316	5396	5476	5556	5636	5716	5796
TXG-0096		5237	5317	5397	5477	5557	5637	5717	5797
TXG-0098		5238	5318	5398	5478	5558	5638	5718	5798
TXG-0105		5239	5319	5399	5479	5559	5639	5719	5799
TXG-0106		5240	5320	5400	5480	5560	5640	5720	5800
TXG-0108		5241	5321	5401	5481	5561	5641	5721	5801
TXG-0110		5242	5322	5402	5482	5562	5642	5722	5802
TXG-0111		5243	5323	5403	5483	5563	5643	5723	5803
TXG-0112		5244	5324	5404	5484	5564	5644	5724	5804
TXG-0113		5245	5325	5405	5485	5565	5645	5725	5805
TXG-0115		5246	5326	5406	5486	5566	5646	5726	5806
TXG-0118		5247	5327	5407	5487	5567	5647	5727	5807
TXG-0121		5248	5328	5408	5488	5568	5648	5728	5808
TXG-0123		5249	5329	5409	5489	5569	5649	5729	5809
TXG-0124		5250	5330	5410	5490	5570	5650	5730	5810
TXG-0130		5251	5331	5411	5491	5571	5651	5731	5811
TXG-0134		5252	5332	5412	5492	5572	5652	5732	5812
TXG-0135		5253	5333	5413	5493	5573	5653	5733	5813
TXG-0136		5254	5334	5414	5494	5574	5654	5734	5814
TXG-0137		5255	5335	5415	5495	5575	5655	5735	5815
TXG-0138		5256	5336	5416	5496	5576	5656	5736	5816
TXG-0140		5257	5337	5417	5497	5577	5657	5737	5817

TXG-0145		5258	5338	5418	5498	5578	5658	5738	5818
TXG-0147		5259	5339	5419	5499	5579	5659	5739	5819
TXG-0150		5260	5340	5420	5500	5580	5660	5740	5820
TXG-0152		5261	5341	5421	5501	5581	5661	5741	5821
TXG-0153		5262	5342	5422	5502	5582	5662	5742	5822
TXG-0154		5263	5343	5423	5503	5583	5663	5743	5823
TXG-0160		5264	5344	5424	5504	5584	5664	5744	5824
TXG-0165		5265	5345	5425	5505	5585	5665	5745	5825
TXG-0167		5266	5346	5426	5506	5586	5666	5746	5826
TXG-0169		5267	5347	5427	5507	5587	5667	5747	5827
TXG-0171		5268	5348	5428	5508	5588	5668	5748	5828
TXG-0172		5269	5349	5429	5509	5589	5669	5749	5829
TXG-0173		5270	5350	5430	5510	5590	5670	5750	5830
TXG-0174		5271	5351	5431	5511	5591	5671	5751	5831
TXG-0177		5272	5352	5432	5512	5592	5672	5752	5832
TXG-0179		5273	5353	5433	5513	5593	5673	5753	5833
TXG-0182		5274	5354	5434	5514	5594	5674	5754	5834
TXG-0191		5275	5355	5435	5515	5595	5675	5755	5835
TXG-0192		5276	5356	5436	5516	5596	5676	5756	5836
TXG-0194		5277	5357	5437	5517	5597	5677	5757	5837
TXG-0195		5278	5358	5438	5518	5598	5678	5758	5838
TXG-0196		5279	5359	5439	5519	5599	5679	5759	5839
TXG-0205		5280	5360	5440	5520	5600	5680	5760	5840
TXG-0208		5281	5361	5441	5521	5601	5681	5761	5841
TXG-0211		5282	5362	5442	5522	5602	5682	5762	5842
TXG-0212		5283	5363	5443	5523	5603	5683	5763	5843
TXG-0213		5284	5364	5444	5524	5604	5684	5764	5844
TXG-0214		5285	5365	5445	5525	5605	5685	5765	5845
TXG-0215		5286	5366	5446	5526	5606	5686	5766	5846
TXG-0216		5287	5367	5447	5527	5607	5687	5767	5847
TXG-0217		5288	5368	5448	5528	5608	5688	5768	5848
TXG-0218		5289	5369	5449	5529	5609	5689	5769	5849
TXG-0226		5290	5370	5450	5530	5610	5690	5770	5850
TXG-0227	C1	5291	5371	5451	5531	5611	5691	5771	5851
TXG-0228	C1	5292	5372	5452	5532	5612	5692	5772	5852
TXG-0229	C1	5293	5373	5453	5533	5613	5693	5773	5853
TXG-0230	C1	5294	5374	5454	5534	5614	5694	5774	5854
TXG-0231		5295	5375	5455	5535	5615	5695	5775	5855
TXG-0237		5296	5376	5456	5536	5616	5696	5776	5856

[0126] In some embodiments, the antibody or antigen-binding fragment includes a heavy

chain variable region (HCVR) comprising an amino acid sequence having at least 90%, *e.g.*, at least 91%, at least 92%, at least 93%, at least 93%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, sequence identity to an HCVR identified as such in Tables 1A-1B and Sequence Listing. In some embodiments, the antibody or antigen-binding fragment includes a HCVR comprising an amino acid sequence having at least 90%, *e.g.*, at least 91%, at least 92%, at least 93%, at least 93%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, sequence identity to the HCVR of an antibody being any one of TXG-0001, TXG-0002, TXG-0004, TXG-0005, TXG-0006, TXG-0008, TXG-0009, TXG-0048, TXG-0057, TXG-0060, TXG-0063, TXG-0066, TXG-0070, TXG-0072, TXG-0074, TXG-0076, TXG-0078, TXG-0080, TXG-0081, TXG-0087, TXG-0088, TXG-0091, TXG-0094, TXG-0098, TXG-0099, TXG-0100, TXG-0104, TXG-0109, TXG-0112, TXG-0114, TXG-0115, TXG-0120, TXG-0129, TXG-0136, TXG-0141, TXG-0144, TXG-0153, TXG-0154, TXG-0170, TXG-0173, TXG-0174, TXG-0175, TXG-0180, TXG-0181, TXG-0183, TXG-0187, TXG-0189, TXG-0192, TXG-0197, TXG-0198, TXG-0200, TXG-0201, TXG-0202, TXG-0203, TXG-0204, TXG-0209, TXG-0210, TXG-0228, or TXG-0230.

[0127] In some embodiments, the antibody or antigen-binding fragment includes a light chain variable region (LCVR) comprising an amino acid sequence having at least 90%, *e.g.*, at least 91%, at least 92%, at least 93%, at least 93%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, sequence identity to an LCVR identified as such in Tables 1A-1B and Sequence Listing. In some embodiments, the antibody or antigen-binding fragment includes a LCVR comprising an amino acid sequence having at least 90%, *e.g.*, at least 91%, at least 92%, at least 93%, at least 93%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, sequence identity to the HCVR of an antibody being any one of TXG-0001, TXG-0002, TXG-0004, TXG-0005, TXG-0006, TXG-0008, TXG-0009, TXG-0048, TXG-0057, TXG-0060, TXG-0063, TXG-0066, TXG-0070, TXG-0072, TXG-0074, TXG-0076, TXG-0078, TXG-0080, TXG-0081, TXG-0087, TXG-0088, TXG-0091, TXG-0094, TXG-0098, TXG-0099, TXG-0100, TXG-0104, TXG-0109, TXG-0112, TXG-0114, TXG-0115, TXG-0120, TXG-0129, TXG-0136, TXG-0141, TXG-0144, TXG-0153, TXG-0154, TXG-0170, TXG-0173, TXG-0174, TXG-0175, TXG-0180, TXG-0181, TXG-0183, TXG-0187, TXG-0189, TXG-0192, TXG-0197, TXG-0198, TXG-0200, TXG-0201, TXG-0202, TXG-0203, TXG-0204, TXG-0209, TXG-0210, TXG-0228, or TXG-0230.

[0128] In some embodiments, the antibody or antigen-binding fragment of the disclosure includes: (a) a HCVR comprising an amino acid sequence having at least 90%, *e.g.*, at least 91%, at least 92%, at least 93%, at least 93%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, sequence identity to an HCVR identified as such in Tables 1A-1B and Sequence Listing; and b) a LCVR comprising an amino acid sequence having at least 90%, *e.g.*, at least 91%, at least 92%, at least 93%, at least 93%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, sequence identity to an LCVR identified as such in Tables 1A-1B and Sequence Listing. In some embodiments, the antibody or antigen-binding fragment includes: a HCVR and a LCVR which respectively are 90%, *e.g.*, at least 91%, at least 92%, at least 93%, at least 93%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, identical to the HCVR and LCVR of an antibody of Table 1A or Table 1B. In some embodiments, the antibody or antigen-binding fragment includes: a HCVR and a LCVR which respectively are 90%, *e.g.*, at least 91%, at least 92%, at least 93%, at least 93%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, identical to the HCVR and LCVR of an antibody selected from the group consisting of TXG-0001, TXG-0002, TXG-0004, TXG-0005, TXG-0006, TXG-0008, TXG-0009, TXG-0048, TXG-0057, TXG-0060, TXG-0063, TXG-0066, TXG-0070, TXG-0072, TXG-0074, TXG-0076, TXG-0078, TXG-0080, TXG-0081, TXG-0087, TXG-0088, TXG-0091, TXG-0094, TXG-0098, TXG-0099, TXG-0100, TXG-0104, TXG-0109, TXG-0112, TXG-0114, TXG-0115, TXG-0120, TXG-0129, TXG-0136, TXG-0141, TXG-0144, TXG-0153, TXG-0154, TXG-0170, TXG-0173, TXG-0174, TXG-0175, TXG-0180, TXG-0181, TXG-0183, TXG-0187, TXG-0189, TXG-0192, TXG-0197, TXG-0198, TXG-0200, TXG-0201, TXG-0202, TXG-0203, TXG-0204, TXG-0209, TXG-0210, TXG-0228, or TXG-0230.

[0129] In some embodiments, the antibody or antigen-binding fragment includes the HCVR and LCVR of an antibody of Table 1A or Table 1B. In some embodiments, the antibody or antigen-binding fragment includes the HCVR and LCVR of an antibody being any one of TXG-0001, TXG-0002, TXG-0004, TXG-0005, TXG-0006, TXG-0008, TXG-0009, TXG-0048, TXG-0057, TXG-0060, TXG-0063, TXG-0066, TXG-0070, TXG-0072, TXG-0074, TXG-0076, TXG-0078, TXG-0080, TXG-0081, TXG-0087, TXG-0088, TXG-0091, TXG-0094, TXG-0098, TXG-0099, TXG-0100, TXG-0104, TXG-0109, TXG-0112, TXG-0114, TXG-0115, TXG-0120, TXG-0129, TXG-0136, TXG-0141, TXG-0144, TXG-0153, TXG-0154, TXG-0170, TXG-0173, TXG-0174, TXG-0175, TXG-0180, TXG-0181, TXG-0183, TXG-0187, TXG-0189, TXG-0192,

TXG-0197, TXG-0198, TXG-0200, TXG-0201, TXG-0202, TXG-0203, TXG-0204, TXG-0209, TXG-0210, TXG-0228, or TXG-0230. In some embodiments, the antibody or antigen-binding fragment of the disclosure is selected from Table 1A or Table 1B. In some embodiments, the antibody or antigen-binding fragment is being any one of TXG-0001, TXG-0002, TXG-0004, TXG-0005, TXG-0006, TXG-0008, TXG-0009, TXG-0048, TXG-0057, TXG-0060, TXG-0063, TXG-0066, TXG-0070, TXG-0072, TXG-0074, TXG-0076, TXG-0078, TXG-0080, TXG-0081, TXG-0087, TXG-0088, TXG-0091, TXG-0094, TXG-0098, TXG-0099, TXG-0100, TXG-0104, TXG-0109, TXG-0112, TXG-0114, TXG-0115, TXG-0120, TXG-0129, TXG-0136, TXG-0141, TXG-0144, TXG-0153, TXG-0154, TXG-0170, TXG-0173, TXG-0174, TXG-0175, TXG-0180, TXG-0181, TXG-0183, TXG-0187, TXG-0189, TXG-0192, TXG-0197, TXG-0198, TXG-0200, TXG-0201, TXG-0202, TXG-0203, TXG-0204, TXG-0209, TXG-0210, TXG-0228, or TXG-0230.

[0130] In some embodiments, the antibody or antigen-binding fragment of the disclosure further includes a constant region (*e.g.*, an Fc region). In some embodiments, the constant region is an IgA, IgD, IgE, IgG, or IgM heavy chain constant region. In some embodiments, the heavy chain constant region is of the same isotype and subclass as the antibody identified in Tables 1A-1B. In some embodiments, the antibody or antigen-binding fragment of the disclosure includes a constant region of the type IgA (*e.g.*, IgA1 or IgA2), IgD, IgE, IgG (*e.g.*, IgG1, IgG2, IgG3 and IgG4) or IgM. In some embodiments, the constant region is an IgG constant region.

[0131] In some embodiments, the antibody or antigen-binding fragment of the disclosure further includes a kappa type light chain constant region. In some embodiments, the antibody or antigen-binding fragment of the disclosure further includes a lambda type light chain constant region.

[0132] In some embodiments, the antibody or antigen-binding fragment of the disclosure comprises a hinge domain. In some embodiments, the hinge domain comprises a stabilizing mutation.

[0133] In some embodiments, the antibody or antigen-binding fragment of the disclosure comprises a variant Fc region. The variant Fc region may comprise one or more amino acid modifications that reduce the affinity of the variant Fc Region for an FcγR receptor. Exemplary amino acid modifications that reduce the affinity of the variant Fc Region for an FcγR receptor include L234A; L235A; or L234A and L235A, according to Kabat (EU index) numbering

system. The variant Fc region may comprise one or more amino acid modifications that enhance the serum half-life of the variant Fc region. Exemplary amino acid modifications that enhance the serum half-life of the variant Fc region include M252Y; M252Y and S254T; M252Y and T256E; M252Y, S254T and T256E; or K288D and H435K, according to Kabat (EU index) numbering system.

[0134] In some embodiments, the antibody or antigen-binding fragment of the disclosure is a human antibody or antigen-binding fragment. One of ordinary skill in the art will understand that the term “human” antibody includes antibodies having variable and constant regions derived from human germline immunoglobulin sequences whether in a human cell or grafted into a non-human cell, *e.g.*, a mouse cell. The human antibodies of the disclosure can include amino acid residues not encoded by human germline immunoglobulin sequences (*e.g.*, mutations introduced by random or site-specific mutagenesis *in vitro* or by somatic mutation *in vivo*), for example in the CDRs, such as CDR3. However, the term “human antibody,” as used herein, is not intended to include antibodies in which CDR sequences derived from the germline of another mammalian species (*e.g.*, mouse) have been grafted onto human FWR sequences. The term includes antibodies recombinantly produced in a non-human mammal or in cells of a non-human mammal.

[0135] In some embodiments, the antibody or antigen-binding fragment is a humanized antibody, a chimeric antibody, or a hybrid antibody, or an antigen-binding fragment of any thereof. The term “humanized antibody” as used herein encompasses antibodies comprising heavy and light chain variable region sequences from a non-human species (*e.g.*, a mouse) but in which at least a portion of the VH and/or VL sequence has been altered to be more “human-like,” *i.e.*, more similar to human germline variable sequences. One type of humanized antibody is a CDR-grafted antibody in which human CDR sequences are introduced into non-human VH and VL sequences to replace the corresponding non-human CDR sequences. Another type of humanized antibody is a FWR-grafted antibody in which human FWR sequences are introduced into non-human VH and VL sequences to replace corresponding non-human FWR sequences. In some embodiments, the antibodies or antigen-binding fragments of the disclosure include a murine antibody, phage display antibody, or nanobody / VHH containing the frameworks and/or CDRs described in this disclosure (*e.g.*, in Tables 1A-1B, A-2B, and Sequence Listing). As used herein, the term “chimeric antibody” encompasses antibodies having the variable domain from a

first antibody and the constant domain from a second antibody, wherein the first and second antibodies are from different species. As used herein, the term “hybrid antibody” encompasses antibodies having the variable domain from a first antibody and the constant domain from a second antibody, wherein the first and second antibodies are from different animals, or wherein the variable domain, but not the constant region, is from a first animal. For example, a variable domain can be taken from an antibody isolated from a human and expressed with a fixed constant region not isolated from that antibody. Hybrid antibodies are synthetic and non-naturally occurring because the variable and constant regions they contain are not isolated from a single natural source. In some embodiments, the hybrid antibodies of the disclosure includes a light chain from a first antibody and a heavy chain from a second antibody, wherein the first and second antibodies are from different species. In some embodiments, the chimeric antibodies of the disclosure includes a non-human light chain which is combined with a heavy chain or set of heavy chain CDRs disclosed in this application.

[0136] In some embodiments, the antibody is a monoclonal antibody. In some embodiments, the antibody or antigen-binding fragment is an engineered antibody or engineered antibody fragment. Non-limiting examples of engineered antibody fragment include a single-chain variable fragment (scFv), a nanobody, a diabody, a triabody, a minibody, an F(ab')₂ fragment, an F(ab) fragment, a VH domain, a VL domain, a single chain variable fragment (scFv), a single domain antibody (sdAb), a VNAR domain, and a VHH domain. In some embodiments, the antibody or antigen-binding fragment of the disclosure is a single-chain antibody fragment (scFv), a F(ab) fragment, a F(ab') fragment, a Fab'-SH, a F(ab')₂ fragment, or a Fv fragment.

[0137] In some embodiments, the antibody or antigen-binding fragment has a binding affinity (*e.g.*, ability to bind, with varying degrees of specificity) to an epitope in a subunit of the SARS-CoV-2 S protein. One skilled in the art will understand that the term “epitope” refers to an antigenic determinant (*e.g.*, a CoV-S polypeptide) that interacts with a specific antigen-binding site of an antigen-binding polypeptide, *e.g.*, a variable region of an antibody molecule, known as a paratope. A single antigen can have more than one epitope. Thus, different antibodies may bind to different areas on an antigen and may have different biological effects. The term “epitope” also refers to a site on an antigen to which B and/or T cells respond. It also refers to a region of an antigen that is bound by an antibody. Epitopes can be defined as structural or functional.

Functional epitopes are generally a subset of the structural epitopes and have those residues that directly contribute to the affinity of the interaction. Epitopes can be linear or conformational, that is, composed of non-linear amino acids. In some embodiments, epitopes can include determinants that are chemically active surface groupings of molecules such as amino acids, sugar side chains, phosphoryl groups, or sulfonyl groups, and, in some embodiments, can have specific three-dimensional structural characteristics, and/or specific charge characteristics.

[0138] Methods for determining the epitope of an antigen-binding polypeptide, *e.g.*, antibody or antigen-binding fragment or polypeptide, include alanine scanning mutational analysis, peptide blot analysis, peptide cleavage analysis, crystallographic studies and NMR analysis. In addition, methods such as epitope excision, epitope extraction and chemical modification of antigens can be employed. Another method that can be used to identify the amino acids within a polypeptide with which an antigen-binding polypeptide (*e.g.*, antibody or fragment or polypeptide) interacts is hydrogen/deuterium exchange detected by mass spectrometry.

[0139] As described in greater detail below, the vast majority of known antibodies against SARS-CoV-2 recognize one of three major epitope regions of the spike protein: the RBD of the S1 subunit, the NTD of the S1 subunit, and the S2 subunit. In particular, neutralizing antibodies (nAbs) against each of these epitope regions have been identified and reported, with the broadest nAbs targeting epitopes in the S2 subunit or the RBD of the S1 subunit. In contrast, antibodies specific for the NTD of the S1 subunit primarily target a single supersite, have a limited genetic vocabulary and, because the NTD is not particularly well conserved across CoVs, are generally understood to be of limited breadth (Suryadevara et al., *J. Clin. Invest.* Jun 1;132(11), 2022). Recently, NTD-specific antibodies targeting a moderately conserved epitope outside the NTD supersite neutralized several SARS-CoV-2 variants of concern (VoCs) have been reported, but their breadth did not extend beyond SARS-CoV-2 to other human CoVs (Wang et al., *BioRxiv*. Preprint. 2022 Feb 1; doi: 10.1101/2022.02.01.478695).

[0140] In some embodiments of the present disclosure, the antibody or antigen-binding fragment has a binding affinity to an epitope the S1 subunit of the SARS-CoV-2 S protein. In some embodiments, the antibody or antigen-binding fragment has a binding affinity to a RBD of the S1 subunit. In some embodiments, the subunit of the S protein of SARS-CoV-2 is the S2 subunit. In some embodiments, the antibody or antigen-binding fragment has a binding affinity

to a NTD of the S1 subunit.

[0141] In some embodiments, the SARS-CoV-2 S protein may include one or more amino acid substitutions. In some embodiments, the SARS-CoV-2 S protein includes one or more of the following Proline substitutions: F817P, A892P, A899P, A942P, K986P, and V987P. In some embodiments, the SARS-CoV-2 S protein includes one or more of the following Alanine substitutions: R683A and R685A. In some embodiments, the one or more amino acid substitutions includes D614G substitution. In some embodiments, the SARS-CoV-2 S protein has the amino acid sequence provided in **FIG. 15A**. In some embodiments, the S protein of SARS-CoV-2 has the amino acid sequence provided in **FIG. 15B**.

[0142] In some embodiments, the SARS-CoV-2 S protein includes one or more amino acid substitutions at a position being any one of K417, L452, E484, N501, D614, or a combination thereof. In some embodiments, the SARS-CoV-2 S protein includes an amino acid substitution at position K417. In some embodiments, the K417 amino acid substitution is a conservative amino acid substitution. In some embodiments, the amino acid substitution at position K417 is K417T or K417N. In some embodiments, the K417 amino acid substitution is a non-conservative amino acid substitution. In some embodiments, the L452 amino acid substitution is a conservative amino acid substitution. In some embodiments, the amino acid substitution at position L452 is L452R. In some embodiments, the L452 amino acid substitution is a non-conservative amino acid substitution. In some embodiments, the SARS-CoV-2 S protein includes an amino acid substitution at position E484. In some embodiments, the E484 amino acid substitution is a conservative amino acid substitution. In some embodiments, the E484 amino acid substitution is a non-conservative amino acid substitution. In some embodiments, the amino acid substitution at position E484 is E484K or E484Q. In some embodiments, the SARS-CoV-2 S protein includes an amino acid substitution at position N501. In some embodiments, the N501 amino acid substitution is a conservative amino acid substitution. In some embodiments, the N501 amino acid substitution is a non-conservative amino acid substitution. In some embodiments, the amino acid substitution at position N501 is N501Y. In some embodiments, the SARS-CoV-2 S protein includes an amino acid substitution at position D614. In some embodiments, the D614 amino acid substitution is a conservative amino acid substitution. In some embodiments, the D614 amino acid substitution is a non-conservative amino acid substitution. In some embodiments, the amino acid substitution at position D614 is D614G.

[0143] In some embodiments, the SARS-CoV-2 S protein includes one or more amino acid substitutions that is any one of K417T, K417N, L452R, E484K, E484Q, N501Y, D614G, or a combination thereof. In some embodiments, the SARS-CoV-2 S protein includes a combination of the following amino acid substitutions: K417N, E484K, and N501Y. In some embodiments, the SARS-CoV-2 S protein includes a combination of the following amino acid substitutions: K417T, E484K, and N501Y. In some embodiments, the SARS-CoV-2 S protein includes a combination of the following amino acid substitutions: L452R and E484Q. In some embodiments, the antibody or antigen-binding fragment has binding affinity for a trimeric form of the CoV-S protein. In some embodiments, the antibody or antigen-binding fragment has binding affinity for a pre-fusion trimeric form of the CoV-S protein. In some embodiments, the antibody or antigen-binding fragment has binding affinity for a stabilized prefusion spike protein (*e.g.*, an S2P-stabilized pre-fusion spike protein) in monomeric or multimeric (*e.g.*, trimeric) form. In some embodiments, the antibody or antigen-binding fragment has binding affinity for a non-prefusion spike protein in monomeric or multimeric (*e.g.*, trimeric) form. In some embodiments, the antibody or antigen-binding fragment has binding affinity for a non-S2P-stabilized pre-fusion spike protein in monomeric or multimeric (*e.g.*, trimeric) form. Pre-fusion and non-prefusion conformations of the spike protein are described in, *e.g.*, Cai Y. *et al.* Science Vol. 369, Issue 6511, pp. 1586-1592, 2020; Xu C. *et al.* Science Advances, Vol. 7, no. 1, Jan 2021; Wrobel AG *et al.* Nat Comms 11, 5337, 2020; and Zhang J. *et al.* Science March 16, 2021; all of which are hereby incorporated by reference in their entirety.

[0144] Generally, binding affinity of an antigen-binding molecule (*e.g.*, antibody) or antigen-binding fragment to its target antigen can be used as a measure of the strength of a non-covalent interaction between two molecules, *e.g.*, an antibody or antigen-binding fragment thereof and an antigen (*e.g.*, coronavirus S protein antigen). In some cases, binding affinity can be used to describe monovalent interactions (intrinsic activity). Binding affinity between two molecules can be quantified by determination of the equilibrium dissociation constant (K_D). In turn, K_D can be determined by measurement of the kinetics of complex formation and dissociation using, *e.g.*, the surface plasmon resonance (SPR) method (Biacore). The rate constants corresponding to the association and the dissociation of a monovalent complex are referred to as the association rate constants k_a (or k_{on}) and dissociation rate constant k_d (or k_{off}), respectively. K_D is related to k_a and k_d through the equation $K_D = k_d / k_a$. The value of the

dissociation constant can be determined directly by various methods, and can be computed even for complex mixtures by methods such as those set forth in Caceci *et al.* (1984, *Byte* 9: 340-362). For example, the K_D can be established using a double-filter nitrocellulose filter binding assay such as that disclosed by Wong & Lohman (1993, *Proc. Natl. Acad. Sci. USA* 90: 5428- 5432). As shown in Examples 9 and 12 below, binding affinity of the antibodies and fragments described herein can also be assayed using a Catterra LSA SPR biosensor equipped with a HC30M chip.

[0145] Other assays to evaluate the binding ability (*e.g.*, binding affinity and/or specificity) of the antigen-binding molecules (*e.g.*, antibodies) and antigen-binding fragments of the present disclosure towards target antigens include, for example, ELISAs, Western blots, RIAs, and flow cytometry analysis. The binding kinetics and binding affinity of the antibody also can be assessed by standard assays known in the art, such as Surface Plasmon Resonance (SPR), *e.g.* by using a Biacore™ system, or KinExA. In some embodiments, the binding affinity of an antibody or an antigen-binding fragment for a target antigen (*e.g.*, coronavirus S protein antigen) can be calculated by the Scatchard method described by Frankel *et al.*, *Mol. Immunol.*, 16: 101-106, 1979. It will be understood that the binding affinity of an antibody or antigen-binding fragment for a target antigen is the strength of interaction between the antibody or antigen-binding fragment with the target antigen, whereas the binding specificity of an antibody or antigen-binding fragment for a target antigen relates to the affinity to the target antigen relative to other antigens. It will also be understood that an antibody or antigen-binding fragment that “specifically binds” a target antigen (such as S protein) is an antigen-binding fragment that binds the target antigen but does not significantly bind other antigens. In some embodiments, the antibody or antigen-binding fragment “specifically binds” a target antigen if it does not significantly bind other antigens but binds the target antigen with high affinity, *e.g.*, with an equilibrium dissociation constant (K_D) of 100 nM or less, such as 60 nM or less, for example, 30 nM or less, such as, 15 nM or less, or 10 nM or less, or 5 nM or less, or 1 nM or less, or 500 pM or less, or 400 pM or less, or 300 pM or less, or 200 pM or less, or 100 pM or less. In some embodiments, the antibody or antigen-binding fragment binds a target antigen with high affinity, *e.g.*, with a K_D of less than 1 μ M. In some embodiments, the antibodies or antigen-binding fragments of the disclosure that specifically bind a target antigen, such as a CoV-S protein (*e.g.*, SARS-CoV-2 S protein), have a binding affinity to the target antigen expressed as K_D , of at least

about 10^{-8} M, as measured by real-time, label free bio-layer interferometry assay, for example, at 25° C. or 37°C, *e.g.*, an Octet® HTX biosensor, or by surface plasmon resonance, *e.g.*, BIACORE™, or by solution-affinity ELISA. In some embodiments, the antibody or antigen-binding fragment has a measurable binding affinity and/or binding specificity, *e.g.*, with an equilibrium dissociation constant (K_D) value of less than 1 mM, less than 100 μ M, less than 10 μ M, less than 1 μ M, less than 900 nM, less than 800 nM, less than 700 nM, less than 600 nM, less than 500 nM, for example, less than 400 nM, less than 300 nM, less than 200 nM, less than 150 nM, less than 120 nM, less than 100 nM, less than 90 nM, less than 80 nM, less than 70 nM, less than 60 nM, less than 50 nM, less than 40 nM, less than 20 nM, less than 15 nM, less than 10 nM, less than 5 nM, less than 5 nM, or less than 1 nM.

[0146] In some embodiments, the binding affinity and/or binding specificity of an antigen-binding molecule (*e.g.*, antibody or antigen-binding fragment) to a CoV-S target antigen is determined based on a quantity/number of target and optionally non-target antigen sequence reads and/or unique molecular identifiers (UMIs) associated with the antigen binding molecule via a process termed “barcode-enabled antigen mapping by sequencing” (BEAM-seq) (see, *e.g.*, Examples 6 and 7 and FIGS. 2, 3, and 4 below. Antigen sequence reads and/or UMIs can be associated bioinformatically with antigen binding molecule sequences via shared partition barcode sequences. For example, binding affinity and/or binding specificity of an antigen binding molecule to the CoV-S antigen can be determined based on independent observations of quantity/number of UMIs associated with the CoV-S antigen and optionally non-target antigen from one or more partitions, wherein each of the one or more partitions comprise a cell expressing the same antigen-binding molecule. For other example, binding affinity and/or binding specificity of an antigen binding molecule to the CoV-S antigen can be determined based on independent observations of quantity/number of UMIs associated with the antigen from one or more partitions, wherein each of the one or more partitions comprise a cell expressing an antigen-binding molecule belonging to the same clonotype group. For example, high (*e.g.*, over 40) target antigen UMI counts can be used to predict high binding affinity. As demonstrated in the Examples below, an antibody can be predicted to have specific binding affinity for the target CoV-S antigen if it is associated with high target antigen counts and low non-target antigen counts.

[0147] In some embodiments, the antibody or antigen-binding fragment has a binding

affinity and/or binding specificity with an equilibrium dissociation constant (K_D) value of less than 500 nM, for example, less than 400 nM, less than 300 nM, less than 200 nM, less than 150 nM, less than 120 nM, less than 100 nM, less than 90 nM, less than 80 nM, less than 70 nM, less than 60 nM, less than 50 nM, less than 40 nM, less than 20 nM, less than 15 nM, less than 10 nM, less than 5 nM, less than 5 nM, or less than 1 nM.

[0148] In some embodiments, the antibody or antigen-binding fragment has a binding affinity with a K_D value lower than the binding affinity between a SARS-CoV-2 S protein and its receptor ACE2, which has been previously estimated to have a K_D value of about 120 nM. Accordingly, in some embodiment of the disclosure, the antibody or antigen-binding fragment has a binding affinity with a K_D value of less than 120 nM. In some embodiments, the antibody or antigen-binding fragment has a K_D value of less than 120 nM and includes three heavy chain CDRs (HCDR1, HCDR2 and HCDR3), and three light chain CDRs (LCDR1, LCDR2 and LCDR3), wherein the heavy chain CDRs and light chain CDRs are independently selected from the HCDRs and LCDRs of the antibodies of Table 4.

[0149] In some embodiments, the antibody or antigen-binding fragment has a binding affinity with an equilibrium dissociation constant (K_D) value of less than 120 nM and includes three heavy chain CDRs (HCDR1, HCDR2 and HCDR3), and three light chain CDRs (LCDR1, LCDR2 and LCDR3), wherein the heavy chain CDRs and light chain CDRs are independently selected from the HCDRs and LCDRs of the following group of antibodies: TXG-0072, TXG-0098, TXG-0112, TXG-0115, TXG-0136, TXG-0153, TXG-0154, TXG-0173, TXG-0174, TXG-0192, TXG-0228, and TXG-0230.

[0150] In some embodiments, the antibody or antigen-binding fragment includes a HCVR which includes an amino acid sequence having at least 90% sequence identity to the HCVR of an antibody of Table 4. In some embodiments, the antibody or antigen-binding fragment includes a HCVR which includes an amino acid sequence having at least 90% sequence identity, for example, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to the HCVR of an antibody being any one of TXG-0072, TXG-0098, TXG-0112, TXG-0115, TXG-0136, TXG-0153, TXG-0154, TXG-0173, TXG-0174, TXG-0192, TXG-0228, or TXG-0230. In some embodiments, the antibody or antigen-binding fragment includes a HCVR which includes an amino acid sequence having at least 90% sequence identity, for example, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to the HCVR of

TXG-0072. In some embodiments, the antibody or antigen-binding fragment includes a HCVR which includes an amino acid sequence having at least 90% sequence identity, for example, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to the HCVR of TXG-0098. In some embodiments, the antibody or antigen-binding fragment includes a HCVR which includes an amino acid sequence having at least 90% sequence identity, for example, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to the HCVR of TXG-0112. In some embodiments, the antibody or antigen-binding fragment includes a HCVR which includes an amino acid sequence having at least 90% sequence identity, for example, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to the HCVR of TXG-0115.

[0151] In some embodiments, the antibody or antigen-binding fragment includes a HCVR which includes an amino acid sequence having at least 90% sequence identity, for example, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to the HCVR of TXG-0136. In some embodiments, the antibody or antigen-binding fragment includes a HCVR which includes an amino acid sequence having at least 90% sequence identity, for example, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to the HCVR of TXG-0153. In some embodiments, the antibody or antigen-binding fragment includes a HCVR which includes an amino acid sequence having at least 90% sequence identity, for example, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to the HCVR of TXG-0154. In some embodiments, the antibody or antigen-binding fragment includes a HCVR which includes an amino acid sequence having at least 90% sequence identity, for example, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to the HCVR of TXG-0173. In some embodiments, the antibody or antigen-binding fragment includes a HCVR which includes an amino acid sequence having at least 90% sequence identity, for example, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to the HCVR of TXG-0174. In some embodiments, the antibody or antigen-binding fragment includes a HCVR which includes an amino acid sequence having at least 90% sequence identity, for example, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to the HCVR of TXG-0192. In some embodiments, the antibody or antigen-binding fragment includes a HCVR which includes an amino acid sequence having at least 90% sequence identity, for example, at least 95%, at least 96%, at least 97%, at

least 98%, or at least 99% sequence identity to the HCVR of TXG-0228. In some embodiments, the antibody or antigen-binding fragment includes a HCVR which includes an amino acid sequence having at least 90% sequence identity, for example, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to the HCVR of TXG-0230.

[0152] In some embodiments, the antibody or antigen-binding fragment includes a HCVR which includes an amino acid sequence having at least 100% sequence identity to the HCVR of an antibody being any one of TXG-0072, TXG-0098, TXG-0112, TXG-0115, TXG-0136, TXG-0153, TXG-0154, TXG-0173, TXG-0174, TXG-0192, TXG-0228, or TXG-0230.

[0153] In some embodiments, the antibody or antigen-binding fragment includes a HCVR which includes an amino acid sequence having at least 100% sequence identity to the HCVR of TXG-0072. In some embodiments, the antibody or antigen-binding fragment includes a HCVR which includes an amino acid sequence having at least 100% sequence identity to the HCVR of TXG-0098. In some embodiments, the antibody or antigen-binding fragment includes a HCVR which includes an amino acid sequence having at least 100% sequence identity to the HCVR of TXG-0112. In some embodiments, the antibody or antigen-binding fragment includes a HCVR which includes an amino acid sequence having at least 100% sequence identity to the HCVR of TXG-0115. In some embodiments, the antibody or antigen-binding fragment includes a HCVR which includes an amino acid sequence having at least 100% sequence identity to the HCVR of TXG-0136. In some embodiments, the antibody or antigen-binding fragment includes a HCVR which includes an amino acid sequence having at least 100% sequence identity to the HCVR of TXG-0153. In some embodiments, the antibody or antigen-binding fragment includes a HCVR which includes an amino acid sequence having at least 100% sequence identity to the HCVR of TXG-0154. In some embodiments, the antibody or antigen-binding fragment includes a HCVR which includes an amino acid sequence having at least 100% sequence identity to the HCVR of TXG-0173. In some embodiments, the antibody or antigen-binding fragment includes a HCVR which includes an amino acid sequence having at least 100% sequence identity to the HCVR of TXG-0174. In some embodiments, the antibody or antigen-binding fragment includes a HCVR which includes an amino acid sequence having at least 100% sequence identity to the HCVR of TXG-0192. In some embodiments, the antibody or antigen-binding fragment includes a HCVR which includes an amino acid sequence having at least 100% sequence identity to the HCVR of TXG-0228. In some embodiments, the antibody or antigen-binding fragment includes a HCVR

which includes an amino acid sequence having at least 100% sequence identity to the HCVR of TXG-0230.

[0154] In some embodiments, the antibody or antigen-binding fragment includes a LCVR which includes an amino acid sequence having at least 90% sequence identity, for example, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to the LCVR of an antibody being any one of TXG-0072, TXG-0098, TXG-0112, TXG-0115, TXG-0136, TXG-0153, TXG-0154, TXG-0173, TXG-0174, TXG-0192, TXG-0228, or TXG-0230. In some embodiments, the antibody or antigen-binding fragment includes a LCVR which includes an amino acid sequence having at least 90% sequence identity, for example, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to the LCVR of TXG-0072. In some embodiments, the antibody or antigen-binding fragment includes a LCVR which includes an amino acid sequence having at least 90% sequence identity, for example, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to the LCVR of TXG-0098. In some embodiments, the antibody or antigen-binding fragment includes a LCVR which includes an amino acid sequence having at least 90% sequence identity, for example, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to the LCVR of TXG-0112. In some embodiments, the antibody or antigen-binding fragment includes a LCVR which includes an amino acid sequence having at least 90% sequence identity, for example, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to the LCVR of TXG-0115.

[0155] In some embodiments, the antibody or antigen-binding fragment includes a LCVR which includes an amino acid sequence having at least 90% sequence identity, for example, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to the LCVR of TXG-0136. In some embodiments, the antibody or antigen-binding fragment includes a LCVR which includes an amino acid sequence having at least 90% sequence identity, for example, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to the LCVR of TXG-0153. In some embodiments, the antibody or antigen-binding fragment includes a LCVR which includes an amino acid sequence having at least 90% sequence identity, for example, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to the LCVR of TXG-0154. In some embodiments, the antibody or antigen-binding fragment includes a LCVR which includes an amino acid sequence having at least 90% sequence identity, for example, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%

sequence identity to the LCVR of TXG-0173. In some embodiments, the antibody or antigen-binding fragment includes a LCVR which includes an amino acid sequence having at least 90% sequence identity, for example, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to the LCVR of TXG-0174. In some embodiments, the antibody or antigen-binding fragment includes a LCVR which includes an amino acid sequence having at least 90% sequence identity, for example, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to the LCVR of TXG-0192. In some embodiments, the antibody or antigen-binding fragment includes a LCVR which includes an amino acid sequence having at least 90% sequence identity, for example, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to the LCVR of TXG-0228. In some embodiments, the antibody or antigen-binding fragment includes a LCVR which includes an amino acid sequence having at least 90% sequence identity, for example, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to the LCVR of TXG-0230.

[0156] In some embodiments, the antibody or antigen-binding fragment includes a LCVR which includes an amino acid sequence having at least 100% sequence identity to the LCVR of an antibody being any one of TXG-0072, TXG-0098, TXG-0112, TXG-0115, TXG-0136, TXG-0153, TXG-0154, TXG-0173, TXG-0174, TXG-0192, TXG-0228, or TXG-0230. In some embodiments, the antibody or antigen-binding fragment includes a LCVR which includes an amino acid sequence having at least 100% sequence identity to the LCVR of TXG-0072. In some embodiments, the antibody or antigen-binding fragment includes a LCVR which includes an amino acid sequence having at least 100% sequence identity to the LCVR of TXG-0098. In some embodiments, the antibody or antigen-binding fragment includes a HCVR which includes an amino acid sequence having at least 100% sequence identity to the LCVR of TXG-0112. In some embodiments, the antibody or antigen-binding fragment includes a LCVR which includes an amino acid sequence having at least 100% sequence identity to the LCVR of TXG-0115. In some embodiments, the antibody or antigen-binding fragment includes a LCVR which includes an amino acid sequence having at least 100% sequence identity to the LCVR of TXG-0136. In some embodiments, the antibody or antigen-binding fragment includes a LCVR which includes an amino acid sequence having at least 100% sequence identity to the LCVR of TXG-0153. In some embodiments, the antibody or antigen-binding fragment includes a LCVR which includes an amino acid sequence having at least 100% sequence identity to the LCVR of TXG-0154. In some

embodiments, the antibody or antigen-binding fragment includes a LCVR which includes an amino acid sequence having at least 100% sequence identity to the LCVR of TXG-0173. In some embodiments, the antibody or antigen-binding fragment includes a LCVR which includes an amino acid sequence having at least 100% sequence identity to the LCVR of TXG-0174. In some embodiments, the antibody or antigen-binding fragment includes a LCVR which includes an amino acid sequence having at least 100% sequence identity to the LCVR of TXG-0192. In some embodiments, the antibody or antigen-binding fragment includes a LCVR which includes an amino acid sequence having at least 100% sequence identity to the LCVR of TXG-0228. In some embodiments, the antibody or antigen-binding fragment includes a LCVR which includes an amino acid sequence having at least 100% sequence identity to the LCVR of TXG-0230.

[0157] In some embodiments, the antigen-binding molecule or antigen-binding fragment thereof includes all framework regions (FWR) from the antibody being any one of TXG-0001, TXG-0002, TXG-0004, TXG-0005, TXG-0006, TXG-0008, TXG-0009, TXG-0048, TXG-0057, TXG-0060, TXG-0063, TXG-0066, TXG-0070, TXG-0072, TXG-0074, TXG-0076, TXG-0078, TXG-0080, TXG-0081, TXG-0087, TXG-0088, TXG-0091, TXG-0094, TXG-0098, TXG-0099, TXG-0100, TXG-0104, TXG-0109, TXG-0112, TXG-0114, TXG-0115, TXG-0120, TXG-0129, TXG-0136, TXG-0141, TXG-0144, TXG-0153, TXG-0154, TXG-0170, TXG-0173, TXG-0174, TXG-0175, TXG-0180, TXG-0181, TXG-0183, TXG-0187, TXG-0189, TXG-0192, TXG-0197, TXG-0198, TXG-0200, TXG-0201, TXG-0202, TXG-0203, TXG-0204, TXG-0209, TXG-0210, TXG-0228, or TXG-0230. In some embodiments, the antigen-binding molecule or antigen-binding fragment further includes a heavy chain constant region. In some embodiments, the heavy chain constant region is an IgA, IgD, IgE, IgG, or IgM heavy chain constant region. In some embodiments, the heavy chain constant region is of the same isotype and subclass as the antibody identified in Tables 1A-1B. In some embodiments, the heavy chain constant region is of the same isotype and subclass as the antibody being any one of TXG-0001, TXG-0002, TXG-0004, TXG-0005, TXG-0006, TXG-0008, TXG-0009, TXG-0048, TXG-0057, TXG-0060, TXG-0063, TXG-0066, TXG-0070, TXG-0072, TXG-0074, TXG-0076, TXG-0078, TXG-0080, TXG-0081, TXG-0087, TXG-0088, TXG-0091, TXG-0094, TXG-0098, TXG-0099, TXG-0100, TXG-0104, TXG-0109, TXG-0112, TXG-0114, TXG-0115, TXG-0120, TXG-0129, TXG-0136, TXG-0141, TXG-0144, TXG-0153, TXG-0154, TXG-0170, TXG-0173, TXG-0174, TXG-0175, TXG-0180, TXG-0181, TXG-0183, TXG-0187, TXG-0189, TXG-0192, TXG-0197, TXG-0198,

TXG-0200, TXG-0201, TXG-0202, TXG-0203, TXG-0204, TXG-0209, TXG-0210, TXG-0228, or TXG-0230.

[0158] In some embodiments, the antibody or antigen-binding fragment further includes a light chain constant region. In some embodiments, the light chain constant region is a kappa type or lambda type light chain constant region. In some embodiments, the light chain constant region is the same light chain constant region of the antibody identified in Tables 1A-1B. In some embodiments, the light chain constant region is the same light chain constant region of the antibody being any one of TXG-0001, TXG-0002, TXG-0004, TXG-0005, TXG-0006, TXG-0008, TXG-0009, TXG-0048, TXG-0057, TXG-0060, TXG-0063, TXG-0066, TXG-0070, TXG-0072, TXG-0074, TXG-0076, TXG-0078, TXG-0080, TXG-0081, TXG-0087, TXG-0088, TXG-0091, TXG-0094, TXG-0098, TXG-0099, TXG-0100, TXG-0104, TXG-0109, TXG-0112, TXG-0114, TXG-0115, TXG-0120, TXG-0129, TXG-0136, TXG-0141, TXG-0144, TXG-0153, TXG-0154, TXG-0170, TXG-0173, TXG-0174, TXG-0175, TXG-0180, TXG-0181, TXG-0183, TXG-0187, TXG-0189, TXG-0192, TXG-0197, TXG-0198, TXG-0200, TXG-0201, TXG-0202, TXG-0203, TXG-0204, TXG-0209, TXG-0210, TXG-0228, or TXG-0230.

[0159] As illustrated in Tables 7-8 and FIG. 31, in some embodiments of the disclosure, the antigen-binding molecule or antigen-binding fragment has a binding affinity for the spike (S) protein of two, three, four, five or more variants of SARS-CoV-2. Non-limiting examples of SARS-CoV-2 variants include alpha, beta, delta, gamma, kappa, and omicron. In some embodiments, at least one of the SARS-CoV-2 variants is omicron. In some embodiments, the antigen-binding molecule or antigen-binding fragment has a binding affinity for the spike protein of the beta and gamma variants. Exemplary antibodies with binding affinity for the spike protein of the beta and gamma variants include TXG-0001, TXG-0002, TXG-0004, TXG-0005, TXG-0006, TXG-0008, TXG-0009, TXG-0048, TXG-0057, TXG-0060, TXG-0063, TXG-0070, TXG-0072, TXG-0078, TXG-0088, TXG-0091, TXG-0094, TXG-0098, TXG-0099, TXG-0109, TXG-0112, TXG-0114, TXG-0115, TXG-0120, TXG-0136, TXG-0141, TXG-0144, TXG-0153, TXG-0154, TXG-0174, TXG-0175, TXG-0180, TXG-0181, TXG-0183, TXG-0187, TXG-0192, TXG-0198, TXG-0200, TXG-0201, TXG-0202, TXG-0203, TXG-0204, TXG-0209, TXG-0210, TXG-0228, and TXG-0230.

[0160] In some embodiments, the antigen-binding molecule or antigen-binding fragment has a binding affinity for the spike protein of the beta and kappa variants. Exemplary antibodies

with binding affinity for the spike protein of the beta and kappa variants include TXG-0001, TXG-0002, TXG-0004, TXG-0005, TXG-0006, TXG-0008, TXG-0009, TXG-0048, TXG-0057, TXG-0060, TXG-0063, TXG-0070, TXG-0072, TXG-0078, TXG-0091, TXG-0094, TXG-0098, TXG-0099, TXG-0109, TXG-0112, TXG-0114, TXG-0115, TXG-0120, TXG-0136, TXG-0141, TXG-0144, TXG-0154, TXG-0174, TXG-0175, TXG-0180, TXG-0181, TXG-0183, TXG-0187, TXG-0192, TXG-0198, TXG-0200, TXG-0201, TXG-0202, TXG-0203, TXG-0204, TXG-0209, TXG-0210, TXG-0228, and TXG-0230.

[0161] In some embodiments, the antigen-binding molecule or antigen-binding fragment has a binding affinity for the spike protein of the beta and omicron variants. Exemplary antibodies with binding affinity for the spike protein of the beta and omicron variants include TXG-0057, TXG-0063, TXG-0070, TXG-0072, TXG-0088, TXG-0091, TXG-0094, TXG-0098, TXG-0099, TXG-0109, TXG-0112, TXG-0114, TXG-0115, TXG-0120, TXG-0141, TXG-0144, TXG-0153, TXG-0174, TXG-0180, TXG-0183, TXG-0187, TXG-0192, TXG-0198, TXG-0200, TXG-0201, TXG-0202, TXG-0203, TXG-0204, TXG-0209, TXG-0210, TXG-0228, and TXG-0230.

[0162] In some embodiments, the antigen-binding molecule or antigen-binding fragment has a binding affinity for the spike protein of the gamma and kappa variants. Exemplary antibodies with binding affinity for the spike protein of the gamma and kappa variants include TXG-0001, TXG-0002, TXG-0004, TXG-0005, TXG-0006, TXG-0008, TXG-0009, TXG-0048, TXG-0057, TXG-0060, TXG-0063, TXG-0070, TXG-0072, TXG-0074, TXG-0076, TXG-0078, TXG-0091, TXG-0094, TXG-0098, TXG-0099, TXG-0104, TXG-0109, TXG-0112, TXG-0114, TXG-0115, TXG-0120, TXG-0129, TXG-0136, TXG-0141, TXG-0144, TXG-0154, TXG-0170, TXG-0173, TXG-0174, TXG-0175, TXG-0180, TXG-0181, TXG-0183, TXG-0187, TXG-0192, TXG-0197, TXG-0198, TXG-0200, TXG-0201, TXG-0202, TXG-0203, TXG-0204, TXG-0209, TXG-0210, TXG-0228, and TXG-0230.

[0163] In some embodiments, the antigen-binding molecule or antigen-binding fragment has a binding affinity for the spike protein of the gamma and omicron variants. Exemplary antibodies with binding affinity for the spike protein of the gamma and omicron variants include TXG-0057, TXG-0063, TXG-0070, TXG-0072, TXG-0088, TXG-0091, TXG-0094, TXG-0098, TXG-0099, TXG-0109, TXG-0112, TXG-0114, TXG-0115, TXG-0120, TXG-0129, TXG-0141, TXG-0144, TXG-0153, TXG-0174, TXG-0180, TXG-0183, TXG-0187, TXG-0192, TXG-0197,

TXG-0198, TXG-0200, TXG-0201, TXG-0202, TXG-0203, TXG-0204, TXG-0209, TXG-0210, TXG-0228, and TXG-0230.

[0164] In some embodiments, the antigen-binding molecule or antigen-binding fragment has a binding affinity for the spike protein of the kappa and omicron variants. Exemplary antibodies with binding affinity for the spike protein of the kappa and omicron variants include TXG-0057, TXG-0063, TXG-0070, TXG-0072, TXG-0091, TXG-0094, TXG-0098, TXG-0099, TXG-0109, TXG-0112, TXG-0114, TXG-0115, TXG-0120, TXG-0129, TXG-0141, TXG-0144, TXG-0174, TXG-0180, TXG-0183, TXG-0187, TXG-0192, TXG-0197, TXG-0198, TXG-0200, TXG-0201, TXG-0202, TXG-0203, TXG-0204, TXG-0209, TXG-0210, TXG-0228, and TXG-0230.

[0165] In some embodiments, the antigen-binding molecule or antigen-binding fragment has a binding affinity for the spike protein of the beta, gamma, and omicron variants. Exemplary antibodies with binding affinity for the spike protein of the beta, gamma, and omicron variants include TXG-0057, TXG-0063, TXG-0070, TXG-0072, TXG-0088, TXG-0091, TXG-0094, TXG-0098, TXG-0099, TXG-0109, TXG-0112, TXG-0114, TXG-0115, TXG-0120, TXG-0141, TXG-0144, TXG-0153, TXG-0174, TXG-0180, TXG-0183, TXG-0187, TXG-0192, TXG-0198, TXG-0200, TXG-0201, TXG-0202, TXG-0203, TXG-0204, TXG-0209, TXG-0210, TXG-0228, and TXG-0230.

[0166] In some embodiments, the antigen-binding molecule or antigen-binding fragment has a binding affinity for the spike protein of the beta, kappa, and omicron variants. Exemplary antibodies with binding affinity for the spike protein of the beta, kappa, and omicron variants include TXG-0057, TXG-0063, TXG-0070, TXG-0072, TXG-0091, TXG-0094, TXG-0098, TXG-0099, TXG-0109, TXG-0112, TXG-0114, TXG-0115, TXG-0120, TXG-0141, TXG-0144, TXG-0174, TXG-0180, TXG-0183, TXG-0187, TXG-0192, TXG-0198, TXG-0200, TXG-0201, TXG-0202, TXG-0203, TXG-0204, TXG-0209, TXG-0210, TXG-0228, and TXG-0230.

[0167] In some embodiments, the antigen-binding molecule or antigen-binding fragment has a binding affinity for the spike protein of the gamma, kappa, and omicron variants. Exemplary antibodies with binding affinity for the spike protein of the gamma, kappa, and omicron variants include TXG-0057, TXG-0063, TXG-0070, TXG-0072, TXG-0091, TXG-0094, TXG-0098, TXG-0099, TXG-0109, TXG-0112, TXG-0114, TXG-0115, TXG-0120, TXG-0129, TXG-0141, TXG-0144, TXG-0174, TXG-0180, TXG-0183, TXG-0187, TXG-0192,

TXG-0197, TXG-0198, TXG-0200, TXG-0201, TXG-0202, TXG-0203, TXG-0204, TXG-0209, TXG-0210, TXG-0228, and TXG-0230.

[0168] In some embodiments, the antigen-binding molecule or antigen-binding fragment has a binding affinity for the WT spike and all four beta, gamma, kappa, and omicron variants. Exemplary antibodies with binding affinity for the WT spike and all four beta, gamma, kappa, and omicron variants include TXG-0057, TXG-0063, TXG-0070, TXG-0072, TXG-0091, TXG-0094, TXG-0098, TXG-0099, TXG-0109, TXG-0112, TXG-0114, TXG-0115, TXG-0120, TXG-0141, TXG-0144, TXG-0174, TXG-0180, TXG-0183, TXG-0187, TXG-0192, TXG-0198, TXG-0200, TXG-0201, TXG-0202, TXG-0203, TXG-0204, TXG-0209, TXG-0210, TXG-0228, and TXG-0230.

[0169] It is understood that coronavirus infection and vaccination induce antibody-mediated and T cell-mediated immunity, which can beneficially reduce disease severity and transmission. Such immunity can be embodied in polyclonal populations of naive immune cells as well as recalled antigen-experienced immune cells which can target new, previously seen, or evolutionarily-related antigens by searching an immensely diverse antibody repertoire space. Thus, broad and neutralizing antibodies are typically quite rare and their discovery often requires very deep sampling of the pathogen-specific antibody response. However, once identified, broadly neutralizing antibodies are vitally important, as they can inform the design of rational vaccine immunogens that focus the immune response toward highly conserved regions of viral vulnerability, and can represent a significant advance in the development of prophylactic and therapeutic antibodies that can maintain their efficacy in the face of rapidly evolving SARS-CoV2 mutants. As described in greater detail below, several antibodies described herein are pan-coronavirus antibodies that bind with high affinity to the NTD of SARS-CoV-2 S protein and to a spike protein of one or more SARS-CoV variants (e.g., beta, gamma, kappa, and omicron), endemic human coronaviruses (HCoVs), and variants of thereof (e.g., HCoV-229E, HCoV-OC43, and HCoV-HKU1). These broadly protective antibodies against the NTD of the S1 subunit can be a particularly valuable addition to potential therapeutic antibody cocktails comprising anti-SARS-CoV-2 antibodies targeting other epitope regions of the SARS-CoV2 spike protein, such as the S2 subunit or the RBD of the S1 subunit, as increased epitope diversity from such a cocktail can provide added protection against viral escape. Accordingly, without being bound to any particular theory, broad and potentially neutralizing NTD-targeting antibodies,

such as those disclosed herein, could be particularly useful in therapeutic combination against SARS-CoV-2 and other coronaviruses and in combination with RBD-binding antibodies or non-S1 binding therapeutic antibodies (e.g., S2-targeting antibodies).

[0170] In some embodiments, the antigen-binding molecule or antigen-binding fragment has a high affinity to N-terminal domain of SARS-CoV-2 S protein (NTD) and/or to a spike protein of the omicron variant. Exemplary antibodies having these binding characteristics include TXG-0001, TXG-0002, TXG-0004, TXG-0005, TXG-0008, TXG-0009, TXG-0048, TXG-0057, TXG-0060, TXG-0063, TXG-0066, TXG-0070, TXG-0072, TXG-0074, TXG-0076, TXG-0078, TXG-0080, TXG-0081, TXG-0087, TXG-0088, TXG-0091, TXG-0094, TXG-0098, TXG-0099, TXG-0109, TXG-0114, TXG-0115, TXG-0120, TXG-0129, TXG-0136, TXG-0141, TXG-0144, TXG-0153, TXG-0170, TXG-0173, TXG-0174, TXG-0175, TXG-0180, TXG-0181, TXG-0183, TXG-0187, TXG-0189, TXG-0197, TXG-0198, TXG-0200, TXG-0201, TXG-0202, TXG-0203, TXG-0204, TXG-0209, TXG-0210, TXG-0228, and TXG-0230. Of these antibodies, at least five antibodies were found to have a high affinity to both (i) N-terminal domain of SARS-CoV-2 S protein (NTD) and (ii) a spike protein of the omicron variant. Exemplary antibodies having these binding characteristics include TXG-0072, TXG-0099, TXG-0114, TXG-0203, and TXG-0230.

[0171] In some embodiments, the antigen-binding molecule or antigen-binding fragment has a binding affinity for one or more endemic human coronaviruses (HCoV), or a variant of any thereof. Non-limiting examples of endemic HCoV include HCoV-229E, HCoV-OC43, and HCoV-HKU1. Exemplary antibodies with binding affinity for HCoV-229E include TXG-0078, TXG-0112, TXG-0114, TXG-0136, TXG-0192, TXG-0203, TXG-0228, and TXG-0230. As shown in Table 9, all of these eight antibodies exhibit high affinity for HCoV-229E.

[0172] Examples of antibodies exhibiting affinity for HCoV-OC43 include TXG-0006, TXG-0048, TXG-0070, TXG-0078, TXG-0100, TXG-0114, TXG-0136, TXG-0154, TXG-0192, and TXG-0203. Of these antibodies, at least four were found to have high affinity for the endemic human coronavirus HCoV-OC43 (see, e.g., TXG-0100, TXG-0114, TXG-0136, TXG-0192, and TXG-0203 of Table 9)

[0173] In some embodiments, the antigen-binding molecule or antigen-binding fragment has binding affinity for HCoV-OC43, HCoV-229E, SARS-CoV-2 omicron and the N-terminal domain of SARS-CoV-2. Exemplary antibodies having this ultra-broad binding affinity include TXG-0114, TXG-0192, and TXG-0203. In some embodiments, the antigen-binding molecule or

antigen-binding fragment binds HCoV-OC43, HCoV-229E, SARS-CoV-2 omicron and the N-terminal domain of SARS-CoV-2 with high affinity. Examples of antibodies having this property include TXG-0114 and TXG-0203.

[0174] In some embodiments, the antigen-binding molecule or antigen-binding fragment of the disclosure has binding affinity for the WT spike, all four variants (*i.e.*, beta, gamma, kappa, and omicron) as well as the endemic coronaviruses HCoV-OC43 and HCoV-229E. Exemplary antibodies having this ultra-broad binding affinity include TXG-0114, TXG-0192, and TXG-0203.

[0175] In some embodiments, the antibody or antigen-binding fragment has a high binding affinity (nM) for the endemic HKU1 coronavirus spike protein. In some embodiments, the antibody or antigen-binding fragment is any one of TXG-0078, TXG-0112, TXG-0114, TXG-0136, TXG-0187, TXG-0192, TXG-0203, TXG-0228, or TXG-0230.

[0176] In some embodiments, the antibody or antigen-binding fragment has a sub-nanomolar binding affinity for a SARS-CoV-2 S protein, a fragment thereof, or a multimeric form thereof. For example, in some embodiments of the disclosure, the antibody or antigen-binding fragment has a binding affinity with a K_D value of less than 500 pM, for example, less than 100 pM, less than 50 pM, less than 10 pM, or less than 5 pM. In some embodiments, the antibody or antigen-binding fragment with sub-nanomolar binding affinity for a SARS-CoV-2 S protein is any one of TXG-0072, TXG-0098, TXG-0112, TXG-0115, TXG-0136, TXG-0153, TXG-0154, TXG-0173, TXG-0174, TXG-0192, TXG-0228, or TXG-0230. One skilled in the art will appreciate that when an antibody is said to “be any one of” or “be selected from a group,” this can mean that the antibody comprises all six CDRs from any one of the antibodies selected from the group. In some embodiments, the antibody can comprise the HCVR and LCVR from any one of the antibodies selected from the group. In some embodiments, the antibody can be any one of the antibodies in the group.

[0177] In some embodiments, the antibody or antigen-binding fragment has a sub-nanomolar binding affinity for HCoV and/or for a SARS-CoV-2 S variant being any one of beta, gamma, delta, or kappa. In some embodiments, the antibody or antigen-binding fragment has a sub-picomolar binding affinity for HCoV and/or for a SARS-CoV-2 S variant being any one of beta, gamma, delta, or kappa.

[0178] In some embodiments, the antibody or antigen-binding fragment potently

neutralizes live SARS-CoV 2 and has binding affinity to the trimeric forms of wild-type SARS-CoV-2 S and beta, gamma, kappa variants. Exemplary antibodies having these binding affinity properties include TXG-0001, TXG-0002, TXG-0004, TXG-0005, TXG-0006, TXG-0008, TXG-0009, TXG-0057, TTXG-0094, TXG-0109, TXG-0115, TXG-0120, TXG-0141, TXG-0144, TXG-0154, TXG-0180, TXG-0181, TXG-0183, TXG-0200, TXG-0201, TXG-0202, TXG-0204, TXG-0209, and TXG-0210. In some embodiments, such antibodies also have binding affinity for the SARS-CoV-2 delta variant.

[0179] In some embodiments, the antibody or antigen-binding fragment potentially neutralizes live SARS-CoV 2, and has binding affinity to the N-terminal domain (NTD) of the S1 subunit. The neutralization potency of an antibody is generally quantified by the inhibitory concentration (IC) values (e.g., IC₅₀) in live SARS-CoV-2 assays. Generally, an antibody is determined to potentially neutralize SARS-CoV 2 when its IC₅₀ is less than 1,000 nM/mL (see also, Table 11). As discussed in greater detail below, broadly protective antibodies against the NTD of the S1 subunit can be a particularly valuable addition to potential therapeutic antibody cocktails comprising anti-SARS-CoV-2 antibodies targeting either the S2 subunit or the RBD of the S1 subunit. In some embodiments, the antibody or antigen-binding fragment of the present disclosure potentially neutralizes live SARS-CoV 2, and has binding affinity to the NTD of the S1 subunit and to the trimeric forms of wild-type SARS-CoV-2 S, as well as to trimeric forms of the gamma and kappa variants. Exemplary antibodies having these binding affinity properties include TXG-0076, TXG-0104, TXG-0170, and TXG-0173. In some embodiments, such antibodies also have binding affinity for the SARS-CoV-2 delta variant.

[0180] In some embodiments, the antibody or antigen-binding fragment potentially neutralizes live SARS-CoV 2, and has binding affinity to the N-terminal domain of the S1 subunit and to the trimeric form of wild-type SARS-CoV-2 S, as well as to trimeric forms of the beta, gamma, and kappa variants. Exemplary antibodies having these binding affinity properties include TXG-0063 and TXG-0099. In some embodiments, such antibodies also have binding affinity for the SARS-CoV-2 delta variant.

[0181] In some embodiments, the antibody or antigen-binding fragment potentially neutralizes live SARS-CoV 2, and has binding affinity to the N-terminal domain (NTD) of the S1 subunit and to the trimeric form of wild-type SARS-CoV-2 S, as well as to the trimeric form of the kappa variant. Exemplary antibodies having these binding affinity properties include

TXG-0066.

[0182] In some embodiments, the antibody or antigen-binding fragment potentially neutralizes live SARS-CoV 2, and has binding affinity to the trimeric form of wild-type SARS-CoV-2 S, as well as to the trimeric forms of the gamma and kappa variants. Exemplary antibodies having these binding affinity properties include TXG-0129 and TXG-0197.

[0183] In some embodiments, the antibody or antigen-binding fragment potentially neutralizes live SARS-CoV 2 and has binding affinity to the trimeric form of wild-type SARS-CoV-2 S, as well as to the trimeric forms of the beta and gamma variants. Exemplary antibodies having these binding affinity properties include TXG-0088.

[0184] In some embodiments, the antibody or antigen-binding fragment potentially neutralizes live SARS-CoV 2 and does not have binding affinity to the N-terminal domain of the S1 subunit, but has binding affinity to the trimeric form of wild-type SARS-CoV-2 S protein, as well as to trimeric forms of HCoV, the beta, gamma, and kappa variants. Exemplary antibodies having these binding affinity properties include is TXG-0091.

[0185] In some embodiments, the antibody or antigen-binding fragment potentially neutralizes live SARS-CoV 2 and has binding affinity to the N-terminal domain of the S1 subunit and to the trimeric form of wild-type SARS-CoV-2 S, as well as to trimeric forms of the HCoV, beta, gamma, and kappa variants. Exemplary antibodies having these binding affinity properties include TXG-0078.

[0186] In some embodiments, the antibody or antigen-binding fragment potentially neutralizes live SARS-CoV 2 and has binding affinity to wild-type SARS-CoV-2 S protein. Exemplary antibodies having these binding affinity properties include TXG-0001, TXG-0002, TXG-0004, TXG-0005, TXG-0006, TXG-0008, TXG-0009, TXG-0057, TXG-0063, TXG-0066, TXG-0076, TXG-0078, TXG-0080, TXG-0081, TXG-0088, TXG-0091, TXG-0094, TXG-0099, TXG-0100, TXG-0104, TXG-0109, TXG-0120, TXG-0129, TXG-0141, TXG-0144, TXG-0170, TXG-0180, TXG-0181, TXG-0183, TXG-0189, TXG-0197, TXG-0198, TXG-0200, TXG-0201, TXG-0202, TXG-0204, TXG-0209, and TXG-0210.

[0187] In some embodiments, the antibody or antigen-binding fragment potentially neutralizes live SARS-CoV 2 and has binding affinity to the N-terminal domain of the S1 subunit. Exemplary antibodies having these binding affinity properties include TXG-0063, TXG-0066, TXG-0076, TXG-0078, TXG-0099, TXG-0104, TXG-0170, TXG-0173, and TXG-0174.

[0188] In some embodiments, the antibody or antigen-binding fragment potentially neutralizes live SARS-CoV 2 and has binding affinity to the beta variant. Exemplary antibodies having these binding affinity properties include TXG-0001, TXG-0002, TXG-0004, TXG-0005, TXG-0006, TXG-0008, TXG-0009, TXG-0057, TXG-0063, TXG-0078, TXG-0088, TXG-0091, TXG-0094, TXG-0099, TXG-0109, TXG-0115, TXG-0120, TXG-0141, TXG-0144, TXG-0153, TXG-0154, TXG-0174, TXG-0180, TXG-0181, TXG-0183, TXG-0198, TXG-0200, TXG-0201, TXG-0202, TXG-0204, TXG-0209, and TXG-0210.

[0189] In some embodiments, the antibody or antigen-binding fragment potentially neutralizes live SARS-CoV 2 and has binding affinity to the gamma variant. Exemplary antibodies having these binding affinity properties include TXG-0001, TXG-0002, TXG-0004, TXG-0005, TXG-0006, TXG-0008, TXG-0009, TXG-0057, TXG-0063, TXG-0076, TXG-0078, TXG-0088, TXG-0091, TXG-0094, TXG-0099, TXG-0104, TXG-0109, TXG-0115, TXG-0120, TXG-0129, TXG-0141, TXG-0144, TXG-0153, TXG-0154, TXG-0170, TXG-0173, TXG-0174, TXG-0180, TXG-0181, TXG-0183, TXG-0197, TXG-0198, TXG-0200, TXG-0201, TXG-0202, TXG-0204, TXG-0209, and TXG-0210.

[0190] In some embodiments, the antibody or antigen-binding fragment potentially neutralizes live SARS-CoV 2 and has binding affinity to the kappa variant. Exemplary antibodies having these properties include TXG-0001, TXG-0002, TXG-0004, TXG-0005, TXG-0006, TXG-0008, TXG-0009, TXG-0057, TXG-0063, TXG-0066, TXG-0076, TXG-0078, TXG-0091, TXG-0094, TXG-0099, TXG-0104, TXG-0109, TXG-0115, TXG-0120, TXG-0129, TXG-0141, TXG-0144, TXG-0154, TXG-0170, TXG-0173, TXG-0174, TXG-0180, TXG-0181, TXG-0183, TXG-0197, TXG-0198, TXG-0200, TXG-0201, TXG-0202, TXG-0204, TXG-0209, and TXG-0210. In some embodiments, such antibodies potentially neutralize live SARS-CoV 2 and have binding affinity to the delta variant.

[0191] In some embodiments, the antibody or antigen-binding fragment potentially neutralizes live SARS-CoV 2 and has binding affinity to HCoV-HKU1 (isolate N5) S1 protein. Exemplary antibodies having these properties include TXG-0078 and TXG-0091.

[0192] In some embodiments, the antibodies and antigen-binding fragments of the disclosure bind to a target antigen, such as a CoV-S protein (*e.g.*, SARS-CoV-2 S protein), and compete for binding with another antigen-binding polypeptide (*e.g.*, antibody or antigen-binding fragment thereof) to the target antigen. Accordingly, also provided herein are antibodies or

antigen-binding fragments thereof that compete for binding with an antibody disclosed herein, *e.g.*, in Table 1A or Table 1B.

[0193] The term “competes” as used herein, refers to an antibody or antigen-binding fragment that binds to a target antigen, and inhibits or blocks the binding of another antigen-binding polypeptide (*e.g.*, antibody or antigen-binding fragment thereof) to the target antigen. The term also includes competition between two antigen-binding polypeptides *e.g.*, antibodies, in both orientations, *i.e.*, a first antibody that binds and blocks binding of second antibody and *vice versa*. In some embodiments, the first antigen-binding polypeptide (*e.g.*, antibody or antigen-binding fragment) and second antigen-binding polypeptide (*e.g.*, antibody or antigen-binding fragment thereof) may bind to the same epitope. Alternatively, the first and second antigen-binding polypeptides (*e.g.*, antibodies or antigen-binding fragments) may bind to different, but, for example, overlapping epitopes, wherein binding of one inhibits or blocks the binding of the second antibody, *e.g.*, via steric hindrance. Competition between antigen-binding polypeptides (*e.g.*, antibodies or antigen-binding fragments) may be measured by methods known in the art, for example, by a real-time, label-free bio-layer interferometry assay. Epitope mapping (*e.g.*, via alanine scanning or hydrogen-deuterium exchange (HDX)) can be used to determine whether two or more antibodies are non-competing (*e.g.* on a spike protein RBD monomer), competing for the same epitope, or competing but with diverse micro-epitopes (*e.g.*, identified through HDX). In some embodiments, competition between a first and second anti-CoV-S antigen-binding polypeptide (*e.g.*, antibody or antigen-binding fragment thereof) is determined by measuring the ability of an immobilized first anti-CoV-S antigen-binding polypeptide (*e.g.*, antibody) (not initially complexed with CoV-S protein) to bind to soluble CoV-S protein complexed with a second anti-CoV-S antigen-binding polypeptide (*e.g.*, antibody or antigen-binding fragment thereof). A reduction in the ability of the first anti-CoV-S antigen-binding polypeptide (*e.g.*, antibody or antigen-binding fragment thereof) to bind to the complexed CoV-S protein, relative to uncomplexed CoV-S protein, indicates that the first and second anti-CoV-S antigen-binding polypeptides (*e.g.*, antibodies or antigen-binding fragments thereof) compete. The degree of competition can be expressed as a percentage of the reduction in binding. Such competition can be measured using a real time, label-free bio-layer interferometry assay, *e.g.*, on an Octet RED384 biosensor (Pall ForteBio Corp.), ELISA (enzyme-linked immunosorbent assays) or SPR (surface plasmon resonance).

[0194] In some embodiments, the antibodies and antigen-binding fragments of the disclosure have a neutralizing activity (*e.g.*, antagonistic activity) against SARS-CoV-2, *e.g.*, able to bind to and neutralize the activity of SARS-CoV-S, as determined by *in vitro* or *in vivo* assays. The ability of the antibodies of the disclosure to bind to, block and/or neutralize the activity of SARS-CoV-2 may be measured using any standard method known to those skilled in the art, including binding assays, or activity assays, as described herein. For example, the binding affinity and dissociation constants of anti-SARS-CoV-2 antigen-binding polypeptides for SARS-CoV-2 can be determined by surface plasmon resonance (SPR) assay. Alternatively, neutralization assays were used to determine infectivity of SARS-CoV-2 S protein-containing virus-like particles. One of ordinary skill in the art will understand that a neutralizing or antagonistic CoV-S antigen-binding polypeptide, *e.g.*, antibody or antigen-binding fragment, generally refers to a molecule that inhibits an activity of CoV-S to any detectable degree, *e.g.*, inhibits or reduces the ability of CoV-S to bind to a receptor such as ACE2, to be cleaved by a protease such as TMPRSS2, or to mediate viral entry into a host cell or mediate viral reproduction in a host cell. In some embodiments, the antibodies and antigen-binding fragments of the disclosure have a neutralization activity IC_{50} value of less than 150 ng/ml for viral neutralization, as determined by a quantitative focus reduction neutralization test (FRNT) described previously by Zost *et al.* (Nature, 584:443–449, 2020). In some embodiments, the antibodies and antigen-binding fragments of the disclosure have blocking activity IC_{50} value of less than 150 ng/ml for blocking ACE2. In some embodiments, the antibodies and antigen-binding fragments of the disclosure have blocking activity IC_{50} value of less than 10 ng/ml for S2P ectodomain binding. In some embodiments, the antibodies and antigen-binding fragments of the disclosure have blocking activity IC_{50} value of less than 10 ng/ml for RBD ectodomain binding. In some embodiments, the antibody or antigen-binding fragment neutralizes at least 50% of 200 times the tissue culture infectious dose ($200 \times TCID_{50}$) of the coronavirus at an antibody concentration of 12.5 $\mu\text{g/ml}$ or less. Here, $TCID_{50}$ represents the viral load at which 50% of cells are infected when a solution containing the virus is added to cell culture. In some embodiments, neutralizing antibodies are effective at antibody concentrations of $<3.125 \mu\text{g/ml}$, $<.8 \mu\text{g/ml}$, $<.2 \mu\text{g/ml}$, or $<.1 \mu\text{g/ml}$.

[0195] In some embodiments, the antibody or antigen-binding fragment has a neutralizing activity against SARS-CoV-2 with an IC_{50} value below 1 $\mu\text{g/mL}$, below 200 ng/mL, or below 40

ng/mL. In some embodiments, the antibody or antigen-binding fragment has a neutralizing activity against SARS-CoV-2 with an IC_{50} value ranging from 200 ng/mL to 1,000 ng/mL. In some embodiments, the antibody or antigen-binding fragment has a neutralizing activity against SARS-CoV-2 with an IC_{50} value ranging from 40 ng/mL to 200 ng/mL. In some embodiments, the antibody or antigen-binding fragment has a neutralizing activity against SARS-CoV-2 with an IC_{50} value ranging from 8 ng/mL to 40 ng/mL.

[0196] In some embodiments, the antibody or antigen-binding fragment has a neutralizing activity against SARS-CoV-2 with an IC_{50} value that is 1 μ g/mL or less. In some embodiments, the antibody or antigen-binding fragment having a neutralizing activity against SARS-CoV-2 with an IC_{50} value of 1 μ g/mL or less is any one of TXG-0001, TXG-0002, TXG-0004, TXG-0005, TXG-0006, TXG-0008, TXG-0009, TXG-0057, TXG-0063, TXG-0066, TXG-0076, TXG-0078, TXG-0080, TXG-0081, TXG-0088, TXG-0091, TXG-0094, TXG-0099, TXG-0100, TXG-0104, TXG-0109, TXG-0115, TXG-0120, TXG-0129, TXG-0141, TXG-0144, TXG-0153, TXG-0154, TXG-0170, TXG-0173, TXG-0174, TXG-0180, TXG-0181, TXG-0183, TXG-0189, TXG-0197, TXG-0198, TXG-0200, TXG-0201, TXG-0202, TXG-0204, TXG-0209, or TXG-0210.

[0197] In some embodiments, the antibody or antigen-binding fragment has a neutralizing activity against SARS-CoV-2 with an IC_{50} value that is from 200 ng/mL to 1 μ g/mL. In some embodiments, the antibody or antigen-binding fragment having a neutralizing activity against SARS-CoV-2 with an IC_{50} value ranging from 200 ng/mL to 1 μ g/mL is any one of TXG-0005, TXG-0008, TXG-0057, TXG-0066, TXG-0076, TXG-0091, TXG-0094, TXG-0099, TXG-0104, TXG-0141, TXG-0144, TXG-0170, TXG-0180, TXG-0183, TXG-0198, or TXG-0201.

[0198] In some embodiments, the antibody or antigen-binding fragment has a neutralizing activity against SARS-CoV-2 with an IC_{50} value that is from 40 ng/mL to 200 ng/mL. In some embodiments, the antibody or antigen-binding fragment having a neutralizing activity against SARS-CoV-2 with an IC_{50} value ranging from 40 ng/mL to 200 ng/mL is any one of TXG-0001, TXG-0002, TXG-0004, TXG-0009, TXG-0063, TXG-0078, TXG-0080, TXG-0081, TXG-0088, TXG-0100, TXG-0115, TXG-0181, TXG-0189, TXG-0197, TXG-0200, TXG-0202, TXG-0204, TXG-0209, or TXG-0210.

[0199] In some embodiments, the antibody or antigen-binding fragment has a neutralizing activity against SARS-CoV-2 with an IC_{50} value that is 200 ng/mL or less. In some

embodiments, the antibody or antigen-binding fragment having a neutralizing activity against SARS-CoV-2 with an IC_{50} value of 200 ng/mL or less is any one of TXG-0078, TXG-0080, TXG-0081, TXG-0088, TXG-0100, TXG-0109, TXG-0115, TXG-0120, TXG-0126, TXG-0128, TXG-0129, TXG-0154, TXG-0181, TXG-0189, TXG-0197, TXG-0200, TXG-0202, TXG-0204, TXG-0209, or TXG-0210.

[0200] In some embodiments, the antibody or antigen-binding fragment has a neutralizing activity against SARS-CoV-2 with an IC_{50} value that is 100 ng/mL or less. In some embodiments, the antibody or antigen-binding fragment having a neutralizing activity against SARS-CoV-2 with an IC_{50} value of 100 ng/mL or less is any one of TXG-0001, TXG-0004, TXG-0006, TXG-0009, TXG-0063, TXG-0080, TXG-0088, TXG-0109, TXG-0120, TXG-0129, TXG-0154, TXG-0189, TXG-0197, TXG-0200, TXG-0202, TXG-0204, TXG-0209, or TXG-0210.

[0201] In some embodiments, the antibody or antigen-binding fragment has a neutralizing activity against SARS-CoV-2 with an IC_{50} value that is 40 ng/mL or less. In some embodiments, the antibody or antigen-binding fragment having a neutralizing activity against SARS-CoV-2 with an IC_{50} value of 40 ng/mL or less is any one of TXG-0006, TXG-0109, TXG-0120, TXG-0126, TXG-0129, or TXG-0154.

[0202] Some embodiments of the disclosure provide antibodies or antigen-binding fragments thereof that have a binding affinity to the NTD of a SARS-CoV-2 S protein and potentially neutralizes live SARS-CoV-2. In some embodiments, the antibody or antigen-binding fragment is any one of TXG-0066, TXG-0072, TXG-0078, TXG-0104, TXG-0116, TXG-0136, TXG-0170, TXG-0173, or TXG-0174. In some embodiments, the antibody or antigen-binding fragment is selected from the group consisting of TXG-0173 and TXG-0174. In some embodiments, the antibody or antigen-binding fragment is TXG-0174. In some embodiments, the antibody or antigen-binding has a binding affinity to the NTD of an S protein from a SARS-CoV-2 delta variant. In some embodiments, the antibody or antigen-binding fragment is any one of TXG-0072, TXG-0078, TXG-0091, TXG-0099, TXG-0116, TXG-0137, TXG-0170, or TXG-0174.

[0203] Some embodiments of the disclosure provide antibodies or antigen-binding fragments thereof that have a binding affinity primarily to the RBD of a SARS-CoV-2 S protein and potentially neutralizes live SARS-CoV-2. In some embodiments, such antibody or antigen-

binding fragment is any one of TXG-0001, TXG-0002, TXG-0004, TXG-0005, TXG-0006, TXG-0008, TXG-0009, TXG-0063, TXG-0094, TXG-0100, TXG-0115, TXG-0120, TXG-0126, TXG-0128, TXG-0129, TXG-0141, TXG-0153, TXG-0154, TXG-0180, TXG-0181, TXG-0197, TXG-0198, TXG-0200, TXG-0201, TXG-0202, TXG-0204, TXG-0209, or TXG-0210. In some embodiments, the antibody or antigen-binding fragment is any one of TXG-0057, TXG-0063, TXG-0091, TXG-0094, TXG-0109, TXG-0115, TXG-0120, TXG-0128, TXG-0141, TXG-0144, TXG-0153, TXG-0154, TXG-0180, TXG-0181, TXG-0183, TXG-0197, TXG-0198, TXG-0200, TXG-0201, TXG-0202, TXG-0204, TXG-0207, TXG-0209, or TXG-0210. In some embodiments, the antibody or antigen-binding fragment is any one of TXG-0057, TXG-0063, TXG-0091, TXG-0094, TXG-0120, TXG-0181, or TXG-0183. In some embodiments, the antibody or antigen-binding fragment is any one of TXG-0109, TXG-0128, TXG-0141, TXG-0144, TXG-0180, TXG-0197, TXG-0198, TXG-0200, TXG-0201, TXG-0202, TXG-0204, TXG-0207, TXG-0209, or TXG-0210. In some embodiments, the antibody or antigen-binding fragment is any one of TXG-0001, TXG-0002, TXG-0004, TXG-0005, TXG-0006, TXG-0008, TXG-0009, TXG-0080, TXG-0081, TXG-0088, TXG-0100, TXG-0126, TXG-0129, or TXG-0189. In some embodiments, the antibody or antigen-binding fragment is any one of TXG-0115, TXG-0153, or TXG-0154. In some embodiments, the antibody or antigen-binding fragment is TXG-0153. In some embodiments, the antibody or antigen-binding fragment is TXG-0115 or TXG-0154.

[0204] In some embodiments, the antibody or antigen-binding fragment has a binding affinity primarily to the RBD of an S protein from a SARS-CoV-2 delta variant and potently neutralizes live SARS-CoV-2. In some embodiments, the antibody or antigen-binding fragment is any one of TXG-0001, TXG-0002, TXG-0004, TXG-0005, TXG-0006, TXG-0008, TXG-0009, TXG-0063, TXG-0094, TXG-0100, TXG-0120, TXG-0126, TXG-0128, TXG-0129, TXG-0141, TXG-0180, TXG-0181, TXG-0197, TXG-0198, TXG-0200, TXG-0201, TXG-0202, TXG-0204, TXG-0209, or TXG-0210. In some embodiments, the antibody or antigen-binding fragment is any one of TXG-0063, TXG-0094, TXG-0120, TXG-0128, TXG-0180, TXG-0181, TXG-0197, TXG-0198, TXG-0200, TXG-0201, TXG-0202, TXG-0204, or TXG-0209. In some embodiments, the antibody or antigen-binding fragment is TXG-0154. In some embodiments, the antibody or antigen-binding fragment has a binding affinity for a SARS-CoV-2 S protein and is any one of TXG-0112, TXG-0192, TXG-0228, or TXG-0230.

[0205] In some embodiments, the antibody or antigen-binding fragment has a binding affinity primarily to the RBD of an S protein from a SARS-CoV-2 delta variant. In some embodiments, the antibody or antigen-binding fragment is any one of TXG-0063, TXG-0094, TXG-0120, or TXG-0181. In some embodiments, the antibody or antigen-binding fragment is any one of TXG-0128, TXG-0180, TXG-0197, TXG-0198, TXG-0200, TXG-0201, TXG-0202, TXG-0204, or TXG-0209. In some embodiments, the antibody or antigen-binding fragment is any one of TXG-0001, TXG-0002, TXG-0004, TXG-0005, TXG-0006, TXG-0008, TXG-0009, TXG-0100, TXG-0126, TXG-0129, TXG-0141, or TXG-0210. In some embodiments, the antibody or antigen-binding fragment has a binding affinity for an S protein of a SARS-CoV-2 delta variant and is any one of TXG-0115, TXG-0136, TXG-0192, or TXG-0230. In some embodiments, such antibodies and antigen-binding fragments have a neutralizing activity against live SARS-CoV-2. In some embodiments, the antibody or antigen-binding fragment is TXG-0115.

[0206] In some embodiments, the antibody or antigen-binding fragment has a binding affinity for an S protein from a SARS-CoV-2 delta variant and is any one of TXG-0112, TXG-0173, or TXG-0228. In some embodiments, such antibody or antigen-binding fragment potently neutralizes live SARS-CoV-2. In some embodiments, the antibody or antigen-binding fragment is TXG-0173.

[0207] In some embodiments, the antibody or antigen-binding fragment has a binding affinity for a SARS-CoV-2 S protein and targets a distinct epitope from FDA approved antibodies such as Casirivimab, Imdevimab, Bamlanivimab, Etesevimab, and Sotrovimab. In some embodiments, such antibody or antigen binding-fragment. In some embodiments, such antibody or antigen-binding fragment is any one of TXG-0076, TXG-0099, TXG-0114, TXG-0187, or TXG-0203. In some embodiments, the antibody or antigen-binding fragment potently neutralizes live SARS-CoV-2 and is TXG-0076 or TXG-0099. In some embodiments, the antibody or antigen-binding fragment has a high binding affinity (nM) for an S protein from a wild-type SARS-CoV-2 or from the gamma, kappa, and beta variants. In some embodiments, the antibody or antigen-binding fragment is any one of TXG-0053, TXG-0099, TXG-0114, TXG-0187, or TXG-0203. In some embodiments, the antibody or antigen-binding fragment has a high binding affinity (nM) for an NTD of a SARS-CoV-2 S protein. In some embodiments, the antibody or antigen-binding fragment is any one of TXG-0064, TXG-0076, TXG-0099, or TXG-

0146. In some embodiments, the antibody or antigen-binding fragment has a high binding affinity (nM) for the endemic HKU1 coronavirus spike protein. In some embodiments, the antibody or antigen-binding fragment is any one of TXG-0053, TXG-0114, TXG-0187, and TXG-0203.

[0208] Some embodiments of the disclosure provide antibodies or antigen-binding fragments thereof that have a binding affinity for a spike protein of a SARS-CoV-2 delta variant and targets a distinct delta variant epitope from FDA approved antibodies such as Casirivimab, Imdevimab, Bamlanivimab, Etesevimab, and Sotrovimab. In some embodiments, such antibody or antigen-binding fragment is any one of TXG-0080, TXG-0175, or TXG-0232. In some embodiments, the antibody or antigen-binding fragment potently neutralizes live SARS-CoV-2 and is TXG-0080 or TXG-0175. In some embodiments, the antibody or antigen-binding fragment has a high binding affinity (nM) for an S protein from a wild-type SARS-CoV-2 or for an S protein from the gamma, kappa, and beta variants. In some embodiments, the antibody or antigen-binding fragment having a high binding affinity (nM) for an S protein from a wild-type SARS-CoV-2 or from the gamma, kappa, and beta variants is any one of TXG-0099, TXG-0114, TXG-0187, or TXG-0203. In some embodiments, the antibody or antigen-binding fragment has a binding affinity for a S protein from a SARS-CoV-2 delta variant and is any one of TXG-0057, TXG-0076, TXG-0081, TXG-0088, TXG-0104, TXG-0109, TXG-0114, TXG-0144, TXG-0183, TXG-0187, TXG-0189, or TXG-0203. In some embodiments, the antibody or antigen-binding fragment having has a binding affinity for a SARS-CoV-2 S protein potently neutralizes live SARS-CoV-2. In some embodiments, the antibody or antigen-binding fragment having a binding affinity for a SARS-CoV-2 S protein and potently neutralizing live SARS-CoV-2 is any one of TXG-0057, TXG-0076, TXG-0081, TXG-0088, TXG-0104, TXG-0109, TXG-0144, TXG-0183, or TXG-0189. In some embodiments, the antibody or antigen-binding fragment has a high binding affinity (nM) for an S protein from a wild-type SARS-CoV-2 or for an S protein from the gamma and kappa variants. In some embodiments, the antibody or antigen-binding fragment having a high binding affinity (nM) for an S protein from a wild-type SARS-CoV-2 or from the gamma and kappa variants is any one of TXG-0057, TXG-0076, TXG-0104, TXG-0109, TXG-0114, TXG-0144, TXG-0183, TXG-0187, or TXG-0203. In some embodiments, the antibody or antigen-binding fragment has a high binding affinity (nM) for an S protein from a wild-type SARS-CoV-2 or from the beta, gamma, and kappa variants. In some embodiments, the antibody

or antigen-binding fragment having a high binding affinity (nM) for an S protein from a wild-type SARS-CoV-2 or from the beta, gamma, and kappa variants is any one of TXG-0057, TXG-0109, TXG-0114, TXG-0144, TXG-0183, TXG-0187, TXG-0203.

[0209] In some embodiments, the isolated antibodies or antigen-binding fragments as described herein are recombinant antibodies and antigen-binding fragments. In some embodiments, the antibodies or antigen-binding fragments as described herein are isolated (*e.g.*, purified) antibodies and antigen-binding fragments. As described above, when referring to polypeptides, *e.g.*, antigen-binding polypeptides, antibodies, and antigen-binding fragments, one skilled in the art will understand that the term “isolated protein”, “isolated polypeptide” or “isolated antibody” is a protein, polypeptide or antibody that by virtue of its origin or source of derivation (1) is not associated with naturally associated components that accompany it in its native state, (2) is substantially free of other proteins from the same species, (3) is expressed by a recombinant cell from a different species, or (4) does not occur in nature. Thus, a polypeptide that is chemically synthesized or biosynthesized in a recombinant cellular system different from the cell from which it naturally originates can be “isolated” from its naturally associated components. A protein may also be rendered substantially free of naturally-associated components by isolation or purification, using one or more protein purification techniques.

[0210] Examples of isolated antibodies include anti- SARS-CoV S protein antibodies that have been purified using SARS-CoV S protein or a portion thereof, anti- SARS-CoV S protein antibodies that have been synthesized by a hybridoma or other recombinant cell line *in vitro*, and a human anti-SARS-CoV S protein antibody derived from a transgenic mouse. Examples of purification techniques suitable for the purification of the antibodies and antigen-binding fragments disclosed herein include affinity chromatography, anion exchange chromatography (AEX), cation exchange chromatography (CEX), hydroxyapatite chromatography, size exclusion chromatography (SEC), hydrophobic interaction chromatography (HIC), metal affinity chromatography, mixed mode chromatography (MMC), centrifugation, diafiltration, and ultrafiltration.

[0211] Generally, a polypeptide (*e.g.*, antibody or antigen-binding fragment) is “substantially pure,” “substantially homogeneous,” or “substantially purified” when at least about 60 to 75% of a sample exhibits a single species of polypeptide. The polypeptide may be monomeric or multimeric. A substantially pure polypeptide generally includes about 50%, 60%,

70%, 80% or 90% W/W of a protein sample, more usually about 95%, 96%, 97%, 98%, or in some embodiments, over 99% pure. Protein purity or homogeneity may be indicated by a number of means available in the art, such as polyacrylamide gel electrophoresis of a protein sample, followed by visualizing a single polypeptide band upon staining the gel with a suitable stain available in the art. For certain purposes, higher resolution may be provided by using HPLC or other means available in the art for purification. Accordingly, in some embodiments, the isolated antibodies and antigen-binding fragments of the disclosure have a purity of greater than 80% such as, for example, a purity of greater than 85%, 90%, 95%, 96%, 97%, 98%, or 99%.

[0212] In some embodiments, an anti-SARS-CoV-S antigen-binding polypeptide (*e.g.*, antibody or antigen-binding fragment) described herein is not an antibody or antigen-binding fragment described in the following patent publications CN111620946A, CN111690059A, US10787501, and WO2015179535. In some embodiments, the an anti-SARS-CoV-S antigen-binding polypeptide (*e.g.*, antibody or antigen-binding fragment) described herein is not an antibody or antigen-binding fragment described in the following documents Jakob Kreye et al., 2020; Seth Zost et al., (Nature Medicine, July 10, 2020); Xiaojian Han et al., (BioRxiv, Aug 21, 2020); Tal Noy-Porat et al., (Nature Comm., Aug. 27, 2020); Ederne Rujas et al. (BioRxiv, Oct 16, 2020), 2020; Renhong Yan et al., (BioRxiv, 2020); Christoph Kreer et al., (Cell, Aug 20, 2020; Vol. 182, Issue 4, pp. 843-854); Yunlong Cao et al., (Cell, July 9, Vol. 182, Issue 1, 2020); and Thomas Rogers et al., (Science Aug 21, 2020: Vol. 369, Issue 6506, pp. 956-963) .

Nucleic acids

[0213] The term “nucleic acid,” in its broadest sense, includes any compound and/or substance that comprise a polymer of nucleotides linked via a phosphodiester bond. These polymers are often referred to as oligonucleotides. Exemplary nucleic acids include ribonucleic acids (RNAs), deoxyribonucleic acids (DNAs), threose nucleic acids (TNAs), glycol nucleic acids (GNAs), peptide nucleic acids (PNAs), locked nucleic acids (LNAs) or hybrids thereof. They may also include RNAi-inducing agents, RNAi agents, siRNAs, shRNAs, miRNAs, antisense RNAs, ribozymes, catalytic DNA, tRNA, RNAs that induce triple helix formation, aptamers, vectors, etc.

[0214] As discussed in greater detail below, the nucleic acids of the disclosure may encode any one of the antigen-binding molecules or antigen-binding fragment described herein. In some embodiments, the nucleic acids disclosed herein encode an amino acid sequence comprising the

VL and/or an amino acid sequence comprising the VH of an antibody described herein (*e.g.*, the light and/or heavy chains of the antibody). In some embodiments, the nucleic acids encode three or more CDRs of an antibody described in Tables 1A-1B and Sequence Listing (*e.g.*, HCDR1, HCDR2 and HCDR3; or LCDR1, CDR2 and LCDR3). In some embodiments, the nucleic acids may encode the HCDR1, HCDR2, and HCDR3 of an antibody of Table 1A or Table 1B. In some embodiments, the nucleic acids may encode the HCDR1, HCDR2, and HCDR3 of an antibody being any one of TXG-0001, TXG-0002, TXG-0004, TXG-0005, TXG-0006, TXG-0008, TXG-0009, TXG-0048, TXG-0070, TXG-0078, TXG-0081, TXG-0087, TXG-0114, TXG-0115, TXG-0154, TXG-0174, TXG-0175, TXG-0180, TXG-0192, or TXG-0203. In some embodiments, the nucleic acids may encode the LCDR1, LCDR2, and LCDR3 of an antibody of Table 1A or Table 1B. In some embodiments, the nucleic acids may encode the LCDR1, LCDR2, and LCDR3 of an antibody being any one of TXG-0001, TXG-0002, TXG-0004, TXG-0005, TXG-0006, TXG-0008, TXG-0009, TXG-0048, TXG-0070, TXG-0078, TXG-0081, TXG-0087, TXG-0114, TXG-0115, TXG-0154, TXG-0174, TXG-0175, TXG-0180, TXG-0192, or TXG-0203.

[0215] In some embodiments, the nucleic acids may encode all six CDRs (*e.g.*, HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3) of an antibody of Table 1A or Table 1B. In some embodiments, the nucleic acids may encode all six CDRs from an antibody being any one of TXG-0001, TXG-0002, TXG-0004, TXG-0005, TXG-0006, TXG-0008, TXG-0009, TXG-0048, TXG-0057, TXG-0060, TXG-0063, TXG-0066, TXG-0070, TXG-0072, TXG-0074, TXG-0076, TXG-0078, TXG-0080, TXG-0081, TXG-0087, TXG-0088, TXG-0091, TXG-0094, TXG-0098, TXG-0099, TXG-0100, TXG-0104, TXG-0109, TXG-0112, TXG-0114, TXG-0115, TXG-0120, TXG-0129, TXG-0136, TXG-0141, TXG-0144, TXG-0153, TXG-0154, TXG-0170, TXG-0173, TXG-0174, TXG-0175, TXG-0180, TXG-0181, TXG-0183, TXG-0187, TXG-0189, TXG-0192, TXG-0197, TXG-0198, TXG-0200, TXG-0201, TXG-0202, TXG-0203, TXG-0204, TXG-0209, TXG-0210, TXG-0228, or TXG-0230. In some embodiments, the nucleic acids may encode all six complementary determining regions (CDRs) from an antibody being any one of TXG-0001, TXG-0002, TXG-0004, TXG-0005, TXG-0006, TXG-0008, TXG-0009, TXG-0048, TXG-0070, TXG-0078, TXG-0081, TXG-0087, TXG-0114, TXG-0115, TXG-0154, TXG-0174, TXG-0175, TXG-0180, TXG-0192, or TXG-0203.

[0216] In some embodiments, the nucleic acids may further encode the heavy chain

framework regions HFWR1, HFWR2, HFWR3, and HFWR4 of the same antibody or antigen-binding fragment as set forth in Tables 2A-2B and Sequence Listing. In some embodiments, the nucleic acids may further encode the light chain framework regions LFWR1, LFWR2, LFWR3, and LFWR4 of the same antibody or antigen-binding fragment as set forth in Tables 2A-2B and Sequence Listing.

[0217] As discussed above, the nucleic acids encoding the antigen-binding molecules or antigen-binding fragments may be DNA molecules or RNA molecules.

[0218] The nucleic acid molecules provided can contain naturally occurring sequences, or sequences that differ from those that occur naturally, but, due to the degeneracy of the genetic code, encode the same polypeptide, *e.g.*, antibody. For example, just as polypeptide variants can be described in terms of their identity with a referenced amino acid sequence, the nucleic acid molecules encoding the polypeptide variants can have a certain identity with those that encode the referenced amino acid sequence. For example, nucleic acid molecule variants encoding an antibody of the disclosure, a variant thereof, or an antigen-fragment thereof can be at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, preferably at least 75%, at least 80%, more preferably at least 85%, at least 90%, and most preferably at least 95% (*e.g.*, 96%, 97%, 98%, or 99%) identical to the nucleic acid encoding a referenced antibody or an antigen-fragment thereof. Thus, in some embodiments, the nucleic acid molecule encoding an antibody of the disclosure, a variant thereof, or an antigen-fragment thereof can be at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, preferably at least 75%, at least 80%, more preferably at least 85%, at least 90%, and most preferably at least 95% (*e.g.*, 96%, 97%, 98%, or 99%) identical to the nucleic acid encoding an antibody or antigen-binding fragment thereof having an amino acid sequence set forth in the Sequence Listing.

[0219] In some embodiments, the nucleic acids include a nucleotide sequence encoding an amino acid sequence having at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, preferably at least 75%, at least 80%, more preferably at least 85%, at least 90%, and most preferably at least 95% (*e.g.*, 96%, 97%, 98%, or 99%) sequence identity to a HCVR of an antibody of the disclosure or an antigen-binding fragment thereof. Non-limiting examples of such nucleic acid sequences are listed in SEQ ID NOS: 3085-3888 and 6181-6580 of the Sequence Listing. In some embodiments, the nucleic acid molecule includes a nucleotide sequence encoding an amino acid sequence having at least 50%, at least 55%, at least 60%, at

least 65%, at least 70%, preferably at least 75%, at least 80%, more preferably at least 85%, at least 90%, and most preferably at least 95% (*e.g.*, 96%, 97%, 98%, or 99%) sequence identity to an LCVR of an antibody of the disclosure or an antigen-binding fragment thereof. Non-limiting examples of such nucleic acid sequences are also listed in SEQ ID NOS: 3889-4694 and 6581-6980 of the Sequence Listing. In some embodiments, the nucleic acids include a first nucleic acid sequence having at least 70% sequence identity to a nucleic acid sequence being any one of SEQ ID NOS: 3085-3888 and 6181-6580; and a second nucleic acid sequence having at least 70% sequence identity to a nucleic acid sequence being any one of SEQ ID NOS: 3889-4694 and 6581-6980.

[0220] Generally, the length of the nucleic acids of the present disclosure is greater than about 30 nucleotides in length (*e.g.*, at least or greater than about 35, 40, 45, 50, 55, 60, 70, 80, 90, 100, 120, 140, 160, 180, 200, 250, 300, 350, 400, 450, 500, 600, 700, 800, 900, 1,000, 1,100, 1,200, 1,300, 1,400, 1,500, 1,600, 1,700, 1,800, 1,900, 2,000, 2,500, and 3,000, 4,000, 5,000, 6,000, 7,000, 8,000, 9,000, 10,000, 20,000, 30,000, 40,000, 50,000, 60,000, 70,000, 80,000, 90,000 or up to and including 100,000 nucleotides).

[0221] In some embodiments, the nucleic acid of the present disclosure includes from about 30 to about 100,000 nucleotides (*e.g.*, from 30 to 50, from 30 to 100, from 30 to 250, from 30 to 500, from 30 to 1,000, from 30 to 1,500, from 30 to 3,000, from 30 to 5,000, from 30 to 7,000, from 30 to 10,000, from 30 to 25,000, from 30 to 50,000, from 30 to 70,000, from 100 to 250, from 100 to 500, from 100 to 1,000, from 100 to 1,500, from 100 to 3,000, from 100 to 5,000, from 100 to 7,000, from 100 to 10,000, from 100 to 25,000, from 100 to 50,000, from 100 to 70,000, from 100 to 100,000, from 500 to 1,000, from 500 to 1,500, from 500 to 2,000, from 500 to 3,000, from 500 to 5,000, from 500 to 7,000, from 500 to 10,000, from 500 to 25,000, from 500 to 50,000, from 500 to 70,000, from 500 to 100,000, from 1,000 to 1,500, from 1,000 to 2,000, from 1,000 to 3,000, from 1,000 to 5,000, from 1,000 to 7,000, from 1,000 to 10,000, from 1,000 to 25,000, from 1,000 to 50,000, from 1,000 to 70,000, from 1,000 to 100,000, from 1,500 to 3,000, from 1,500 to 5,000, from 1,500 to 7,000, from 1,500 to 10,000, from 1,500 to 25,000, from 1,500 to 50,000, from 1,500 to 70,000, from 1,500 to 100,000, from 2,000 to 3,000, from 2,000 to 5,000, from 2,000 to 7,000, from 2,000 to 10,000, from 2,000 to 25,000, from 2,000 to 50,000, from 2,000 to 70,000, and from 2,000 to 100,000).

[0222] The nucleic acids of the disclosure are not limited to sequences that encode

polypeptides (*e.g.*, antibodies); some or all of the non-coding sequences that lie upstream or downstream from a coding sequence (*e.g.*, the coding sequence of an antibody) can also be included. Those of ordinary skill in the art of molecular biology are familiar with routine procedures for isolating nucleic acid molecules. In the event the nucleic acid molecule is a ribonucleic acid (RNA), molecules can be produced, for example, by *in vitro* transcription.

[0223] The nucleic acids of the disclosure, including variants and naturally-occurring nucleic acid sequences, can be produced using a number of methods including, for example, those described in Sambrook 2012, *supra*. For example, the sequence of a nucleic acid molecule can be modified with respect to a naturally-occurring sequence from which it is derived using a variety of techniques including, but not limited to, classic mutagenesis techniques and recombinant DNA techniques, such as but not limited to site-directed mutagenesis, chemical treatment of a nucleic acid molecule to induce mutations, restriction enzyme cleavage of a nucleic acid fragment, ligation of nucleic acid fragments, PCR amplification and/or mutagenesis of selected regions of a nucleic acid sequence, recombinational cloning, and chemical synthesis, including chemical synthesis of oligonucleotide mixtures and ligation of mixture groups to “build” a mixture of nucleic acid molecules, and combinations thereof.

Modified nucleic acids

[0224] In some embodiments, the nucleic acid is an RNA molecule. In some embodiments, the RNA molecule is a messenger RNA (mRNA) molecule. In some embodiments, the nucleic acid comprises one or more modified nucleosides (termed “modified nucleic acid” or “modified nucleic acid molecule”) which have useful properties including the lack of a substantial induction of the innate immune response of a cell into which the nucleic acid (*e.g.*, mRNA) is introduced. In some embodiments, one or more chemical modifications can be located on the nucleobase of the nucleotide. In some embodiments, one or more chemical modifications can be located on the sugar moiety of the nucleotide. In some embodiments, one or more chemical modifications can be located on the phosphate backbone of the nucleotide.

[0225] Modified nucleosides and nucleotides can be prepared according to methods known in the art, for example, Ogata et al. *Journal of Organic Chemistry* 74:2585-2588, 2009; Purmal et al. *Nucleic Acids Research* 22(1): 72-78, 1994; Fukuhara et al. *Biochemistry* 1(4): 563-568, 1962; and Xu et al. *Tetrahedron* 48(9): 1729-1740, 1992.

[0226] Modified nucleic acids (*e.g.*, mRNAs) need not be uniformly modified along the

entire length of the molecules. Different nucleotide modifications and/or backbone structures may exist at various positions in the nucleic acid. One of ordinary skill in the art will appreciate that the nucleotide analogs or other modification(s) may be located at any position(s) of a nucleic acid such that the function of the nucleic acid is not substantially decreased. A modification may also be a 5' or 3' terminal modification. The nucleic acids of the disclosure may contain at a minimum one and at maximum 100% modified nucleotides, or any intervening percentage, such as at least 50% modified nucleotides, at least 80% modified nucleotides, or at least 90% modified nucleotides.

[0227] For example, the modified nucleic acids (*e.g.*, mRNAs) may contain a modified pyrimidine such as uracil or cytosine. In some embodiments, at least 5%, at least 10%, at least 25%, at least 50%, at least 80%, at least 90% or 100% of the uracil in the nucleic acid may be replaced with a modified uracil. The modified uracil can be replaced by a compound having a single unique structure, or can be replaced by a plurality of compounds having different structures (*e.g.*, 2, 3, 4 or more unique structures). In some embodiments, at least 5%, at least 10%, at least 25%, at least 50%, at least 80%, at least 90% or 100% of the cytosine in the nucleic acid may be replaced with a modified cytosine. The modified cytosine can be replaced by a compound having a single unique structure, or can be replaced by a plurality of compounds having different structures (*e.g.*, 2, 3, 4 or more unique structures).

[0228] In some embodiments, modified nucleosides may include pyridin-4-one ribonucleoside, 5-aza-uridine, 2-thio-5-aza-uridine, 2-thiouridine, 4-thio-pseudouridine, 2-thio-pseudouridine, 5-hydroxyuridine, 3-methyluridine, 5-carboxymethyl-uridine, 1-carboxymethyl-pseudouridine, 5-propynyl-uridine, 1-propynyl-pseudouridine, 5-aurinomethyluridine, 1-aurinomethyl-pseudouridine, 5-aurinomethyl-2-thio-uridine, 1-aurinomethyl-4-thio-uridine, 5-methyl-uridine, 1-methyl-pseudouridine, 4-thio-1-methyl-pseudouridine, 2-thio-1-methyl-pseudouridine, 1-methyl-1-deaza-pseudouridine, 2-thio-1-methyl-1-deaza-pseudouridine, dihydrouridine, dihydropseudouridine, 2-thio-dihydrouridine, 2-thio-dihydropseudouridine, 2-methoxyuridine, 2-methoxy-4-thio-uridine, 4-methoxy-pseudouridine, and 4-methoxy-2-thio-pseudouridine. In some embodiments, modified nucleosides include 5-aza-cytidine, pseudoisocytidine, 3-methyl-cytidine, N4-acetylcytidine, 5-formylcytidine, N4-methylcytidine, 5-hydroxymethylcytidine, 1-methyl-pseudoisocytidine, pyrrolo-cytidine, pyrrolo-pseudoisocytidine, 2-thio-cytidine, 2-thio-5-methyl-cytidine, 4-thio-pseudoisocytidine, 4-thio-1-

methyl-pseudoisocytidine, 4-thio-1-methyl-1-deaza-pseudoisocytidine, 1-methyl-1-deaza-pseudoisocytidine, zebularine, 5-aza-zebularine, 5-methyl-zebularine, 5-aza-2-thio-zebularine, 2-thio-zebularine, 2-methoxy-cytidine, 2-methoxy-5-methyl-cytidine, 4-methoxy-pseudoisocytidine, and 4-methoxy-1-methyl-pseudoisocytidine.

[0229] In other embodiments, modified nucleosides may include 2-aminopurine, 2, 6-diaminopurine, 7-deaza-adenine, 7-deaza-8-aza-adenine, 7-deaza-2-aminopurine, 7-deaza-8-aza-2-aminopurine, 7-deaza-2,6-diaminopurine, 7-deaza-8-aza-2,6-diaminopurine, 1-methyladenosine, N6-methyladenosine, N6-isopentenyladenosine, N6-(cis-hydroxyisopentenyl)adenosine, 2-methylthio-N6-(cis-hydroxyisopentenyl) adenosine, N6-glycinylicarbamoyladenosine, N6-threonylicarbamoyladenosine, 2-methylthio-N6-threonylicarbamoyladenosine, N6,N6-dimethyladenosine, 7-methyladenine, 2-methylthio-adenine, and 2-methoxy-adenine.

[0230] In other embodiments, modified nucleosides may include inosine, 1-methyl-inosine, wyosine, wybutosine, 7-deaza-guanosine, 7-deaza-8-aza-guanosine, 6-thio-guanosine, 6-thio-7-deaza-guanosine, 6-thio-7-deaza-8-aza-guanosine, 7-methyl-guanosine, 6-thio-7-methyl-guanosine, 7-methylinosine, 6-methoxy-guanosine, 1-methylguanosine, N2-methylguanosine, N2,N2-dimethylguanosine, 8-oxo-guanosine, 7-methyl-8-oxo-guanosine, 1-methyl-6-thio-guanosine, N2-methyl-6-thio-guanosine, and N2,N2-dimethyl-6-thio-guanosine.

[0231] In some embodiments, the nucleotide may be modified on the major groove face and can include replacing hydrogen on C-5 of uracil with a methyl group or a halo group. In some embodiments, a modified nucleoside is 5'-O-(1-Thiophosphate)-Adenosine, 5'-O-(1-Thiophosphate)-Cytidine, 5'-O-(1-Thiophosphate)-Guanosine, 5'-O-(1-Thiophosphate)-Uridine or 5'-O-(1-Thiophosphate)-Pseudouridine.

Pharmaceutical compositions and lipid nanoparticles

[0232] As discussed above, the nucleic acids and compositions of the disclosure can be incorporated into formulations suitable for various downstream applications, for example, pharmaceutical compositions.

[0233] In some embodiments, such compositions include one or more of the antibodies, antigen-binding fragments, and/or nucleic acids as disclosed herein in an amount, a combination, or in a form that is not found in nature. For example, in some embodiments, the compositions of the disclosure include one or more of the antibodies, antigen-binding fragments, and/or nucleic

acids as disclosed herein that have been isolated (*e.g.*, purified) to an extent that they no longer in a form in which they would be found in nature. In another example, in some embodiments, the compositions of the disclosure include the antibodies, antigen-binding fragments, and/or nucleic acids of the disclosure in amounts that do not occur in nature. In yet another example, in some embodiments, the antibodies, antigen-binding fragments, and/or nucleic acids of the disclosure are combined in formulations and/or combinations that do not occur in nature. In some embodiments, such compositions include a therapeutically or prophylactically effective amount of an antibody or antigen-binding fragment thereof in admixture with a suitable excipient, *e.g.*, a pharmaceutically acceptable carrier. In some embodiments, an effective amount of a composition sufficient for achieving a therapeutic or prophylactic effect, ranges from about 0.000001 mg per kilogram body weight per administration to about 10,000 mg per kilogram body weight per administration. Suitably, the dosage ranges are from about 0.0001 mg per kilogram body weight per administration to about 100 mg per kilogram body weight per administration.

[0234] Generally, pharmaceutically acceptable carriers suitable for use in the compositions of the disclosure include, but are not limited to, means any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like that are physiologically compatible. Non-limiting examples of pharmaceutically acceptable carriers are water, saline, phosphate buffered saline, dextrose, glycerol, ethanol and the like, as well as combinations thereof. In some embodiments, the compositions of the disclosure include isotonic agents, for example, sugars, polyalcohols such as mannitol, sorbitol, or sodium chloride in the composition. Other examples of pharmaceutically acceptable substances are wetting agents or minor amounts of auxiliary substances such as wetting or emulsifying agents, preservatives or buffers, which enhance the shelf life or effectiveness of the antibody. Additional pharmaceutically acceptable carriers suitable for use in the compositions of the disclosure include, but are not limited to, excipients, diluents, antioxidants, preservatives, coloring, flavoring and diluting agents, emulsifying agents, suspending agents, solvents, fillers, bulking agents, buffers, delivery vehicles, tonicity agents, cosolvents, wetting agents, complexing agents, buffering agents, antimicrobials, and surfactants.

[0235] In one aspect, the antibodies, antigen-binding fragments, and/or nucleic acids of the disclosure can be incorporated into compositions suitable for various downstream applications, for example, pharmaceutical compositions. Exemplary compositions of the disclosure include

pharmaceutical compositions which generally include one or more of the antibodies, antigen-binding fragments, and/or nucleic acids as described herein and a pharmaceutically acceptable excipient, *e.g.*, carrier or diluent. In some embodiments, the composition is a sterile composition. In some embodiments, the composition is a lyophilized, desiccated, or freeze-dried composition. In some embodiments, the composition is formulated as a vaccine. In some embodiments, the composition further includes an adjuvant.

[0236] In some embodiments of the disclosure, the compositions of the disclosure are formulated into a lipid nanoparticle (LNP) comprising at least one lipid. In principle, there are no particular limitations with regard to methods and processes to be used for the making of the LNPs disclosed herein. Suitable methods and processes for making LNPs include, but not limited to, continuous mixing methods, direct dilution processes, and in-line dilution processes. Additional examples of suitable methods for making LNPs are described in, for example, Semple et al. (2010) *Nat. Biotechnol.* 28:172-176; Jayarama et al. (2012), *Angew. Chem. Int. Ed.*, 51: 8529-8533; and Maier et al. (2013) *Molecular Therapy* 21, 1570-1578, U.S. Patent Nos. 10,898,574 and 10,702,600, which are herein incorporated by reference.

[0237] In some embodiments, the LNPs according to embodiments of the present disclosure may be prepared by standard T-tube mixing techniques, turbulent mixing, trituration mixing, agitation promoting orders self-assembly, or passive mixing of all the elements with self-assembly of elements into nanoparticles. In some embodiments, the LNPs disclosed herein may be produced via a continuous mixing method, *e.g.*, a process that includes providing an aqueous solution comprising an antigen-binding molecule or nucleic acid (*e.g.*, mRNA) in a first reservoir, providing an organic lipid solution in a second reservoir (wherein the lipids present in the organic lipid solution are solubilized in an organic solvent, *e.g.*, a lower alkanol such as ethanol), and mixing the aqueous solution with the organic lipid solution such that the organic lipid solution mixes with the aqueous solution so as to substantially instantaneously produce a lipid vesicle (*e.g.*, liposome) encapsulating the antigen-binding molecule or nucleic acid within the lipid vesicle. This process and the apparatus for carrying out this process are known and described in detail in, for example, U.S. Patent Publication No. 20040142025, the disclosure of which is herein incorporated by reference in its entirety.

[0238] The action of continuously introducing lipid and buffer solutions into a mixing environment, such as in a mixing chamber, causes a continuous dilution of the lipid solution with

the buffer solution, thereby producing a lipid vesicle substantially instantaneously upon mixing. In this process, the lipid solution is diluted sufficiently rapidly in a hydration process with sufficient force to effectuate vesicle generation. By mixing the aqueous solution comprising an antigen-binding molecule or nucleic acid with the organic lipid solution, the organic lipid solution undergoes a continuous stepwise dilution in the presence of the buffer solution (i.e., aqueous solution) to produce an LNP.

[0239] The LNPs of the present disclosure can be assessed for size using devices that size nanoparticles, e.g., in solution, such as the Malvern™ Zetasizer™. In some embodiments, the LNPs formed using the continuous mixing method can have a size of from about 30 nm to about 150 nm, from about 40 nm to about 150 nm, from about 50 nm to about 150 nm, from about 60 nm to about 130 nm, from about 70 nm to about 110 nm, from about 70 nm to about 100 nm, from about 80 nm to about 100 nm, from about 90 nm to about 100 nm, from about 70 to about 90 nm, from about 80 nm to about 90 nm, from about 70 nm to about 80 nm, less than about 120 nm, 110 nm, 100 nm, 90 nm, or 80 nm, or about 30 nm, 35 nm, 40 nm, 45 nm, 50 nm, 55 nm, 60 nm, 65 nm, 70 nm, 75 nm, 80 nm, 85 nm, 90 nm, 95 nm, 100 nm, 105 nm, 110 nm, 115 nm, 120 nm, 125 nm, 130 nm, 135 nm, 140 nm, 145 nm, or 150 nm (or any fraction thereof or range therein). In some embodiments, the LNPs thus formed do not aggregate and are optionally sized to achieve a substantially uniform particle size.

[0240] In some embodiments, the LNPs disclosed herein may be produced via a direct dilution process that includes forming a lipid vesicle (e.g., liposome) solution and immediately and directly introducing the lipid vesicle solution into a collection vessel containing a controlled amount of dilution buffer. In some embodiments, the collection vessel includes one or more elements configured to stir the contents of the collection vessel to facilitate dilution. In one aspect, the amount of dilution buffer present in the collection vessel is substantially equal to the volume of lipid vesicle solution introduced thereto. As a non-limiting example, a lipid vesicle solution in 45% ethanol when introduced into the collection vessel containing an equal volume of dilution buffer will advantageously yield smaller particles.

[0241] In yet some other embodiments, the LNPs disclosed herein may be produced via an in-line dilution process in which a third reservoir containing dilution buffer is fluidly coupled to a second mixing region. In these embodiments, the lipid vesicle (e.g., liposome) solution formed in a first mixing region is immediately and directly mixed with dilution buffer in the second

mixing region. In some embodiments, the second mixing region includes a T-connector arranged so that the lipid vesicle solution and the dilution buffer flows meet as opposing 180° flows; however, connectors providing shallower angles can be used, *e.g.*, from about 20° to about 180° (*e.g.*, about 90°). A pump mechanism delivers a controllable flow of buffer to the second mixing region. In one embodiment, the flow rate of dilution buffer provided to the second mixing region is controlled to be substantially equal to the flow rate of lipid vesicle solution introduced thereto from the first mixing region. This embodiment advantageously allows for more control of the flow of dilution buffer mixing with the lipid vesicle solution in the second mixing region, and therefore also the concentration of lipid vesicle solution in buffer throughout the second mixing process. Such control of the dilution buffer flow rate advantageously allows for small particle size formation at reduced concentrations.

[0242] These processes and the apparatuses for carrying out these direct dilution and in-line dilution processes are known and described in detail in, for example, U.S. Patent Publication No. 20070042031, the disclosure of which is herein incorporated by reference.

[0243] The LNPs formed using the direct dilution and in-line dilution processes can have a size of from about 30 nm to about 150 nm, from about 40 nm to about 150 nm, from about 50 nm to about 150 nm, from about 60 nm to about 130 nm, from about 70 nm to about 110 nm, from about 70 nm to about 100 nm, from about 80 nm to about 100 nm, from about 90 nm to about 100 nm, from about 70 to about 90 nm, from about 80 nm to about 90 nm, from about 70 nm to about 80 nm, less than about 120 nm, 110 nm, 100 nm, 90 nm, or 80 nm, or about 30 nm, 35 nm, 40 nm, 45 nm, 50 nm, 55 nm, 60 nm, 65 nm, 70 nm, 75 nm, 80 nm, 85 nm, 90 nm, 95 nm, 100 nm, 105 nm, 110 nm, 115 nm, 120 nm, 125 nm, 130 nm, 135 nm, 140 nm, 145 nm, or 150 nm (or any fraction thereof or range therein). In some embodiments, the nanoparticles thus formed do not aggregate and are optionally sized to achieve a substantially uniform particle size.

[0244] If needed, the lipid nanoparticles of the present disclosure can be sized by any of the methods available for sizing liposomes and/or lipid nanoparticles. The sizing may be conducted in order to achieve a desired size range and relatively narrow distribution of particle sizes.

[0245] Several techniques are available for sizing the particles to a desired size. One sizing method, used for liposomes and equally applicable to the present particles, is described in U.S. Pat. No. 4,737,323, the disclosure of which is herein incorporated by reference. Sonicating a

particle suspension either by bath or probe sonication produces a progressive size reduction down to particles of less than about 50 nm in size. Homogenization is another method which relies on shearing energy to fragment larger particles into smaller ones. In a typical homogenization procedure, particles are recirculated through a standard emulsion homogenizer until selected particle sizes, typically between about 60 and about 80 nm, are observed. In both methods, the particle size distribution can be monitored by conventional laser-beam particle size discrimination, or QELS.

[0246] In some embodiments, the LNPs disclosed herein have an average diameter of less than about 1000 nm, about 500 nm, about 250 nm, about 200 nm, about 150 nm, about 100 nm, about 75 nm, about 50 nm, or about 25 nm. In some embodiments, the LNPs have an average diameter ranging from about 70 nm to 100 nm. In some embodiments, the LNPs have an average diameter ranging from about 88 nm to about 92 nm, from 82 nm to about 86 nm, or from about 80 nm to about 95 nm.

[0247] In some embodiments, the LNP has a mean diameter ranging from about 10 nm to about 200 nm. In some embodiments, the LNP has a mean diameter ranging from about 10 nm to about 500 nm, from about 20 to about 400 nm, from about 30 to about 300 nm, or from about 40 to about 200 nm. In some embodiments, the LNP has a mean diameter ranging from about 50 to about 150 nm, from about 50 to about 200 nm, from about 80 to about 100 nm, or from about 80 to about 200 nm.

[0248] In some embodiments, the compositions of the disclosure may be formulated into a LNP that includes one or more of ionizable cationic lipid, cationic lipid, anionic lipid, neutral lipid, sterol, and PEG-modified lipid. In some embodiments, the lipid may be a cationic lipid such as, but not limited to, DLin-DMA, DLin-D-DMA, DLin-MC3-DMA (MC3), DLin-KC2-DMA (MC2), DODMA, 98N12-5, C12-200, C14-PEG2000, XTC, MD1, 7C1, and amino alcohol lipids. In some embodiments, the lipid may be an ionizable cationic lipid, such as 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobutyrate (DLin-MC3-DMA), or di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319), ALC-0315, C12-200, LN16, MC3, MD1, SM-102. In some embodiments, the lipid may be a neutral lipid such as, but not limited to, DPSC, DPPC, POPC, DOPE, and SM. Non-limiting examples of lipids suitable for the compositions and methods of the disclosure include DLin-DMA, DLin-K-DMA, 98N12-5, C12-

200, DLin-MC3-DMA, DLin-KC2-DMA, DODMA, PLGA, PEG, PEG-DMG, PEGylated lipids and amino alcohol lipids. The amino alcohol cationic lipid may be the lipids described in and/or made by the methods described in U.S. Patent Publication No. US20130150625, herein incorporated by reference in its entirety. Additional lipids suitable for the compositions and methods of the present disclosure can be found in U.S. Patent Nos. 10,898,574 and 10,702,600, which are incorporated by reference in their entireties.

[0249] In some embodiments, the LNP compositions may further include a neutral lipid, a sterol and a molecule capable of reducing particle aggregation, for example a PEG or PEG-modified lipid. In some embodiments, the LNP further includes phosphatidyl choline. In some embodiments, the sterol is cholesterol.

[0250] In some embodiments, the LNPs of the disclosure further include non-lipid polycations which are useful to promote the lipofection of cells using the present compositions. Examples of suitable non-lipid polycations include hexadimethrine bromide (*e.g.*, POLYBRENE®, Aldrich Chem) or other salts of hexadimethrine. Other suitable polycations include, for example, salts of poly-L-ornithine, poly-L-arginine, poly-L-lysine, poly-D-lysine, polyallylamine, and polyethyleneimine. Addition of these salts is generally after the particles have been formed.

[0251] One skilled in the art will appreciate that the lipid(s) can be combined with the antigen-binding molecules and/or nucleic acids of the disclosure in a wide range molar ratios to produce a LNP. In some embodiments, the mass ratio (wt/wt) of lipid to antigen-binding polypeptide/nucleic acid in the LNP ranges from about 2:1 to about 100:1. In some embodiments, the mass ratio (wt/wt) of lipid to antigen-binding polypeptide/nucleic acid in the LNP is about 100:1 to about 3:1, about 70:1 to 10:1, or 16:1 to 4:1. In some embodiments, the mass ratio (wt/wt) of lipid to antigen-binding polypeptide/nucleic acid in the LNP is about 16:1 to 4:1. In some embodiments, mass ratio (wt/wt) of lipid to antigen-binding polypeptide/nucleic acid in the LNP is about 20:1. In some embodiments, the mass ratio of lipid to nucleic acid in the LNP delivery system is about 8:1.

[0252] In some embodiments, the lipid to antigen-binding polypeptide/nucleic acid ratios (wt/wt) in an LNP may range from about 1 (1:1) to about 100 (100:1), from about 5 (5:1) to about 100 (100:1), from about 1 (1:1) to about 50 (50:1), from about 2 (2:1) to about 50 (50:1), from about 3 (3:1) to about 50 (50:1), from about 4 (4:1) to about 50 (50:1), from about 5 (5:1) to

about 50 (50:1), from about 1 (1:1) to about 25 (25:1), from about 2 (2:1) to about 25 (25:1), from about 3 (3:1) to about 25 (25:1), from about 4 (4:1) to about 25 (25:1), from about 5 (5:1) to about 25 (25:1), from about 5 (5:1) to about 20 (20:1), from about 5 (5:1) to about 15 (15:1), from about 5 (5:1) to about 10 (10:1), or about 5 (5:1), 6 (6:1), 7 (7:1), 8 (8:1), 9 (9:1), 10 (10:1), 11 (11:1), 12 (12:1), 13 (13:1), 14 (14:1), 15 (15:1), 16 (16:1), 17 (17:1), 18 (18:1), 19 (19:1), 20 (20:1), 21 (21:1), 22 (22:1), 23 (23:1), 24 (24:1), or 25 (25:1), or any fraction thereof or range therein. The ratio of the starting materials (input) also falls within this range.

[0253] In some embodiments, the lipid nanoparticles described herein may be made in a sterile environment.

[0254] In some embodiments, the compositions disclosed herein, e.g., LNP compositions, include a first agent (e.g., therapeutic agent or prophylactic agent) which is, comprises, or encodes a first antibody or antigen-binding fragment belonging to bin 1 or bin 2 described in Example 14, and a second agent (e.g., therapeutic agent or prophylactic agent) which is, comprises, or encodes a second antibody or antigen-binding fragment belonging to bin 3, bin 4, or bin 3/4 described in Example 14. In some embodiments, the first agent is, comprises, or encodes a first antibody or antigen-binding fragment belonging to bin 1 described in Example 14, and the second agent is, comprises, or encodes a second antibody or antigen-binding fragment belonging to bin 3, bin 4, or bin 3/4 described in Example 14. In some embodiments, the first agent is, comprises, or encodes a first antibody or antigen-binding fragment belonging to bin 2 described in Example 14, and the second agent is, comprises, or encodes a second antibody or antigen-binding fragment belonging to bin 3, bin 4, or bin 3/4 described in Example 14. In some embodiments, the first agent is, comprises, or encodes a first antibody or antigen-binding fragment belonging to bin 3 described in Example 14, and the second agent is, comprises, or encodes a second antibody or antigen-binding fragment belonging to bin 4 described in Example 14. In some embodiments, the first agent is, comprises, or encodes a first antibody or antigen-binding fragment belonging to bin 3 described in Example 14, and the second agent is, comprises, or encodes a second antibody or antigen-binding fragment belonging to bin 3/4 described in Example 14. In some embodiments, the first agent is, comprises, encodes a first antibody or antigen-binding fragment belonging to bin 4 described in Example 14, and the second agent is, comprises, or encodes a second antibody or antigen-binding fragment belonging to bin 3/4 described in Example 14.

[0255] In some embodiments, the first agent and the second agent are formulated into a single LNP. In some embodiments, the first and the second agents are formulated into separate LNPs, e.g., the first agent is formulated into a first LNP and the second agent is formulated into a second LNP. In some embodiments, the first and the second LNPs may have similar (e.g., identical) physicochemical attributes. In some embodiments, the first and the second LNPs may have different physicochemical properties to achieve desired (e.g., optimal) therapeutic effects.

[0256] As described above, several antibodies described herein are pan-coronavirus antibodies that bind with high affinity to the NTD of SARS-CoV-2 S protein and to a spike protein of one or more SARS-CoV variants (e.g., beta, gamma, kappa, and omicron), endemic human coronaviruses (HCoV), and variants of thereof (e.g., HCoV-229E, HCoV-OC43, and HCoV-HKU1). These broad and potentially neutralizing NTD-targeting antibodies could be particularly useful in therapeutic combination against SARS-CoV-2 and other coronaviruses and in combination with RBD-binding or non-S1 binding therapeutic antibodies.

[0257] In some embodiments, the compositions disclosed herein, e.g., LNP compositions, include (i) a first agent (e.g., therapeutic agent or prophylactic agent) which is, comprises, or encodes a neutralizing NTD-targeting antibody, and (ii) a second agent (e.g., therapeutic agent or prophylactic agent) which is, comprises, or encodes a neutralizing antibody that does not target the NTD. In some embodiments, the second agent is or comprises a neutralizing RBD-targeting antibody. In some embodiments, the neutralizing NTD-targeting antibody is TXG-0060, TXG-0066, TXG-0071, TXG-0076, TXG-0078, TXG-0079, TXG-0099, TXG-0104, TXG-0116, TXG-0119, TXG-0131, TXG-0132, TXG-0137, TXG-0162, TXG-0163, TXG-0164, TXG-0168, TXG-0170, TXG-0173, TXG-0174, TXG-0184, TXG-0136, or an antigen-binding fragment of any thereof (see, e.g., Tables 6 and 9); and the neutralizing antibody that does not bind the NTD is TXG-0001, TXG-0002, TXG-0004, TXG-0005, TXG-0006, TXG-0008, TXG-0009, TXG-0057, TXG-0080, TXG-0081, TXG-0088, TXG-0091, TXG-0093, TXG-0094, TXG-0100, TXG-0109, TXG-0115, TXG-0120, TXG-0126, TXG-0129, TXG-0140, TXG-0141, TXG-0144, TXG-0153, TXG-0154, TXG-0183, TXG-0189, TXG-0197, TXG-0198, TXG-0200, TXG-0201, TXG-0202, TXG-0204, TXG-0210, or an antigen-binding fragment of any thereof (see, e.g., Table 12).

[0258] In some embodiments, the compositions disclosed herein e.g., LNP compositions, include (i) a first agent (e.g., therapeutic agent or prophylactic agent) which is, comprises, or

encodes a potentially neutralizing (e.g., has an IC₅₀ of 1000 ng/ml or less) NTD-targeting antibody, and (ii) a second agent (e.g., therapeutic agent or prophylactic agent) which is, comprises, or encodes a potentially neutralizing RBD antibody. In some embodiments, the potentially neutralizing NTD-targeting antibody is TXG-0066, TXG-0076, TXG-0078, TXG-0099, TXG-0104, TXG-0170, TXG-0173, and TXG-0174, or an antigen-binding fragment of any thereof; and the potentially neutralizing RBD antibody is TXG-0001, TXG-0002, TXG-0004, TXG-0005, TXG-0006, TXG-0008, TXG-0009, TXG-0057, TXG-0080, TXG-0081, TXG-0088, TXG-0091, TXG-0093, TXG-0094, TXG-0100, TXG-0109, TXG-0115, TXG-0120, TXG-0126, TXG-0129, TXG-0140, TXG-0141, TXG-0144, TXG-0153, TXG-0154, TXG-0180, , TXG-0183, TXG-0189, TXG-0197, TXG-0198, TXG-0200, TXG-0201, TXG-0202, TXG-0204, TXG-0209, TXG-0210, or an antigen-binding fragment of any thereof (see, e.g., Table 12).

[0259] In some embodiments, the compositions disclosed herein e.g., LNP compositions, include (i) a first agent (e.g., therapeutic agent or prophylactic agent) which is, comprises, or encodes a neutralizing NTD-targeting antibody with binding affinity for the omicron variant of SARS-CoV-2 or at least one endemic human coronaviruses (HCoVs), and (ii) a second agent (e.g., therapeutic agent or prophylactic agent) which is, comprises, or encodes a neutralizing RBD antibody with binding affinity for the omicron variant of SARS-CoV-2 or at least one endemic human coronaviruses (HCoVs). In some embodiments, the neutralizing NTD-targeting antibody with binding affinity for the omicron variant of SARS-CoV-2 or at least one endemic human coronaviruses (HCoVs) TXG-0072, TXG-0078, TXG-0099, TXG-0174, or an antigen-binding fragment of any thereof; and the neutralizing RBD antibody with binding affinity for the omicron variant of SARS-CoV-2 or at least one endemic human coronaviruses (HCoVs) is TXG-0006, TXG-0049, TXG-0057, TXG-0070, TXG-0080, TXG-0081, TXG-0088, TXG-0091, TXG-0094, TXG-0098, TXG-0109, TXG-0115, TXG-0120, TXG-0129, TXG-0141, TXG-0144, TXG-0153, TXG-0154, TXG-0180, TXG-0183, TXG-0189, TXG-0197, TXG-0198, TXG-0200, TXG-0201, TXG-0202, TXG-0204, TXG-0209, TXG-0210, or an antigen-binding fragment of any thereof.

[0260] In some embodiments, the compositions disclosed herein e.g., LNP compositions, include (i) a first agent (e.g., therapeutic agent or prophylactic agent) which is, comprises, or encodes a neutralizing NTD-targeting antibody with binding affinity for the omicron variant of SARS-CoV-2 or at least one endemic human coronaviruses (HCoVs), and (ii) a second agent

(e.g., therapeutic agent or prophylactic agent) which is, comprises, or encodes a neutralizing RBD antibody with binding affinity for at least one endemic human coronaviruses (HCoV_s). In some embodiments, the neutralizing NTD-targeting antibody with binding affinity for the omicron variant of SARS-CoV-2 or at least one endemic human coronaviruses (HCoV_s) is TXG-0072, TXG-0078, TXG-0099, TXG-0174, or an antigen-binding fragment of any thereof; and the neutralizing RBD antibody with binding affinity for at least one endemic human coronaviruses (HCoV_s) is TXG-0091, TXG-0006, TXG-0154, or an antigen-binding fragment of any thereof.

[0261] In some embodiments, the compositions disclosed herein e.g., LNP compositions, include (i) a first agent (e.g., therapeutic agent or prophylactic agent) which is, comprises, or encodes a potentially neutralizing NTD-targeting antibody with binding affinity for the omicron variant of SARS-CoV-2 or at least one endemic human coronaviruses (HCoV_s), and (ii) a second agent (e.g., therapeutic agent or prophylactic agent) which is, comprises, or encodes a neutralizing RBD antibody with binding affinity for at least one endemic human coronaviruses (HCoV_s). In some embodiments, the potentially neutralizing NTD-targeting antibody with binding affinity for the omicron variant of SARS-CoV-2 or at least one endemic human coronaviruses (HCoV_s) is TXG-0078, TXG-0099, TXG-0174, or an antigen-binding fragment of any thereof; and the neutralizing RBD antibody with binding affinity for at least one endemic human coronaviruses (HCoV_s) is TXG-0006, TXG-0091, TXG-0154, or an antigen-binding fragment of any thereof.

[0262] In some embodiments, the compositions disclosed herein e.g., LNP compositions, include (i) a first agent (e.g., therapeutic agent or prophylactic agent) which is, comprises, or encodes a potentially neutralizing NTD-targeting antibody with binding affinity for the omicron variant of SARS-CoV-2 or at least one endemic human coronaviruses (HCoV_s), and (ii) a second agent (e.g., therapeutic agent or prophylactic agent) which is, comprises, or encodes a neutralizing RBD antibody with binding affinity for the omicron variant of SARS-CoV-2 and at least one endemic human coronaviruses (HCoV_s). In some embodiments, the potentially neutralizing NTD-targeting antibody with binding affinity for the omicron variant of SARS-CoV-2 or at least one endemic human coronaviruses (HCoV_s) is TXG-0078, TXG-0099, TXG-0174, or an antigen-binding fragment of any thereof; and the neutralizing RBD antibody with binding affinity for the omicron variant of SARS-CoV-2 and at least one endemic human coronaviruses (HCoV_s) is TXG-0091 or an antigen-binding fragment thereof.

[0263] In some embodiments, the compositions disclosed herein e.g., LNP compositions, include (i) a first agent (e.g., therapeutic agent or prophylactic agent) which is, comprises, or encodes a potentially neutralizing NTD-targeting antibody with binding affinity for at least one endemic human coronaviruses (HCoV), and (ii) a second agent (e.g., therapeutic agent or prophylactic agent) which is, comprises, or encodes a neutralizing RBD antibody with binding affinity for at least one endemic human coronaviruses (HCoV). In some embodiments, the potentially neutralizing NTD-targeting antibody with binding affinity for at least one endemic human coronaviruses (HCoV) is TXG-0078 or an antigen-binding fragment thereof; and the neutralizing RBD antibody with binding affinity for at least one endemic human coronaviruses (HCoV) is TXG-0006, TXG-0091, TXG-0154, or an antigen-binding fragment of any thereof.

[0264] In some embodiments, the compositions disclosed herein, e.g., LNP compositions, include (i) a first agent (e.g., therapeutic agent or prophylactic agent) which is, comprises, or encodes a TXG-0078 or an antigen-binding fragment thereof, and (ii) a second agent (e.g., therapeutic agent or prophylactic agent) which is or comprises TXG-0091 or an antigen-binding fragment thereof. In some embodiments, the compositions disclosed herein include (i) a first agent (e.g., therapeutic agent or prophylactic agent) which is, comprises, or encodes a NTD-targeting antibody with binding affinity for at least one endemic human coronaviruses (HCoV), and (ii) a second agent (e.g., therapeutic agent or prophylactic agent) which is, comprises, or encodes a neutralizing RBD antibody with binding affinity for at least one endemic human coronaviruses (HCoV). In some embodiments, the NTD-targeting antibody with binding affinity for at least one endemic human coronaviruses (HCoV) is TXG-0078, TXG-0114, TXG-0136, or an antigen-binding fragment of any thereof; and the neutralizing RBD antibody with binding affinity for at least one endemic human coronaviruses (HCoV) is TXG-0091, TXG-0006, TXG-0154, or an antigen-binding fragment of any thereof.

[0265] In some embodiments, the compositions disclosed herein e.g., LNP compositions, include (i) a first agent (e.g., therapeutic agent or prophylactic agent) which is or comprises or encodes an antibody being any one of TXG-0078 or TXG-0174; and an antigen-binding fragment of any thereof; and (ii) a second agent (e.g., therapeutic agent or prophylactic agent) which is or comprises or encodes an antibody being any one of TXG-0001, TXG-0002, TXG-0004, TXG-0005, TXG-0006, TXG-0008, TXG-0009, TXG-0081, TXG-0115, TXG-0154, or TXG-0180; or an antigen-binding fragment of any thereof.

METHODS OF THE DISCLOSUREMethods of treatment

[0266] As discussed above, one aspect of the disclosure relate to methods for treating, preventing, or ameliorating a health condition or viral infection (*e.g.*, reducing the likelihood of a viral infection such as coronavirus infection) by therapeutically or prophylactically administering a composition described herein to a subject in need of such treatment, prevention, or amelioration. In some embodiments, the methods include therapeutically or prophylactically administering to the subject an antigen-binding molecule, or an antigen-binding fragment thereof, that binds to a spike protein of SARS-CoV-2, wherein the antigen-binding molecule or antigen-binding fragment thereof comprises all six CDRs from an antibody identified in the Sequence Listing, and wherein the antigen-binding molecule or antigen-binding fragment thereof has a binding affinity for the spike (S) protein of two, three, four, five or more variants of SARS-CoV-2, and/or for one or more human coronaviruses (HCoVs) that is any one of HCoV-229E, HCoV-OC43, or HCoV-HKU1; or a variant of any thereof. In some embodiments, the one or more HCoVs is HCoV-229E or HCoV-OC43.

[0267] In some embodiments, the antibody is any one of TXG-0001, TXG-0002, TXG-0004, TXG-0005, TXG-0006, TXG-0008, TXG-0009, TXG-0048, TXG-0057, TXG-0060, TXG-0063, TXG-0066, TXG-0070, TXG-0072, TXG-0074, TXG-0076, TXG-0078, TXG-0080, TXG-0081, TXG-0087, TXG-0088, TXG-0091, TXG-0094, TXG-0098, TXG-0099, TXG-0100, TXG-0104, TXG-0109, TXG-0112, TXG-0114, TXG-0115, TXG-0120, TXG-0129, TXG-0136, TXG-0141, TXG-0144, TXG-0153, TXG-0154, TXG-0170, TXG-0173, TXG-0174, TXG-0175, TXG-0180, TXG-0181, TXG-0183, TXG-0187, TXG-0189, TXG-0192, TXG-0197, TXG-0198, TXG-0200, TXG-0201, TXG-0202, TXG-0203, TXG-0204, TXG-0209, TXG-0210, TXG-0228, or TXG-0230. In some embodiments, the antibody is any one of TXG-0001, TXG-0002, TXG-0004, TXG-0005, TXG-0006, TXG-0008, TXG-0009, TXG-0048, TXG-0070, TXG-0078, TXG-0081, TXG-0087, TXG-0114, TXG-0115, TXG-0154, TXG-0174, TXG-0175, TXG-0180, TXG-0192, or TXG-0203.

[0268] In one aspect, provided herein are methods for reducing binding of a spike (S) protein of a coronavirus (CoV-S) to a cell in a subject and/or reducing entry of the coronavirus into a cell of a subject, wherein the methods include therapeutically or prophylactically administering to the subject: (a) an antigen-binding molecule, or an antigen-binding fragment

thereof, that binds to a spike (S) protein of SARS-CoV-2, wherein the antigen-binding molecule or antigen-binding fragment thereof includes all six CDRs from an antibody being any one of TXG-0001, TXG-0002, TXG-0004, TXG-0005, TXG-0006, TXG-0008, TXG-0009, TXG-0048, TXG-0057, TXG-0060, TXG-0063, TXG-0066, TXG-0070, TXG-0072, TXG-0074, TXG-0076, TXG-0078, TXG-0080, TXG-0081, TXG-0087, TXG-0088, TXG-0091, TXG-0094, TXG-0098, TXG-0099, TXG-0100, TXG-0104, TXG-0109, TXG-0112, TXG-0114, TXG-0115, TXG-0120, TXG-0129, TXG-0136, TXG-0141, TXG-0144, TXG-0153, TXG-0154, TXG-0170, TXG-0173, TXG-0174, TXG-0175, TXG-0180, TXG-0181, TXG-0183, TXG-0187, TXG-0189, TXG-0192, TXG-0197, TXG-0198, TXG-0200, TXG-0201, TXG-0202, TXG-0203, TXG-0204, TXG-0209, TXG-0210, TXG-0228, or TXG-0230; and optionally wherein the antigen-binding molecule or antigen-binding fragment thereof has a binding affinity for the spike (S) protein of two, three, four, five or more variants of SARS-CoV-2, and/or for one or more human coronaviruses (HCoVs) being any one of HCoV-229E, HCoV-OC43, HCoV-HKU1, or a combination thereof, or a variant of any thereof; and/or (b) a nucleic acid encoding the antigen-binding molecule or antigen-binding fragment thereof of (a). In some embodiments, the one or more HCoVs is HCoV-229E and/or HCoV-OC43.

[0269] In some embodiments, the binding of the CoV-S protein to a cell in a subject is reduced at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, or at least 2 times, at least 3 times, at least 4 times, at least 5 times, at least 6 times, at least 7 times, at least 8 times, at least 9 times, or at least 10 times, as compared to its binding in a reference subject who has not been administered with the composition. In some embodiments, the entry of the coronavirus into a cell of a subject is reduced at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, or at least 2 times, at least 3 times, at least 4 times, at least 5 times, at least 6 times, at least 7 times, at least 8 times, at least 9 times, or at least 10 times, as compared to its entry in a reference subject who has not been administered with the composition.

[0270] In another aspect, provided herein are methods for inducing an immune response in a subject, wherein the methods include administering to the subject a composition as disclosed herein. In another aspect, provided herein are methods for aiding in the neutralization of two, three, four, five or more variants of SARS-CoV-2, wherein said aiding includes providing: (a) an antigen-binding molecule, or an antigen-binding fragment thereof, that binds to a spike (S) protein of SARS-CoV-2, wherein the antigen-binding molecule or antigen-binding fragment

thereof includes all six CDRs from an antibody being any one of TXG-0001, TXG-0002, TXG-0004, TXG-0005, TXG-0006, TXG-0008, TXG-0009, TXG-0048, TXG-0057, TXG-0060, TXG-0063, TXG-0066, TXG-0070, TXG-0072, TXG-0074, TXG-0076, TXG-0078, TXG-0080, TXG-0081, TXG-0087, TXG-0088, TXG-0091, TXG-0094, TXG-0098, TXG-0099, TXG-0100, TXG-0104, TXG-0109, TXG-0112, TXG-0114, TXG-0115, TXG-0120, TXG-0129, TXG-0136, TXG-0141, TXG-0144, TXG-0153, TXG-0154, TXG-0170, TXG-0173, TXG-0174, TXG-0175, TXG-0180, TXG-0181, TXG-0183, TXG-0187, TXG-0189, TXG-0192, TXG-0197, TXG-0198, TXG-0200, TXG-0201, TXG-0202, TXG-0203, TXG-0204, TXG-0209, TXG-0210, TXG-0228, or TXG-0230; and/or (b) a nucleic acid encoding the antigen-binding molecule or antigen-binding fragment thereof of (a). In some embodiments, the neutralization takes place in a single subject who has been infected by two, three, four, five or more variants of SARS-CoV-2. In some embodiments, the neutralization takes place in plurality of subjects who have each been infected by a different variant.

[0271] In yet another aspect, provided herein are methods for in reducing the viral load of two, three, four, five or more variants of SARS-CoV-2, wherein said aiding includes providing: (a) an antigen-binding molecule, or an antigen-binding fragment thereof, that binds to a spike (S) protein of SARS-CoV-2, wherein the antigen-binding molecule or antigen-binding fragment thereof includes all six CDRs from an antibody being any one of TXG-0001, TXG-0002, TXG-0004, TXG-0005, TXG-0006, TXG-0008, TXG-0009, TXG-0048, TXG-0057, TXG-0060, TXG-0063, TXG-0066, TXG-0070, TXG-0072, TXG-0074, TXG-0076, TXG-0078, TXG-0080, TXG-0081, TXG-0087, TXG-0088, TXG-0091, TXG-0094, TXG-0098, TXG-0099, TXG-0100, TXG-0104, TXG-0109, TXG-0112, TXG-0114, TXG-0115, TXG-0120, TXG-0129, TXG-0136, TXG-0141, TXG-0144, TXG-0153, TXG-0154, TXG-0170, TXG-0173, TXG-0174, TXG-0175, TXG-0180, TXG-0181, TXG-0183, TXG-0187, TXG-0189, TXG-0192, TXG-0197, TXG-0198, TXG-0200, TXG-0201, TXG-0202, TXG-0203, TXG-0204, TXG-0209, TXG-0210, TXG-0228, or TXG-0230; and/or (b) a nucleic acid encoding the antigen-binding molecule or antigen-binding fragment thereof of (a).

[0272] In another aspect, provided herein are methods for aiding in the neutralization of two, three, four, five or more variants of SARS-CoV-2, wherein said aiding includes providing a composition as disclosed herein. In another aspect, provided herein are methods for aiding in reducing the viral load of two, three, four, five or more variants of SARS-CoV-2, wherein said

aiding includes providing a composition as disclosed herein.

[0273] Non-limiting exemplary embodiments of the methods as described herein can include one or more of the following features. In some embodiments, the neutralization and/or the reduction of viral load takes place in a single subject who has been infected by two, three, four, five or more variants of SARS-CoV-2. In some embodiments, the neutralization and/or the reduction of viral load takes place in plurality of subjects who have each been infected by a different SARS-CoV-2 variant. In some embodiments, the antigen-binding molecule or antigen-binding fragment thereof includes all six CDRs from an antibody of Table 1A or Table 1B. In some embodiments, the antigen-binding molecule or antigen-binding fragment thereof includes all six CDRs from an antibody being any one of TXG-0001, TXG-0002, TXG-0004, TXG-0005, TXG-0006, TXG-0008, TXG-0009, TXG-0048, TXG-0070, TXG-0078, TXG-0081, TXG-0087, TXG-0114, TXG-0115, TXG-0154, TXG-0174, TXG-0175, TXG-0180, TXG-0192, or TXG-0203.

[0274] In some embodiments, the coronavirus belongs to a genus being any one or alphacoronavirus, betacoronavirus, gammacoronavirus, or deltacoronavirus. In some embodiments, the coronavirus belongs to a betacoronavirus lineage such as, for example, lineage A, lineage B, lineage C, and lineage D. In some embodiments, the coronavirus is human coronavirus 229E, OC43, HKU1, NL63, SARS-CoV-1, SARS-CoV-2, MERS-CoV, or a variant of any thereof. In some embodiments, the coronavirus is SARS-CoV-2 or a variant thereof. Non-limiting examples of SARS-CoV-2 variants suitable for the compositions and methods of the disclosure include alpha, beta, delta, gamma, kappa, and omicron. In some embodiments, at least one of the SARS-CoV-2 variants is omicron.

[0275] In some embodiments, the methods of the disclosure include administering (e.g., therapeutically or prophylactically) one or more compositions of the disclosure to a subject. In some embodiments, the compositions of the disclosure may be administered prophylactically to the subject, e.g., before the subject is infected or diagnosed with a coronavirus infection, or prior to the development of one or more clinical symptoms, or administered to a subject that is free of infection or has not been suspected of being infected with a coronavirus. In some embodiments, the compositions of the disclosure may be administered therapeutically to the subject, e.g., after the subject is infected or diagnosed with a coronavirus infection, or after symptoms appear, or for treatment of an existing infection or symptom. For example, in some embodiments, the

compositions may be therapeutically or prophylactically administered to a subject who is suspected of being infected with a coronavirus. In some embodiments, the subject has been diagnosed of having a coronavirus infection. In some embodiments, the compositions of the disclosure may be therapeutically or prophylactically administered to a subject who is at risk of having a coronavirus infection. In some embodiments, the subject has been infected with a coronavirus. In some embodiments, the subject has been vaccinated. In some embodiments, the subject has been recovered from a coronavirus infection. In some embodiments, the subject is an immunocompromised subject or has been previously treated for coronavirus infection. In some embodiments, the subject is a mammalian subject. In some embodiments, the mammalian subject is a human subject.

[0276] In some embodiments, the subject is about 5 years old or younger. For example, the subject may be between the ages of about 1 year and about 5 years (*e.g.*, about 1, 2, 3, 4 or 5 years), or between the ages of about 6 months and about 1 year (*e.g.*, about 6, 7, 8, 9, 10, 11 or 12 months). In some embodiments, the subject is about 12 months or younger (*e.g.*, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2 months or 1 month). In some embodiments, the subject is about 6 months or younger.

[0277] In some embodiments, the subject was born full term (*e.g.*, about 37-42 weeks). In some embodiments, the subject was born prematurely, for example, at about 36 weeks of gestation or earlier (*e.g.*, about 36, 35, 34, 33, 32, 31, 30, 29, 28, 27, 26 or 25 weeks). For example, the subject may have been born at about 32 weeks of gestation or earlier. In some embodiments, the subject was born prematurely between about 32 weeks and about 36 weeks of gestation. In such subjects, the compositions of the disclosure may be therapeutically or prophylactically administered later in life, for example, at the age of about 6 months to about 5 years, or older.

[0278] In some embodiments, the subject is pregnant (*e.g.*, in the first, second or third trimester) when administered a composition as disclosed herein. In some embodiments, the subject is a young adult between the ages of about 20 years and about 50 years (*e.g.*, about 20, 25, 30, 35, 40, 45 or 50 years old). In some embodiments, the subject is an elderly subject about 60 years old, about 70 years old or older (*e.g.*, about 60, 65, 70, 75, 80, 85 or 90 years old).

[0279] In some embodiments of the methods disclosed herein, the composition is therapeutically or prophylactically administered at a total dose of about 0.0001 mg/kg to about

40 mg/kg, such as, from about 0.0001 mg/kg to about 100 mg/kg, from about 0.01 mg/kg to about 50 mg/kg, from about 0.1 mg/kg to about 40 mg/kg, from about 0.5 mg/kg to about 30 mg/kg, from about 0.01 mg/kg to about 10 mg/kg, from about 0.1 mg/kg to about 10 mg/kg, or from about 1 mg/kg to about 25 mg/kg, of subject body weight per day, one or more times a day, to obtain the desired therapeutic, diagnostic or prophylactic effect. In some embodiments, the desired dosage may be delivered three times a day, two times a day, once a day, every other day, every third day, every week, every two weeks, every three weeks, or every four weeks.

[0280] In some embodiments, the total dose may be therapeutically or prophylactically administered using multiple administrations (*e.g.*, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or more administrations). When multiple administrations are employed, split dosing regimens may be used. One skilled in the art will understand that a “split dose” is the division of single unit dose or total daily dose into two or more doses. A “single unit dose” is a dose of any therapeutic administered in one dose/at one time/single route/single point of contact, *e.g.*, single administration event. As used herein, a “total daily dose” is an amount given or prescribed in 24-hour period. It may be administered as a single unit dose. In some embodiments, the multiple administrations occur on a schedule according to any one of the following: three times a day, twice a day, once a day, every other day, every third day, weekly, biweekly, every three weeks, every four weeks, and monthly. In some embodiments, the composition is administered by intravenous, intramuscular, subcutaneous, and/or local administration.

[0281] In some embodiments, the administered composition reduces binding of the CoV-S protein to and/or reduces coronavirus entry into a cell of the subject. In some embodiments, the administered composition neutralizes against the coronavirus.

[0282] In some embodiments, the administered composition treats, prevents, or ameliorates a health condition associated with a coronavirus infection in the subject. In some embodiments, the treatment methods of the disclosure include reducing or eliminating the incidence of viral infection, or lowering or depleting the viral load. For example, the treatment methods of the disclosure may reduce a symptom of a condition characterized by a viral infection, including, but not limited to, decreasing viral load, by, *e.g.*, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 100% in the

subject as compared to a reference subject who has not been administered with the composition. In some embodiments, the viral load in the subject is reduced by 5% or greater, 10% or greater, 20% or greater, 30% or greater, 40% or greater, 50% or greater, or 75% or greater relative to the viral load in a reference subject that has not been administered with the composition. In some embodiments, the viral load in the subject is reduced by at least 0.5 log unit, at least 1 log unit, at least 2 log units, at least 3 log units, at least 4 log units, at least 10 log units, at least 15 log units, or by at least 20 log units relative to the viral load in a reference subject that has not been administered with the composition. Those of skill in the art will know the appropriate symptoms or indicators associated with a specific type of ailment and will know how to determine if an individual is a candidate for treatment as disclosed herein.

[0283] In some embodiments, the treatment methods involve therapeutically or prophylactically administering an antigen-binding molecule or antigen-binding fragment and/or an LNP composition of the present disclosure (*e.g.*, of Table 1A or Table 1B), to a subject having one or more signs or symptoms of a disease or infection, *e.g.*, viral infection, for which the antigen-binding polypeptide is effective when administered to the subject at an effective or therapeutically effective amount or dose. An effective or therapeutically effective dose of antigen-binding molecule or antigen-binding fragment and/or LNP composition, for treating or preventing a viral infection refers to the amount of the antibody or fragment sufficient to alleviate one or more signs and/or symptoms of the infection in the treated subject, whether by inducing the regression or elimination of such signs and/or symptoms or by inhibiting the progression of such signs and/or symptoms. Health conditions and symptoms associated with SARS-CoV-2 infection include respiratory tract infections, often in the lower respiratory tract. Accordingly, some embodiments of the disclosure relate to methods of for reducing one or more signs or symptoms associated with coronavirus infection, such as high fever, dry cough, shortness of breath, pneumonia, gastro-intestinal symptoms such as diarrhea, organ failure (kidney failure and renal dysfunction), septic shock, and death in severe cases. In some embodiments, a sign or symptom of a coronavirus infection in a subject is survival or proliferation of virus in the body of the subject, *e.g.*, as determined by viral titer assay (*e.g.*, coronavirus propagation in embryonated chicken eggs or coronavirus spike protein assay). Other signs and symptoms of viral infection include, but are not limited to fever or feeling feverish/chills, cough, sore throat, runny or stuffy nose, sneezing, muscle or body aches,

headaches, fatigue (tiredness), vomiting, diarrhea, respiratory tract infection, chest discomfort, shortness of breath, bronchitis, and pneumonia

[0284] In some embodiments, a therapeutically effective amount of an antigen-binding molecule or antigen-binding fragment and/or an LNP composition disclosed herein reduces the incidence of viral infection by, e.g., at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95% or at least 100%. In some embodiments, a therapeutically effective amount of an antigen-binding molecule or antigen-binding fragment and/or an LNP composition herein reduces the incidence of viral infection by, e.g., at most 10%, at most 15%, at most 20%, at most 25%, at most 30%, at most 35%, at most 40%, at most 45%, at most 50%, at most 55%, at most 60%, at most 65%, at most 70%, at most 75%, at most 80%, at most 85%, at most 90%, at most 95% or at most 100%. In yet other aspects of this embodiment, a therapeutically effective amount of a therapeutic disclosed herein reduces the incidence of viral infection by, e.g., about 10% to about 100%, about 10% to about 90%, about 10% to about 80%, about 10% to about 70%, about 10% to about 60%, about 10% to about 50%, about 10% to about 40%, about 20% to about 100%, about 20% to about 90%, about 20% to about 80%, about 20% to about 70%, about 20% to about 60%, about 20% to about 50%, about 20% to about 40%, about 30% to about 100%, about 30% to about 90%, about 30% to about 80%, about 30% to about 70%, about 30% to about 60%, or about 30% to about 50%.

Combination therapies

[0285] As discussed above, according to some specific examples, the methods of the disclosure include therapeutically or prophylactically administering to a subject one or more additional agents in combination with an antigen-binding molecule or antigen-binding fragment and/or an LNP composition as described herein. In some embodiments, the antigen-binding molecule or antigen-binding fragment and/or an LNP composition may be used or administered in combination with one or more other therapeutic, prophylactic, diagnostic, or imaging agents. By “in combination with,” it is not intended to imply that the agents must be administered at the same time and/or formulated for delivery together, although these methods of delivery are within the scope of the present disclosure. Compositions can be administered concurrently with, prior to, or subsequent to, one or more other desired therapeutics or medical procedures. In general,

each agent will be administered at a dose and/or on a time schedule determined for that agent.

[0286] For example, when antigen-binding molecule or antigen-binding fragment and/or the LNP composition of the disclosure is administered “before,” the additional agent can be administered for about 72 hours, about 60 hours, or about 48 hours, to the pharmaceutical composition containing the anti-CoV-S antibody or antigen-binding fragment thereof. About 36 hours, about 24 hours, about 12 hours, about 10 hours, about 8 hours, about 6 hours, about 4 hours, about 2 hours, about 1 hour, about 30 minutes, about 15 minutes, or about 10 minutes before. When the antigen-binding molecule or antigen-binding fragment and/or the LNP composition of the disclosure is administered “after”, the additional therapy can be administered for about 10 minutes, about 15 minutes, about 30 minutes, about 1 hour, about 2 hours, about 4 hours, about 6 hours, about 8 hours, about 10 hours, about 12 hours, about 24 hours, about 36 hours, about 48 hours, about 60 hours, or about 72 hours after.

[0287] In some embodiments, the present disclosure encompasses the delivery of pharmaceutical, prophylactic, diagnostic, or imaging compositions in combination with agents that may improve their bioavailability, reduce and/or modify their metabolism, inhibit their excretion, and/or modify their distribution within the body.

[0288] It will further be appreciated that therapeutically, prophylactically, diagnostically, or imaging active agents utilized in combination may be administered together in a single composition or administered separately in different compositions. In general, it is expected that agents utilized in combination will be utilized at levels that do not exceed the levels at which they are utilized individually. In some embodiments, the levels utilized in combination will be lower than those utilized individually. In one embodiment, the combinations, each or together may be administered according to appropriate split dosing regimens.

[0289] The particular combination of therapies (therapeutics or procedures) to employ in a combination regimen will take into account compatibility of the desired therapeutics and/or procedures and the desired therapeutic effect to be achieved. It will also be appreciated that the therapies employed may achieve a desired effect for the same disorder (for example, a composition useful for treating cancer in accordance with the invention may be administered concurrently with a chemotherapeutic agent), or they may achieve different effects (e.g., control of any adverse effects).

[0290] The combination therapy may include an antigen-binding molecule or antigen-

binding fragment and/or an LNP composition of the disclosure and any additional therapeutic agent that can be advantageously combined with an anti-CoV-S antibody or antigen-binding fragment of the disclosure.

[0291] For example, an additional therapeutic agent may be used to help reduce viral load in the lungs, such as an antiviral agent (*e.g.*, ribavirin). Antibodies can also be used in combination with other therapies as described above, including vaccines specific to CoV, secondary antibodies specific to CoV, antiviral agents, anti-inflammatory agents, antibodies specifically binds the serine protease TMPRSS2 of a target cell, and additional antibodies or antigen-binding fragment thereof that specifically bind to CoV-S protein. In some embodiments, the additional therapeutic agent include an antibody approved by FDA for treatment of coronavirus infection such as, for example, Remdesivir, Baricitinib, Azithromycin, Nirmatrelvir, Ritonavir, Molnupiravir, Casirivimab, Imdevimab, Bamlanivimab, Etesevimab, Sotrovimab, Cilgavimab, Bebtelovimab, Tocilizumab, and Tixagevimab. Accordingly, in some embodiments, the additional therapeutic agent may be any one of Remdesivir, Baricitinib, Azithromycin, Nirmatrelvir, Ritonavir, Molnupiravir, Casirivimab, Imdevimab, Bamlanivimab, Etesevimab, Sotrovimab, Cilgavimab, Bebtelovimab, Tocilizumab, Tixagevimab, or a combination thereof. In some embodiments, the additional therapeutic agent includes an antibody and/or small molecule entity having affinity for an immune pathway target.

[0292] In some embodiments, the methods disclosed herein include administering (*e.g.*, therapeutically or prophylactically) to a subject a first agent which is, comprises, or encodes a first antibody or antigen-binding fragment belonging to bin 1 or bin 2 described in Example 14, and a second agent (*e.g.*, therapeutic agent or prophylactic agent) which is, comprises, or encodes a second antibody or antigen-binding fragment belonging to bin 3, bin 4, or bin 3/4 described in Example 14. In some embodiments, the first agent is, comprises, or encodes a first antibody or antigen-binding fragment belonging to bin 1 described in Example 14, and the second agent is, comprises, or encodes a second antibody or antigen-binding fragment belonging to bin 3, bin 4, or bin 3/4 described in Example 14. In some embodiments, the first agent is, comprises, or encodes a first antibody or antigen-binding fragment belonging to bin 2 described in Example 14, and the second agent is, comprises, or encodes a second antibody or antigen-binding fragment belonging to bin 3, bin 4, or bin 3/4 described in Example 14. In some embodiments, the first agent is, comprises, or encodes a first antibody or antigen-binding

fragment belonging to bin 3 described in Example 14, and the second agent is, comprises, or encodes a second antibody or antigen-binding fragment belonging to bin 4 described in Example 14. In some embodiments, the first agent is, comprises, or encodes a first antibody or antigen-binding fragment belonging to bin 3 described in Example 14, and the second agent is, comprises, or encodes a second antibody or antigen-binding fragment belonging to bin 3/4 described in Example 14. In some embodiments, the first agent is, comprises, encodes a first antibody or antigen-binding fragment belonging to bin 4 described in Example 14, and the second agent is, comprises, or encodes a second antibody or antigen-binding fragment belonging to bin 3/4 described in Example 14.

[0293] As described above, several antibodies described herein are pan-coronavirus antibodies that bind with high affinity to the NTD of SARS-CoV-2 S protein and to a spike protein of one or more SARS-CoV variants (e.g., beta, gamma, kappa, and omicron), endemic human coronaviruses (HCoV), and variants of thereof (e.g., HCoV-229E, HCoV-OC43, and HCoV-HKU1). These broad and potentially neutralizing NTD-targeting antibodies could be particularly useful in therapeutic combination against SARS-CoV-2 and other coronaviruses and in combination with RBD-binding or non-S1 binding therapeutic antibodies.

[0294] In some embodiments, the methods disclosed herein include administering to a subject (i) a first agent (e.g., therapeutic agent or prophylactic agent) which is, comprises, or encodes a neutralizing NTD-targeting antibody, and (ii) a second agent (e.g., therapeutic agent or prophylactic agent) which is, comprises, or encodes a neutralizing antibody that does not target the NTD. In some embodiments, the second agent is or comprises a neutralizing RBD-targeting antibody. In some embodiments, the neutralizing NTD-targeting antibody is TXG-0060, TXG-0066, TXG-0071, TXG-0076, TXG-0078, TXG-0079, TXG-0099, TXG-0104, TXG-0116, TXG-0119, TXG-0131, TXG-0132, TXG-0137, TXG-0162, TXG-0163, TXG-0164, TXG-0168, TXG-0170, TXG-0173, TXG-0174, TXG-0184, TXG-0136, or an antigen-binding fragment of any thereof (see, e.g., Tables 6 and 9); and the neutralizing antibody that does not bind the NTD is TXG-0001, TXG-0002, TXG-0004, TXG-0005, TXG-0006, TXG-0008, TXG-0009, TXG-0057, TXG-0080, TXG-0081, TXG-0088, TXG-0091, TXG-0093, TXG-0094, TXG-0100, TXG-0109, TXG-0115, TXG-0120, TXG-0126, TXG-0129, TXG-0140, TXG-0141, TXG-0144, TXG-0153, TXG-0154, TXG-0183, TXG-0189, TXG-0197, TXG-0198, TXG-0200, TXG-0201, TXG-0202, TXG-0204, TXG-0210, or an antigen-binding fragment of any thereof (see,

e.g., Table 12).

[0295] In some embodiments, the methods disclosed herein include administering to a subject (i) a first agent (e.g., therapeutic agent or prophylactic agent) which is, comprises, or encodes a potentially neutralizing (e.g., has an IC_{50} of 1000 ng/ml or less) NTD-targeting antibody, and (ii) a second agent (e.g., therapeutic agent or prophylactic agent) which is, comprises, or encodes a potentially neutralizing RBD antibody. In some embodiments, the potentially neutralizing NTD-targeting antibody is TXG-0066, TXG-0076, TXG-0078, TXG-0099, TXG-0104, TXG-0170, TXG-0173, and TXG-0174, or an antigen-binding fragment of any thereof; and the potentially neutralizing RBD antibody is TXG-0001, TXG-0002, TXG-0004, TXG-0005, TXG-0006, TXG-0008, TXG-0009, TXG-0057, TXG-0080, TXG-0081, TXG-0088, TXG-0091, TXG-0093, TXG-0094, TXG-0100, TXG-0109, TXG-0115, TXG-0120, TXG-0126, TXG-0129, TXG-0140, TXG-0141, TXG-0144, TXG-0153, TXG-0154, TXG-0180, , TXG-0183, TXG-0189, TXG-0197, TXG-0198, TXG-0200, TXG-0201, TXG-0202, TXG-0204, TXG-0209, TXG-0210, or an antigen-binding fragment of any thereof (see, e.g., Table 12).

[0296] In some embodiments, the methods disclosed herein include administering to a subject (i) a first agent (e.g., therapeutic agent or prophylactic agent) which is, comprises, or encodes a neutralizing NTD-targeting antibody with binding affinity for the omicron variant of SARS-CoV-2 or at least one endemic human coronaviruses (HCoV), and (ii) a second agent (e.g., therapeutic agent or prophylactic agent) which is, comprises, or encodes a neutralizing RBD antibody with binding affinity for the omicron variant of SARS-CoV-2 or at least one endemic human coronaviruses (HCoV). In some embodiments, the neutralizing NTD-targeting antibody with binding affinity for the omicron variant of SARS-CoV-2 or at least one endemic human coronaviruses (HCoV) is TXG-0072, TXG-0078, TXG-0099, TXG-0174, or an antigen-binding fragment of any thereof; and the neutralizing RBD antibody with binding affinity for the omicron variant of SARS-CoV-2 or at least one endemic human coronaviruses (HCoV) is TXG-0006, TXG-0049, TXG-0057, TXG-0070, TXG-0080, TXG-0081, TXG-0088, TXG-0091, TXG-0094, TXG-0098, TXG-0109, TXG-0115, TXG-0120, TXG-0129, TXG-0141, TXG-0144, TXG-0153, TXG-0154, TXG-0180, TXG-0183, TXG-0189, TXG-0197, TXG-0198, TXG-0200, TXG-0201, TXG-0202, TXG-0204, TXG-0209, TXG-0210, or an antigen-binding fragment of any thereof.

[0297] In some embodiments, the methods disclosed herein include administering to a

subject (i) a first agent (e.g., therapeutic agent or prophylactic agent) which is, comprises, or encodes a neutralizing NTD-targeting antibody with binding affinity for the omicron variant of SARS-CoV-2 or at least one endemic human coronaviruses (HCoVs), and (ii) a second agent (e.g., therapeutic agent or prophylactic agent) which is, comprises, or encodes a neutralizing RBD antibody with binding affinity for at least one endemic human coronaviruses (HCoVs). In some embodiments, the neutralizing NTD-targeting antibody with binding affinity for the omicron variant of SARS-CoV-2 or at least one endemic human coronaviruses (HCoVs) is TXG-0072, TXG-0078, TXG-0099, TXG-0174, or an antigen-binding fragment of any thereof; and the neutralizing RBD antibody with binding affinity for at least one endemic human coronaviruses (HCoVs) is TXG-0091, TXG-0006, TXG-0154, or an antigen-binding fragment of any thereof.

[0298] In some embodiments, the methods disclosed herein include administering to a subject (i) a first agent (e.g., therapeutic agent or prophylactic agent) which is, comprises, or encodes a potentially neutralizing NTD-targeting antibody with binding affinity for the omicron variant of SARS-CoV-2 or at least one endemic human coronaviruses (HCoVs), and (ii) a second agent (e.g., therapeutic agent or prophylactic agent) which is, comprises, or encodes a neutralizing RBD antibody with binding affinity for at least one endemic human coronaviruses (HCoVs). In some embodiments, the potentially neutralizing NTD-targeting antibody with binding affinity for the omicron variant of SARS-CoV-2 or at least one endemic human coronaviruses (HCoVs) is TXG-0078, TXG-0099, TXG-0174, or an antigen-binding fragment of any thereof; and the neutralizing RBD antibody with binding affinity for at least one endemic human coronaviruses (HCoVs) is TXG-0006, TXG-0091, TXG-0154, or an antigen-binding fragment of any thereof.

[0299] In some embodiments, the methods disclosed herein include administering to a subject (i) a first agent (e.g., therapeutic agent or prophylactic agent) which is, comprises, or encodes a potentially neutralizing NTD-targeting antibody with binding affinity for the omicron variant of SARS-CoV-2 or at least one endemic human coronaviruses (HCoVs), and (ii) a second agent (e.g., therapeutic agent or prophylactic agent) which is, comprises, or encodes a neutralizing RBD antibody with binding affinity for the omicron variant of SARS-CoV-2 and at least one endemic human coronaviruses (HCoVs). In some embodiments, the potentially neutralizing NTD-targeting antibody with binding affinity for the omicron variant of SARS-CoV-2 or at least one endemic human coronaviruses (HCoVs) is TXG-0078, TXG-0099, TXG-

0174, or an antigen-binding fragment of any thereof; and the neutralizing RBD antibody with binding affinity for the omicron variant of SARS-CoV-2 and at least one endemic human coronaviruses (HCoVs) is TXG-0091 or an antigen-binding fragment thereof.

[0300] In some embodiments, the methods disclosed herein include administering to a subject (i) a first agent (e.g., therapeutic agent or prophylactic agent) which is, comprises, or encodes a potentially neutralizing NTD-targeting antibody with binding affinity for at least one endemic human coronaviruses (HCoVs), and (ii) a second agent (e.g., therapeutic agent or prophylactic agent) which is, comprises, or encodes a neutralizing RBD antibody with binding affinity for at least one endemic human coronaviruses (HCoVs). In some embodiments, the potentially neutralizing NTD-targeting antibody with binding affinity for at least one endemic human coronaviruses (HCoVs) is TXG-0078 or an antigen-binding fragment thereof; and the neutralizing RBD antibody with binding affinity for at least one endemic human coronaviruses (HCoVs) is TXG-0006, TXG-0091, TXG-0154, or an antigen-binding fragment of any thereof.

[0301] In some embodiments, the methods disclosed herein include administering to a subject (i) a first agent (e.g., therapeutic agent or prophylactic agent) which is, comprises, or encodes a TXG-0078 or an antigen-binding fragment thereof, and (ii) a second agent (e.g., therapeutic agent or prophylactic agent) which is or comprises TXG-0091 or an antigen-binding fragment thereof. In some embodiments, the methods disclosed herein include administering to a subject (i) a first agent (e.g., therapeutic agent or prophylactic agent) which is, comprises, or encodes a NTD-targeting antibody with binding affinity for at least one endemic human coronaviruses (HCoVs), and (ii) a second agent (e.g., therapeutic agent or prophylactic agent) which is, comprises, or encodes a neutralizing RBD antibody with binding affinity for at least one endemic human coronaviruses (HCoVs). In some embodiments, the NTD-targeting antibody with binding affinity for at least one endemic human coronaviruses (HCoVs) is TXG-0078, TXG-0114, TXG-0136, or an antigen-binding fragment of any thereof; and the neutralizing RBD antibody with binding affinity for at least one endemic human coronaviruses (HCoVs) is TXG-0091, TXG-0006, TXG-0154, or an antigen-binding fragment of any thereof.

[0302] In some embodiments, the methods disclosed herein include administering to a subject (i) a first agent (e.g., therapeutic agent or prophylactic agent) which is or comprises or encodes an antibody being any one of TXG-0078, TXG-0174, or an antigen-binding fragment of any thereof; and (ii) a second agent (e.g., therapeutic agent or prophylactic agent) which is or

comprises or encodes an antibody being any one of TXG-0001, TXG-0002, TXG-0004, TXG-0005, TXG-0006, TXG-0008, TXG-0009, TXG-0081, TXG-0115, TXG-0154, or TXG-0180, or an antigen-binding fragment of any thereof.

[0303] As noted above, in some embodiments of the disclosure, the subject may be a non-human animal, and the antigen-binding polypeptides (*e.g.*, antibodies and antigen-binding fragments) discussed herein may be used in a veterinary context to treat and/or prevent disease associated with coronavirus in the non-human animals (*e.g.*, cats, dogs, pigs, cows, horses, goats, rabbits, sheep, *etc.*).

Methods of detection

[0304] As discussed above, one aspect of the present disclosure relates to methods for detecting the presence of SARS-CoV-2 S protein and/or SARS-CoV-2 in a biological sample for, for example, diagnosing, monitoring, or imaging a virus or a disease, a disorder, and/or a health condition. In some embodiments, the antigen-binding molecule or antigen-binding fragment includes the HCDR1, HCDR2, and HCDR3 of an antibody of Table 1A or Table 1B. In some embodiments, the antigen-binding molecule or antigen-binding fragment includes the LCDR1, LCDR2, and LCDR3 of an antibody of Table 1A or Table 1B. In some embodiments, the antigen-binding molecule or antigen-binding fragment includes all six CDRs from an antibody of Table 1A or Table 1B. In some embodiments, the antigen-binding molecule or antigen-binding fragment includes all six CDRs from an antibody being any one of TXG-0001, TXG-0002, TXG-0004, TXG-0005, TXG-0006, TXG-0008, TXG-0009, TXG-0048, TXG-0057, TXG-0060, TXG-0063, TXG-0066, TXG-0070, TXG-0072, TXG-0074, TXG-0076, TXG-0078, TXG-0080, TXG-0081, TXG-0087, TXG-0088, TXG-0091, TXG-0094, TXG-0098, TXG-0099, TXG-0100, TXG-0104, TXG-0109, TXG-0112, TXG-0114, TXG-0115, TXG-0120, TXG-0129, TXG-0136, TXG-0141, TXG-0144, TXG-0153, TXG-0154, TXG-0170, TXG-0173, TXG-0174, TXG-0175, TXG-0180, TXG-0181, TXG-0183, TXG-0187, TXG-0189, TXG-0192, TXG-0197, TXG-0198, TXG-0200, TXG-0201, TXG-0202, TXG-0203, TXG-0204, TXG-0209, TXG-0210, TXG-0228, or TXG-0230, and wherein the antigen-binding molecule or antigen-binding fragment thereof has a binding affinity for the omicron variant of SARS-CoV-2 or one or more endemic human coronaviruses (HCoVs) being any one of 229E, OC43, and HKU1, or a combination thereof. In some embodiments, the antigen-binding molecule or antigen-binding fragment thereof includes all six complementary determining regions (CDRs) from an antibody being any one of TXG-

0001, TXG-0002, TXG-0004, TXG-0005, TXG-0006, TXG-0008, TXG-0009, TXG-0048, TXG-0070, TXG-0078, TXG-0081, TXG-0087, TXG-0114, TXG-0115, TXG-0154, TXG-0174, TXG-0175, TXG-0180, TXG-0192, or TXG-0203; and optionally wherein the antigen-binding molecule or antigen-binding fragment thereof has a binding affinity for the omicron variant of SARS-CoV-2 or one or more endemic human coronaviruses (HCoVs) that is any one of 229E, OC43, HKU1, or a combination thereof.

[0305] In another aspect, provided herein are methods for detecting the presence of SARS-CoV-2 S protein and/or SARS-CoV-2 in a biological sample, wherein the methods include contacting a biological sample with an antigen-binding molecule having an amino acid sequence being any one of TXG-0001, TXG-0002, TXG-0004, TXG-0005, TXG-0006, TXG-0008, TXG-0009, TXG-0048, TXG-0057, TXG-0060, TXG-0063, TXG-0066, TXG-0070, TXG-0072, TXG-0074, TXG-0076, TXG-0078, TXG-0080, TXG-0081, TXG-0087, TXG-0088, TXG-0091, TXG-0094, TXG-0098, TXG-0099, TXG-0100, TXG-0104, TXG-0109, TXG-0112, TXG-0114, TXG-0115, TXG-0120, TXG-0129, TXG-0136, TXG-0141, TXG-0144, TXG-0153, TXG-0154, TXG-0170, TXG-0173, TXG-0174, TXG-0175, TXG-0180, TXG-0181, TXG-0183, TXG-0187, TXG-0189, TXG-0192, TXG-0197, TXG-0198, TXG-0200, TXG-0201, TXG-0202, TXG-0203, TXG-0204, TXG-0209, TXG-0210, TXG-0228, or TXG-0230, or an antigen-binding fragment of any thereof, wherein optionally the antigen-binding molecule or antigen-binding fragment has a binding affinity for the omicron variant of SARS-CoV-2 or one or more endemic HCoVs that is any one of 229E, OC43, HKU1, or a combination thereof.

[0306] Non-limiting exemplary embodiments of the detection methods as described herein can include one or more of the following features. In some embodiments, the biological sample is from a subject suspected of being infected with a coronavirus. In some embodiments, the subject has been diagnosed of having a coronavirus infection. In some embodiments, the subject is at risk of having a coronavirus infection. In some embodiments, the subject has been infected with a coronavirus. In some embodiments, the subject has been vaccinated. In some embodiments, the subject has been recovered from a coronavirus infection. In some embodiments, the methods further include detecting a complex formed between the antigen-binding molecule or antigen-binding fragment with an SARS-CoV-2 S antigen. In some embodiments, said detecting includes visualizing the formed complex using one or more suitable assays and techniques. Non-limiting examples of assays and techniques suitable for the methods

disclosed herein include one or more detection reagents such as an enzyme, a secondary antibody, a colored dye, a fluorescent dye, a chemiluminescent molecule, a molecule containing a radioactive atom, and/or a molecule containing a heavy metal.

[0307] In another aspect, provided herein are methods for aiding in the diagnosis, prognosis, monitoring, and/or evaluation of coronavirus infection and/or treatment thereof in a subject, wherein said aiding includes providing: (a) an antigen-binding molecule having an amino acid sequence being any one of TXG-0001, TXG-0002, TXG-0004, TXG-0005, TXG-0006, TXG-0008, TXG-0009, TXG-0048, TXG-0057, TXG-0060, TXG-0063, TXG-0066, TXG-0070, TXG-0072, TXG-0074, TXG-0076, TXG-0078, TXG-0080, TXG-0081, TXG-0087, TXG-0088, TXG-0091, TXG-0094, TXG-0098, TXG-0099, TXG-0100, TXG-0104, TXG-0109, TXG-0112, TXG-0114, TXG-0115, TXG-0120, TXG-0129, TXG-0136, TXG-0141, TXG-0144, TXG-0153, TXG-0154, TXG-0170, TXG-0173, TXG-0174, TXG-0175, TXG-0180, TXG-0181, TXG-0183, TXG-0187, TXG-0189, TXG-0192, TXG-0197, TXG-0198, TXG-0200, TXG-0201, TXG-0202, TXG-0203, TXG-0204, TXG-0209, TXG-0210, TXG-0228, or TXG-0230, or an antigen-binding fragment of any thereof, and wherein optionally the antigen-binding molecule or antigen-binding fragment thereof has a binding affinity for the omicron variant of SARS-CoV-2 or one or more endemic HCoV's that is any one of 229E, OC43, HKU1, or a combination thereof.

KITS

[0308] Further provided herein are kits for the practice of a method described herein, including methods for preventing, treating, diagnosing, prognosing, monitoring, or imaging a virus (e.g., a coronavirus), a disease, a disorder, and/or a health condition. In some embodiments, provided herein are kits for aiding in the prevention, treatment, diagnosis, prognosis, monitoring, or imaging a virus (e.g., a coronavirus), a disease, a disorder, and/or a health condition. In some embodiments, provided herein are kits for use in detecting the presence of SARS-CoV-2 S protein and/or SARS-CoV-2 in a biological sample. In some embodiments, the kits of the disclosure can include one or more antigen-binding molecules or antigen-binding fragments as disclosed herein.

[0309] Also provided, in some embodiments of the disclosure, are kits for use in (i) inducing an immune response in a subject, (ii) reducing binding of a spike protein of a coronavirus (CoV-S) to a cell in a subject and/or reducing entry of the coronavirus into a cell of a subject, or (iii) treating, preventing, or ameliorating a health condition associated with SARS-

CoV-2 infection in a subject. In some embodiments, the kits of the disclosure can include one or more antigen-binding molecules or antigen-binding fragments as disclosed herein.

[0310] In some embodiments, the subject is suspected of being infected with a coronavirus. In some embodiments, the subject has been diagnosed of having a coronavirus infection. In some embodiments, the subject is at risk of having a coronavirus infection. In some embodiments, the subject has been infected with a coronavirus. In some embodiments, the subject has been vaccinated. In some embodiments, the subject has been recovered from a coronavirus infection.

[0311] A kit can include instructions for use thereof and one or more of the antibodies or antigen-binding fragments thereof, nucleic acids, and compositions as described and provided herein. For example, some embodiments of the disclosure provide kits that include one or more of the antibodies described herein and/or antigen-binding fragments thereof, and instructions for use. In some embodiments, provided herein are kits that include one or more nucleic acids as described herein and instructions for use thereof. In some embodiments, provided herein are kits that include one or more compositions as described herein and instructions for use thereof.

[0312] In some embodiments, the components of a kit can be in separate containers. In some other embodiments, the components of a kit can be combined in a single container. Accordingly, in some embodiments of the disclosure, the kit includes an anti-CoV-S antigen-binding polypeptide, *e.g.*, an antibody or antigen-binding fragment thereof as described herein (*e.g.*, those identified as such in the Sequence Listing), or a pharmaceutical composition thereof in one container (*e.g.*, in a sterile glass or plastic vial, a chromatography column, hollow bore needle, or a syringe cylinder) and a further therapeutic agent in another container (*e.g.*, in a sterile glass or plastic vial, a chromatography column, hollow bore needle, or a syringe cylinder).

[0313] If the kit includes a pharmaceutical composition for parenteral administration to a subject, the kit can include a device (*e.g.*, an injection device or catheter) for performing such administration. For example, the kit can include one or more hypodermic needles or other injection devices as discussed above containing the compositions of the present disclosure (*e.g.*, identified as such in the Sequence Listing).

[0314] In some embodiments, a kit can further include instructions for using the components of the kit to practice a method described herein. For example, the kit can include a package insert including information concerning the pharmaceutical compositions and dosage forms in the kit. Generally, such information aids patients and physicians in using the enclosed

pharmaceutical compositions and dosage forms effectively and safely. For example, the following information regarding a combination of the disclosure may be supplied in the insert: pharmacokinetics, pharmacodynamics, clinical studies, efficacy parameters, indications and usage, contraindications, warnings, precautions, adverse reactions, overdose, proper dosage and administration, how supplied, proper storage conditions, references, manufacturer/distributor information and intellectual property information.

[0315] The instructions for practicing the method are generally recorded on a suitable recording medium. For example, the instructions can be printed on a substrate, such as paper or plastic, *etc.* The instructions can be present in the kit as a package insert, in the labeling of the container of the kit or components thereof (*e.g.*, associated with the packaging or sub-packaging), *etc.* The instructions can be present as an electronic storage data file present on a suitable computer readable storage medium, *e.g.* CD-ROM, diskette, flash drive, *etc.* In some instances, the actual instructions are not present in the kit, but means for obtaining the instructions from a remote source (*e.g.*, via the internet), can be provided. An example of this embodiment is a kit that includes a web address where the instructions can be viewed and/or from which the instructions can be downloaded. As with the instructions, this means for obtaining the instructions can be recorded on a suitable substrate.

[0316] All publications and patent applications mentioned in this disclosure are herein incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference.

[0317] No admission is made that any reference cited herein constitutes prior art. The discussion of the references states what their authors assert, and the Applicant reserves the right to challenge the accuracy and pertinence of the cited documents. It will be clearly understood that, although a number of information sources, including scientific journal articles, patent documents, and textbooks, are referred to herein; this reference does not constitute an admission that any of these documents forms part of the common general knowledge in the art.

[0318] The discussion of the general methods given herein is intended for illustrative purposes only. Other alternative methods and alternatives will be apparent to those of skill in the art upon review of this disclosure, and are to be included within the spirit and purview of this application.

[0319] In another aspect, provided herein are methods of manufacturing a pharmaceutical

composition, the methods including: (a) admixing a lipid solution with an aqueous buffer solution including a buffer agent thereby forming a lipid nanoparticle solution including a lipid nanoparticle (LNP); and (b) adding to the lipid nanoparticle: (i) an antigen-binding molecule, or an antigen-binding fragment include any thereof, including all 6 CDRs from an antibody being any one of TXG-0001, TXG-0002, TXG-0004, TXG-0005, TXG-0006, TXG-0008, TXG-0009, TXG-0048, TXG-0057, TXG-0060, TXG-0063, TXG-0066, TXG-0070, TXG-0072, TXG-0074, TXG-0076, TXG-0078, TXG-0080, TXG-0081, TXG-0087, TXG-0088, TXG-0091, TXG-0094, TXG-0098, TXG-0099, TXG-0100, TXG-0104, TXG-0109, TXG-0112, TXG-0114, TXG-0115, TXG-0120, TXG-0129, TXG-0136, TXG-0141, TXG-0144, TXG-0153, TXG-0154, TXG-0170, TXG-0173, TXG-0174, TXG-0175, TXG-0180, TXG-0181, TXG-0183, TXG-0187, TXG-0189, TXG-0192, TXG-0197, TXG-0198, TXG-0200, TXG-0201, TXG-0202, TXG-0203, TXG-0204, TXG-0209, TXG-0210, TXG-0228, or TXG-0230, wherein optionally the antigen-binding molecule or antigen-binding fragment thereof has a binding affinity for the omicron variant of SARS-CoV-2 or one or more endemic HCoV that is any one of 229E, OC43, HKU1, or a combination thereof; and/or (ii) a nucleic acid encoding the antigen-binding molecule or antigen-binding fragment thereof of (a), thereby forming a LNP formulation including the LNP associated with the antigen-binding molecule or antigen-binding fragment thereof, and/or with the nucleic acid encoding the antigen-binding molecule or antigen-binding fragment thereof.

EXAMPLES

[0320] The practice of the present invention will employ, unless otherwise indicated, conventional techniques of molecular biology, microbiology, cell biology, biochemistry, nucleic acid chemistry, and immunology, which are well known to those skilled in the art. Such techniques are explained fully in the literature, such as Sambrook, J., & Russell, D. W. (2012). *Molecular Cloning: A Laboratory Manual* (4th ed.). Cold Spring Harbor, NY: Cold Spring Harbor Laboratory and Sambrook, J., & Russell, D. W. (2001). *Molecular Cloning: A Laboratory Manual* (3rd ed.). Cold Spring Harbor, NY: Cold Spring Harbor Laboratory (jointly referred to herein as “Sambrook”); Ausubel, F. M. (1987). *Current Protocols in Molecular Biology*. New York, NY: Wiley (including supplements through 2014); Bollag, D. M. *et al.* (1996). *Protein Methods*. New York, NY: Wiley-Liss; Huang, L. *et al.* (2005). *Nonviral Vectors for Gene Therapy*. San Diego: Academic Press; Kaplitt, M. G. *et al.* (1995). *Viral Vectors: Gene Therapy*

and Neuroscience Applications. San Diego, CA: Academic Press; Lefkovits, I. (1997). *The Immunology Methods Manual: The Comprehensive Sourcebook of Techniques*. San Diego, CA: Academic Press; Doyle, A. *et al.* (1998). *Cell and Tissue Culture: Laboratory Procedures in Biotechnology*. New York, NY: Wiley; Mullis, K. B., Ferré, F. & Gibbs, R. (1994). *PCR: The Polymerase Chain Reaction*. Boston: Birkhauser Publisher; Greenfield, E. A. (2014). *Antibodies: A Laboratory Manual* (2nd ed.). New York, NY: Cold Spring Harbor Laboratory Press; Beaucage, S. L. *et al.* (2000). *Current Protocols in Nucleic Acid Chemistry*. New York, NY: Wiley, (including supplements through 2014); and Makrides, S. C. (2003). *Gene Transfer and Expression in Mammalian Cells*. Amsterdam, NL: Elsevier Sciences B.V., the disclosures of which are incorporated herein by reference.

[0321] Additional embodiments are disclosed in further detail in the following examples, which are provided by way of illustration and are not in any way intended to limit the scope of this disclosure or the claims.

EXAMPLE 1

Biological samples

[0322] Sample procurement: The experiments described in the below Examples were performed with peripheral blood mononuclear cells (PBMCs) collected from convalescent human survivors of natural infection with SARS-2. Specifically, Donor 531 PBMCs were purchased from Cellerio (~112m/vial product, Cat. # 1146-4785JY20) and used in these experiments.

[0323] Sample background/timeline: The donor tested positive via nasopharyngeal swab while presenting asymptomatic/presymptomatic on Day 0. Hospitalization was not required. The donor tested negative for SARS-2 on Day 23. Plasma and apheresis sample collection were performed on Day 104. The donor is also seropositive for cytomegalovirus, a ubiquitous human herpesvirus.

EXAMPLE 2

Enrichment of B cells

[0324] A vial of frozen PBMCs was thawed for 1-2 min in a water bath, then transferred into 8-10 mL of 10% Fetal Bovine Serum (FBS) in PBS, and centrifuged for 5 min at 350g. The cell pellet was washed three times by resuspending in 0.04% Bovine Serum Albumin (BSA) in PBS and centrifuging at RT at 350g for 5 min each wash, with the final pellet resuspended to a

concentration of ~20 million cells per mL in a total volume of 5 mL (~100 million cells total). B cells were enriched using the B Cell Isolation Kit II (human; MACS™ Miltenyi) according to manufacturer's instructions, and approximately 50 million cells were applied to each of two LS columns designed for positive selection of cells. The effluent was concentrated and prepared for cell labeling.

EXAMPLE 3

Antigen sourcing, preparation, and conjugation

[0325] Biotinylated antigens were sourced from suppliers as follows:

[0326] 1) Biotinylated trimerized S (SARS-2) was sourced from ACRO Biosystems, catalog # SPN-C82E9-25 (<https://www.acrobiosystems.com/P3345-Biotinylated-SARS-CoV-2-S-protein-HisAvitag™-Superstable-trimer-%28MALs-verified%29.html>). This protein carries a polyhistidine tag at the C-terminus, followed by an Avi tag. Biotinylation of this product is performed using Avitag™ technology. Briefly, the single lysine residue in the Avitag is enzymatically labeled with biotin.

[0327] 2) Biotinylated trimerized S D614G (SARS-2), from ACRO Biosystems, catalog # SPN-C82E3-25 (<https://www.acrobiosystems.com/P3431-Biotinylated-SARS-CoV-2-S-protein-%28D614G%29-HisAvitag™-Super-stable-trimer-%28MALs-verified%29.html>). This protein contains D614G mutation, which has become increasingly common in SARS-CoV-2 viruses from around the world. This protein also carries a polyhistidine tag at the C-terminus, followed by an Avi tag. Biotinylation of this product is performed using Avitag™ technology. Briefly, the single lysine residue in the Avitag is enzymatically labeled with biotin.

[0328] 3) Biotinylated Human Serum Albumin (HSA) HSA-H82E3, from Sapphire (<https://sapphireusa.com/product.jsp?q=ns%3ANS0000368507>).

[0329] Biotinylated antigens were each solubilized per manufacturer's instructions. In each case, they were thawed and dissolved in sterile deionized water for 30-60 minutes at room temperature with occasional gentle mixing for a final concentration of 100 microgram/mL (for HSA) or 200 microgram/mL for both of the trimerized S antigens.

[0330] Solubilized antigens were each conjugated with, *e.g.*, allowed to form a complex with (or bind to) one of the following TotalSeqC reagents, supplied by BioLegend, which each contain a unique barcoded DNA oligonucleotide supplied by the vendor as follows:

[0331] 1) TotalSeq-C0951 PE Streptavidin was conjugated to biotinylated trimerized S

glycoprotein (SARS-2).

[0332] 2) TotalSeq-C0952 PE Streptavidin was conjugated to biotinylated human serum albumin.

[0333] 3) TotalSeq-C0956 APC Streptavidin was conjugated to biotinylated trimerized S D614G glycoprotein (SARS-2).

[0334] 4) TotalSeq-C0957 APC Streptavidin with biotinylated human serum albumin. Briefly, each TotalSeq-C barcoded streptavidin PE or APC reagent was diluted to 0.1 mg/mL and then mixed with biotinylated antigen at a 5X molar excess of antigen to streptavidin, based on a fixed amount of 0.5 µg PE-SA. One fifth of the streptavidin-oligo PE or APC conjugate was added to the antigen every 20 minutes at 4°C. The reaction was then quenched with 5 µl of 4mM biotin (Pierce, Thermo Fisher) for 30 minutes for a total probe volume of 20 µL. The final conjugated antigen probes (streptavidin-antigen complexes) were then immediately used for cell labeling at a dilution of 1:50.

EXAMPLE 4

Cell labeling

[0335] This Example describes experiments performed to stain B cells with a number of barcoded antibodies and conjugated antigens. In these experiments, approximately 4.4 million enriched B cells were first resuspended in labeling buffer (1% BSA in PBS) and performed Fc blocking for 10 minutes on ice using Human TruStain FcX (BioLegend).

[0336] Next, cells were stained with the following cocktail of antibodies, antigens and dyes: CD19 PE-Cy7 (clone SJ25C1, BD Pharmingen) for discrimination of CD19+ cells by using fluorescence-activated cell sorting (FACS).

[0337] Barcoded Antibodies for 10x Single Cell Immune profiling, which included the following TotalSeq-C oligo barcoded antibodies:

[0338] - TotalSeq-C0389 anti-human CD38.

[0339] - TotalSeq-C0154 anti-human CD27.

[0340] - TotalSeq-C0189 anti-human CD24.

[0341] - TotalSeq-C0384 anti-human IgD.

[0342] - TotalSeq-C0100 anti-human CD20.

[0343] - TotalSeq-C0050 anti-human CD19 (clone HIB19, to distinguish it from the flow clone).

- [0344] - TotalSeq-C0049 anti-human CD3E.
- [0345] - TotalSeq-C0045 anti-human CD4.
- [0346] - TotalSeq-C0046 anti-human CD8A.
- [0347] - TotalSeq-C0051 anti-human CD14.
- [0348] - TotalSeq-C0083 anti-human CD16.
- [0349] - TotalSeq-C0090 mouse IgG1 K isotype control.
- [0350] - TotalSeq-C0091 mouse IgG2a K isotype control.
- [0351] - TotalSeq-C0092 mouse IgG2b K isotype control.
- [0352] Final conjugated antigens:
- [0353] - TotalSeq-C0951 PE trimerized S (SARS-2).
- [0354] - TotalSeq-C0952 PE Human Serum Albumin.
- [0355] - TotalSeq-C0956 APC trimerized S D614G (SARS-2).
- [0356] - TotalSeq-C0957 APC Human Serum Albumin.
- [0357] - 7AAD for live/dead cell discrimination.

[0358] Cells were stained in labeling buffer (1% BSA in PBS) in the dark for 30 minutes on ice, then cells were washed 3 times with 2 mL of cold labeling buffer at 350*g for 5 minutes at 4°C, resuspended in cold labeling buffer and a 1:200 addition of live/dead cell discriminating agent 7AAD for 10 minutes on ice in the dark, then washed one more time with labeling buffer at 350*g for 5 minutes at 4°C, then resuspended in labeling buffer and loaded into a Sony MA900 Cell Sorter using a 70 µm sorting chip.

EXAMPLE 5

Antigen-specific enrichment via FACS

[0359] Cells were initially gated on being single, live (7AAD^{negative}) and PE-Cy7-CD19+ and then sorted on their PE and/or APC status directly into master mixed and water based on one of four criteria:

[0360] 1) PE+, representing trimerized S (SARS-2) antigen+ and/or HSA+ control antigen cells (gate Q1 in **FIG. 1**; 2,430 cells);

[0361] 2) APC+, representing trimerized S D614G (SARS-2) antigen and/or HSA control antigen cells (gate Q3 in **FIG. 1**; 728 cells);

[0362] 3) Dual PE+ and APC+, representing a combination of trimerized S (SARS-2) antigen+, trimerized S D614G (SARS-2) antigen+ and/or HSA control antigen-positive cells

(gate Q2 in **FIG. 1**; 828 cells);

[0363] 4) PE and APC negative cells, representing cells not binding either SARS-2 antigen or control HSA antigen (gate Q4 in **FIG. 1**; 5,000 cells).

[0364] In **FIG. 1**, the Y axis represents PE (representing trimerized S (SARS-2) antigen+ and/or HSA+ control antigen cells) signal. The X axis represents APC trimerized S (SARS-2) D614G antigen+ and/or HSA+ control antigen cells. The numbers adjacent to each gate name represent the fraction of events of the parent population (single, live, CD19+ cells) for that gate. FACS data were analyzed with FlowJo.

[0365] The resulting volume was adjusted with additional water to match the recommended volume and target for loading with the 10× 5'V2 Single Cell Immune Profiling kit. FACS data were analyzed using FlowJo. Standard gene expression, V(D)J, and barcoded antigen libraries were constructed using the 10× 5'V2 Single Cell Immune Profiling kit per manufacturer's instructions. Additional information in this regard can be found at “support.10xgenomics.com/permalink/getting-started-immune-profiling-feature-barcoding.”

EXAMPLE 6

Sequencing analysis

[0366] The libraries resulting from the experiments described in Example 6 above were sequenced on a NovaSeq 3 using a NovaSeq S4 200 cycles 2020 v1.5 kit, targeting using read 28, 10, 10, and 90 cycles targeting 20,000, 30,000, or 6000 reads per cell for gene expression, barcoded antigen, or Ig libraries, respectively. Sequence analysis (described further herein, *see, e.g.*, Example 7) identified a total of 239 antibodies. The binding affinity of 161 exemplary antibodies to a trimerized wild-type SARS-CoV-2 spike protein (**FIG. 15A** and SEQ ID NO: 3045) and a SARS-CoV-2 spike protein variant with D614G substitution (**FIG. 15B** and SEQ ID NO: 3046) is summarized in Tables 3A-3B below. In these experiments, the binding affinity of an antigen-binding molecule (*e.g.*, antibody) to a target antigen (wild-type S protein or a variant thereof) was determined based on quantity/numbers of unique molecular identifiers (UMIs) associated with each of the antigen-binding molecules bound to the target antigen. Generally, the higher target antigen UMI counts were used as a predictor of higher binding affinity. When an antibody was found “fluorophore reactive” or “biotin-reactive” then it was categorized as a non-specific antibody, even if it had non-zero target antigen UMI counts. As shown in Tables 3A-3B below, all of the identified antibodies displayed high target antigen counts and low non-target

antigen counts. As such, they were predicted to have specific binding affinity for the target antigen and were distinguishable from non-specific binders.

TABLE 3A: Binding affinity of 159 exemplary antibodies. The integer values displayed in the table below represent antigen UMI counts for each of the individual on-target (Wild-type S or D416G mutant (Mutant S)) and off-target (human serum albumin control/HSA 1, human serum albumin control/HSA 2) antigens.

Antibody	Isotype/ subclass	Light chain	Wild-type S	Mutant S	Total S	HSA 1	HSA 2	HSA (total)
TXG-0001	IGHG1	IGKC	766	466	1232	0	0	0
TXG-0002	IGHG1	IGKC	185	162	347	2	1	3
TXG-0003	IGHG1	IGKC	1451	833	2284	0	4	4
TXG-0004	IGHG1	IGKC	762	478	1240	0	1	1
TXG-0005	IGHA1	IGKC	212	103	315	0	0	0
TXG-0006	IGHG1	IGKC	584	261	845	0	0	0
TXG-0007	IGHG1	IGKC	714	361	1075	0	0	0
TXG-0008	IGHG1	IGKC	774	837	1611	0	1	1
TXG-0009	IGHG2	IGKC	888	705	1593	1	0	1
TXG-0010	IGHM	IGLC2	22	56	78	0	0	0
TXG-0011	IGHM	IGLC2	17	65	82	0	0	0
TXG-0012	IGHM	IGLC2	37	113	150	0	1	1
TXG-0013	IGHM	IGLC2	34	92	126	1	1	2
TXG-0014	IGHM	IGLC2	75	123	198	1	0	1
TXG-0015	IGHM	IGLC2	47	83	130	0	0	0
TXG-0016	IGHM	IGLC2	825	653	1478	0	0	0
TXG-0017	IGHM	IGLC2	81	71	152	0	0	0
TXG-0018	IGHM	IGLC2	2330	1141	3471	0	2	2
TXG-0019	IGHM	IGLC2	2021	789	2810	0	2	2
TXG-0020	IGHM	IGLC2	1692	746	2438	2	0	2
TXG-0024	IGHM	IGLC3	153	335	488	0	0	0
TXG-0025	IGHM	IGLC3	243	300	543	0	0	0
TXG-0026	IGHM	IGLC3	471	575	1046	0	0	0
TXG-0029	IGHM	IGLC1	291	182	473	0	0	0
TXG-0030	IGHM	IGLC1	174	268	442	0	0	0
TXG-0031	IGHM	IGKC	172	315	487	1	4	5
TXG-0032	IGHM	IGKC	389	553	942	1	0	1
TXG-0033	IGHM	IGKC	177	210	387	0	0	0
TXG-0034	IGHA2	IGKC	722	816	1538	0	1	1
TXG-0035	IGHM	IGKC	2048	1606	3654	0	2	2
TXG-0036	IGHM	IGKC	1276	1227	2503	0	1	1
TXG-0037	IGHM	IGLC2	348	259	607	0	3	3
TXG-0038	IGHM	IGLC1	1000	652	1652	4	2	6
TXG-0039	IGHM	IGKC	1354	867	2221	0	0	0
TXG-0040	IGHM	IGKC	1028	514	1542	0	0	0
TXG-0041	IGHM	IGKC	1682	962	2644	1	0	1

TXG-0042	IGHM	IGLC2	323	1077	1400	0	2	2
TXG-0044	IGHM	IGKC	76	64	140	5	1	6
TXG-0045	IGHM	IGKC	929	501	1430	0	0	0
TXG-0046	IGHG1	IGKC	399	193	592	1	0	1
TXG-0047	IGHG1	IGKC	416	263	679	0	1	1
TXG-0048	IGHA1	IGKC	341	226	567	0	0	0
TXG-0050	IGHM	IGLC2	2138	1137	3275	0	1	1
TXG-0052	IGHM	IGKC	1400	1430	2830	0	3	3
TXG-0053	IGHM	IGKC	319	502	821	1	0	1
TXG-0054	IGHM	IGKC	49	139	188	0	2	2
TXG-0055	IGHG1	IGKC	88	80	168	0	0	0
TXG-0057	IGHG1	IGLC1	189	117	306	0	0	0
TXG-0058	IGHG1	IGKC	120	46	166	0	0	0
TXG-0059	IGHG1	IGKC	652	264	916	1	2	3
TXG-0060	IGHG1	IGKC	179	71	250	0	2	2
TXG-0063	IGHG1	IGKC	1193	757	1950	0	0	0
TXG-0064	IGHM	IGLC1	1611	889	2500	0	1	1
TXG-0065	IGHG1	IGKC	203	101	304	0	0	0
TXG-0066	IGHG1	IGLC3	507	314	821	0	0	0
TXG-0069	IGHG1	IGKC	2182	845	3027	0	0	0
TXG-0070	IGHG1	IGKC	326	109	435	0	0	0
TXG-0071	IGHG1	IGKC	356	132	488	0	0	0
TXG-0073	IGHM	IGLC1	695	530	1225	0	0	0
TXG-0074	IGHG1	IGLC2	1164	893	2057	1	0	1
TXG-0075	IGHG1	IGLC2	101	51	152	0	0	0
TXG-0076	IGHG1	IGLC3	212	127	339	1	0	1
TXG-0077	IGHG1	IGKC	880	1620	2500	1	5	6
TXG-0078	IGHG1	IGKC	613	312	925	0	0	0
TXG-0079	IGHG1	IGKC	311	184	495	0	0	0
TXG-0080	IGHG1	IGKC	216	82	298	0	3	3
TXG-0081	IGHA1	IGKC	266	137	403	0	0	0
TXG-0082	IGHM	IGLC3	554	447	1001	0	1	1
TXG-0084	IGHA1	IGLC3	609	476	1085	0	1	1
TXG-0086	IGHG1	IGKC	648	553	1201	0	0	0
TXG-0087	IGHG2	IGKC	126	172	298	2	0	2
TXG-0088	IGHG1	IGKC	321	325	646	0	0	0
TXG-0091	IGHG1	IGLC1	832	433	1265	1	0	1
TXG-0093	IGHG1	IGKC	134	70	204	1	1	2
TXG-0094	IGHG1	IGKC	401	315	716	0	1	1
TXG-0097	IGHG1	IGLC1	1124	973	2097	0	1	1
TXG-0099	IGHG1	IGKC	100	72	172	0	0	0
TXG-0100	IGHG1	IGLC2	268	201	469	0	0	0
TXG-0101	IGHM	IGLC3	523	211	734	0	1	1
TXG-0102	IGHG1	IGKC	193	118	311	0	0	0
TXG-0103	IGHM	IGLC3	706	381	1087	0	0	0
TXG-0104	IGHM	IGKC	649	435	1084	2	0	2
TXG-0107	IGHG1	IGKC	254	449	703	0	2	2
TXG-0109	IGHG1	IGLC1	860	473	1333	2	0	2

TXG-0114	IGHM	IGKC	322	397	719	0	1	1
TXG-0116	IGHG1	IGKC	179	164	343	0	1	1
TXG-0117	IGHG1	IGKC	165	108	273	0	0	0
TXG-0119	IGHG1	IGLC2	358	210	568	0	0	0
TXG-0120	IGHG1	IGKC	1297	672	1969	0	1	1
TXG-0122	IGHG1	IGKC	357	229	586	0	0	0
TXG-0125	IGHG1	IGKC	1202	480	1682	0	2	2
TXG-0126	IGHG1	IGLC2	1102	510	1612	0	0	0
TXG-0127	IGHM	IGLC3	282	185	467	0	0	0
TXG-0128	IGHG1	IGLC1	299	300	599	0	0	0
TXG-0129	IGHG1	IGLC1	552	511	1063	2	1	3
TXG-0131	IGHG1	IGLC1	133	100	233	0	0	0
TXG-0132	IGHG1	IGKC	722	478	1200	0	2	2
TXG-0133	IGHG1	IGLC1	440	116	556	6	0	6
TXG-0139	IGHM	IGKC	456	585	1041	0	0	0
TXG-0141	IGHG1	IGLC2	600	351	951	1	1	2
TXG-0142	IGHG1	IGLC1	570	228	798	0	1	1
TXG-0143	IGHG1	IGLC2	130	104	234	1	0	1
TXG-0144	IGHG1	IGLC2	2041	915	2956	1	1	2
TXG-0146	IGHG1	IGKC	753	1237	1990	0	3	3
TXG-0148	IGHG1	IGKC	415	189	604	0	1	1
TXG-0149	IGHM	IGKC	445	444	889	0	0	0
TXG-0151	IGHM	IGKC	743	877	1620	0	1	1
TXG-0155	IGHG1	IGKC	1155	808	1963	0	1	1
TXG-0156	IGHG1	IGLC1	267	109	376	0	0	0
TXG-0157	IGHG1	IGLC2	395	210	605	0	0	0
TXG-0158	—	IGKC	206	122	328	0	0	0
TXG-0159	IGHM	IGKC	402	217	619	1	0	1
TXG-0161	IGHM	IGLC1	451	540	991	0	0	0
TXG-0162	IGHG1	IGLC1	289	168	457	0	0	0
TXG-0163	IGHG1	IGLC1	212	128	340	0	0	0
TXG-0164	IGHG1	IGLC3	438	311	749	0	0	0
TXG-0166	IGHM	IGLC3	616	1024	1640	1	2	3
TXG-0168	IGHG1	IGLC2	712	334	1046	0	0	0
TXG-0170	IGHG1	IGLC2	1027	439	1466	1	0	1
TXG-0175	IGHG1	IGLC3	178	69	247	0	0	0
TXG-0176	IGHG1	IGLC2	498	163	661	0	0	0
TXG-0178	IGHG1	IGLC2	2357	1129	3486	0	2	2
TXG-0180	IGHG1	IGLC3	1374	831	2205	0	0	0
TXG-0181	IGHG1	IGKC	258	139	397	0	0	0
TXG-0183	IGHG1	IGLC2	727	464	1191	0	1	1
TXG-0184	IGHG1	IGLC3	1061	583	1644	1	0	1
TXG-0185	IGHG1	IGKC	269	134	403	1	0	1
TXG-0186	IGHM	IGKC	1046	372	1418	0	1	1
TXG-0187	IGHG1	IGKC	393	201	594	0	1	1
TXG-0188	IGHG1	IGLC3	1428	682	2110	0	0	0
TXG-0189	IGHG1	IGLC2	628	255	883	0	0	0
TXG-0190	IGHM	IGKC	172	314	486	0	1	1

TXG-0193	IGHG2	IGKC	245	202	447	1	0	1
TXG-0197	IGHG1	IGLC3	653	544	1197	0	0	0
TXG-0198	IGHG1	IGLC2	152	128	280	0	0	0
TXG-0199	IGHM	IGKC	1345	733	2078	0	0	0
TXG-0200	IGHG1	IGKC	373	234	607	0	0	0
TXG-0201	IGHG1	IGKC	541	544	1085	0	0	0
TXG-0202	IGHG1	IGKC	801	556	1357	0	2	2
TXG-0203	IGHM	IGLC3	204	173	377	0	0	0
TXG-0204	IGHG1	IGKC	1539	1024	2563	0	1	1
TXG-0206	IGHM	IGKC	1202	1360	2562	0	3	3
TXG-0207	IGHG1	IGKC	636	398	1034	1	0	1
TXG-0209	IGHG1	IGKC	286	156	442	0	0	0
TXG-0210	IGHG1	IGKC	926	663	1589	0	1	1
TXG-0219	IGHM	IGLC2	86	91	177	0	0	0
TXG-0220	IGHM	IGLC2	204	238	442	0	0	0
TXG-0221	IGHM	IGLC2	164	122	286	0	0	0
TXG-0222	IGHG2	IGKC	38	62	100	2	0	2
TXG-0223	IGHG1	IGKC	872	599	1471	0	0	0
TXG-0224	IGHM	IGKC	2582	1442	4024	0	0	0
TXG-0225	IGHG1	IGLC3	286	121	407	0	1	1
TXG-0232	IGHG1	IGKC	241	241	482	0	0	0
TXG-0233	IGHM	IGKC	96	498	594	0	0	0
TXG-0234	IGHM	IGKC	354	416	770	1	0	1
TXG-0235	IGHG2	IGKC	252	537	789	0	0	0
TXG-0236	IGHM	IGKC	81	347	428	0	0	0
TXG-0238	IGHD	IGKC	470	188	658	0	0	0
TXG-0239	IGHM	IGKC	533	546	1079	7	1	8

TABLE 3B: Binding affinity of 80 exemplary antibodies. The integer values displayed in the table below represent antigen UMI counts for each of the individual on-target (Wild-type S or D416G mutant (Mutant S) and off-target (human serum albumin control/HSA 1, human serum albumin control/HSA 2) antigens.

Antibody	Isotype/ subclass	Light chain	Wild-type S	Mutant S	Total S	HSA 1	HSA 2	HSA (total)
TXG-0021	IGHM	IGKC	64	112	176	0	1	1
TXG-0022	IGHM	IGKC	65	83	148	0	1	1
TXG-0023	IGHM	IGKC	68	193	261	0	0	0
TXG-0027	IGHG2	IGKC	134	122	256	0	2	2
TXG-0028	IGHG1	IGKC	69	43	112	0	1	1
TXG-0043	IGHM	IGLC3	76	95	171	0	0	0
TXG-0049	IGHM	IGKC	209	53	262	0	0	0
TXG-0051	IGHM	IGKC	125	226	351	0	3	3
TXG-0056	IGHM	IGLC2	203	93	296	0	0	0
TXG-0061	IGHM	IGLC1	119	178	297	0	0	0
TXG-0062	IGHG1	IGKC	169	83	252	1	0	1
TXG-0067	IGHG2	IGKC	58	173	231	0	0	0

TXG-0068	IGHG1	IGKC	274	147	421	1	0	1
TXG-0072	IGHG1	IGKC	80	41	121	0	0	0
TXG-0083	IGHM	IGLC3	179	240	419	2	4	6
TXG-0085	IGHM	IGLC1	107	71	178	0	0	0
TXG-0089	IGHG1	IGLC1	170	49	219	0	1	1
TXG-0090	IGHM	IGLC1	185	167	352	0	0	0
TXG-0092	IGHM	IGLC2	60	103	163	0	3	3
TXG-0095	IGHM	IGLC3	68	167	235	0	0	0
TXG-0096	IGHM	IGLC1	163	414	577	0	1	1
TXG-0098	IGHM	IGKC	323	40	363	0	0	0
TXG-0105	IGHM	IGLC3	62	55	117	1	2	3
TXG-0106	IGHM	IGKC	103	120	223	1	1	2
TXG-0108	IGHG2	IGKC	52	88	140	0	0	0
TXG-0110	IGHM	IGLC2	40	210	250	0	0	0
TXG-0111	IGHM	IGLC1	68	183	251	0	2	2
TXG-0112	IGHM	IGKC	76	131	207	0	0	0
TXG-0113	IGHM	IGKC	77	120	197	0	0	0
TXG-0115	IGHM	IGKC	683	322	1005	13	8	21
TXG-0118	IGHM	IGKC	137	98	235	0	0	0
TXG-0121	IGHD	IGLC1	237	60	297	0	0	0
TXG-0123	IGHM	IGKC	98	116	214	0	2	2
TXG-0124	IGHM	IGKC	229	155	384	0	0	0
TXG-0130	IGHM	IGLC2	151	285	436	0	3	3
TXG-0134	IGHM	IGLC3	69	340	409	0	0	0
TXG-0135	IGHM	IGLC2	266	253	519	0	1	1
TXG-0136	IGHM	IGLC3	188	138	326	2	0	2
TXG-0137	IGHG1	IGLC3	172	132	304	0	1	1
TXG-0138	IGHM	IGLC1	65	253	318	0	0	0
TXG-0140	IGHM	IGKC	163	222	385	1	1	2
TXG-0145	IGHM	IGKC	48	160	208	3	36	39
TXG-0147	IGHD	IGKC	466	241	707	2	0	2
TXG-0150	IGHM	IGKC	187	151	338	0	0	0
TXG-0152	IGHM	IGKC	55	207	262	0	0	0
TXG-0153	IGHD	IGKC	63	47	110	0	0	0
TXG-0154	IGHM	IGKC	124	120	244	3	0	3
TXG-0160	IGHM	IGKC	60	381	441	0	0	0
TXG-0165	IGHM	IGLC2	446	261	707	0	0	0
TXG-0167	IGHM	IGKC	40	287	327	0	0	0
TXG-0169	IGHM	IGKC	133	185	318	0	0	0
TXG-0171	IGHM	IGKC	130	64	194	0	0	0
TXG-0172	IGHM	IGKC	48	112	160	0	0	0
TXG-0173	IGHG1	IGLC3	102	107	209	1	1	2
TXG-0174	IGHM	IGKC	40	322	362	0	0	0
TXG-0177	IGHM	IGKC	40	149	189	0	1	1
TXG-0179	IGHM	IGLC2	105	194	299	0	0	0
TXG-0182	IGHG1	IGLC2	175	64	239	0	1	1
TXG-0191	IGHM	IGLC2	45	238	283	0	0	0
TXG-0192	IGHM	IGKC	43	142	185	1	4	5

TXG-0194	IGHG1	IGLC3	90	56	146	2	1	3
TXG-0195	IGHM	IGKC	205	348	553	0	3	3
TXG-0196	IGHM	IGKC	96	149	245	0	2	2
TXG-0205	IGHM	IGLC3	77	100	177	0	0	0
TXG-0208	IGHM	IGKC	61	166	227	6	34	40
TXG-0211	IGHG1	IGKC	175	111	286	0	0	0
TXG-0212	IGHM	IGKC	71	190	261	0	1	1
TXG-0213	IGHM	IGKC	136	154	290	1	0	1
TXG-0214	IGHM	IGKC	91	146	237	0	0	0
TXG-0215	IGHM	IGKC	494	297	791	1	3	4
TXG-0216	IGHM	IGKC	197	66	263	0	0	0
TXG-0217	IGHG1	IGKC	504	308	812	2	0	2
TXG-0218	IGHG1	IGKC	76	42	118	1	0	1
TXG-0226	IGHM	IGKC	158	64	222	0	0	0
TXG-0227	IGHM	IGLC2	100	137	237	0	0	0
TXG-0228	IGHM	IGLC2	59	161	220	0	0	0
TXG-0229	IGHM	IGLC2	9	141	150	0	1	1
TXG-0230	IGHM	IGLC2	44	153	197	0	1	1
TXG-0231	IGHG3	IGKC	71	188	259	0	1	1
TXG-0237	IGHM	IGKC	71	336	407	0	0	0

[0367] It was observed that the antibodies identified in these experiments were diverse in their VH, VL, and isotype/subclass (see Table 3C below).

TABLE 3C:

Isotype/subclass	Count
IgM	121
IgD	4
IgA1	4
IgA2	1
IgG1	99
IgG2	8
IgG3	1

[0368] As demonstrated, BEAM-Ab directly captures full length antibody sequences, enabling rapid expression of the native antibody, including somatic hypermutation. Furthermore, BEAM-Ab is highly reproducible: 220 of 240 screened binders were re-identified in separate samples from the same blood draw.

EXAMPLE 7

Statistical analysis

[0369] Binding antibodies with a maximum spike antigen count greater than 40 UMIs (as summarized in Table 3 above) were selected for further analysis using 10x Genomics “Enclone” (available at <https://bit.ly/enclone>), which is a computational tool developed for clonal grouping to study the adaptive immune system. In this computational tool, the 10x Genomics Chromium Single Cell V(D)J data containing B cell receptor (BCR) and T cell receptor (TCR) RNA sequences are provided as input data to Enclone. Based on the input, Enclone finds and organizes cells arising from the same progenitors into groups (*e.g.*, clonotype families) and compactly displays each clonotype along with its salient features, including mutated amino acids. Antibodies in the dataset were classified into 3 categories, as listed below, via a process termed “barcode-enabled antigen mapping by sequencing” (BEAM-seq):

[0370] Category 1. (*e.g.*, Fluorophore-reactive): Antibodies are classified into this category if the mix of antigens includes target and non-target antigens linked to different fluorophores, and counts are detected for target and non-target antigen linked to fluorophore 1 but not fluorophore 2, which indicates that the antibodies bind to the fluorophore and not the target antigen. In this particular Example, antibodies were classified into this category if counts were detected for only one spike protein and the corresponding albumin labeled with the same fluorophore.

[0371] Category 2. (*e.g.*, Biotin-reactive, streptavidin-reactive, or polyreactive): Antibodies are classified into this category if the mix of antigens includes target and non-target antigens linked to different fluorophores, and counts are detected for target and non-target antigen linked to both fluorophores, which indicates that the antibodies does not bind the antigen but instead binds to a core component of the reagent (*e.g.*, streptavidin, biotin) or is polyreactive (*e.g.*, sticky and non-specific). In this particular Example, antibodies were classified into this category (*e.g.*, classified as biotin-reactive, streptavidin-reactive, or polyreactive, if counts were detected for both spike proteins (trimerized wild-type S and trimerized S D614G) and both albumins (PE-HSA and APC-HSA).

[0372] Category 3. (*e.g.*, Candidate SARS-2-reactive antibodies): Antibodies are classified into this category if counts are detected for target antigen but absent or at lower levels for non-target antigen, which indicates that the antibodies specifically binds the target antigen and has affinity for the target antigen. In this particular Example, antibodies were classified into

this category (*e.g.*, classified as candidate SARS-2-reactive antibodies, if counts were considerably higher for one or both spike proteins relative to the albumins; most antibodies bound the wild-type spike protein and the common population variant D614G. Category 3 antibodies are disclosed herein (see, *e.g.*, Tables 1A-1B and Table 3).

[0373] In a dataset where there is considerable enrichment for genuine antigen-binding cells, the binding affinity of an antigen-binding molecule (*e.g.*, antibody or antigen-binding fragment) to a target antigen (such as S protein) were determined based on a quantity/number of unique molecular identifiers (UMIs) associated with the antigen bound to each cell. BEAM scores are approximately normally distributed, increase exponentially as target antigen-binding relative to expressed antibody and control antigen increases, are correlated with generation probability of the HCDR3 junction, *e.g.*, following the known general relationship of somatic hypermutation (SHM) and increasing affinity, and also reveal that class switching increases predicted relative affinity in concordance with the literature (**FIGS. 2 and 3**). BEAM scores are also generally higher within sublineages that contain more daughter antibodies than narrow sublineages (representative example shown in **FIG. 4**).

EXAMPLE 8

Antibody synthesis, cloning, expression, and purification

[0374] Variable heavy chain and light chain domains of anti-SARS-CoV-2 antibodies were reformatted to IgG1 and synthesized and cloned into mammalian expression vector pTwist CMV BG WPRE Neo utilizing the Twist Bioscience eCommerce portal. Light chain variable domains were reformatted into kappa and lambda frameworks accordingly. Clonal genes were delivered as purified plasmid DNA ready for transient transfection in human embryonic kidney (HEK) Expi293 cells (Thermo Scientific). Cultures in a volume of 1.2 ml were grown to four days, harvested and purified using Protein A resin (PhyNexus) on the Hamilton Microlab STAR platform into 43 mM Citrate 148 mM HEPES, pH 6.

EXAMPLE 9

Further characterization of binding affinity

[0375] This Example describes the results of experiments performed to further characterize binding affinity of select antibodies described herein.

[0376] Antibodies with high predicted binding affinity based on antigen UMI count profiles were selected for further screening and analysis. Subsequently, surface plasmon

resonance (SPR) analyses were performed on the selected antibodies by using a Carterra LSA SPR biosensor equipped with a HC30M chip at 25°C in HBS-TE (10 mM HEPES pH 7.4, 150 mM NaCl, 3 mM EDTA, 0.05% Tween-20). Antibodies were diluted to 5 µg/ml in sodium acetate buffer, pH 4.5, and amine-coupled to the sensor chip by EDC/NHS activation, followed by ethanolamine HCl quenching. Increasing concentrations of ligand were flowed over the sensor chip in HBSTE (10 mM HEPES pH 7.4, 150 mM NaCl, 3 mM EDTA, 0.05% Tween-20) with 0.5 mg/ml BSA with 5 minute association and 15 minute dissociation. Following each injection cycle the surface was regenerated with 2x 30 second injections of IgG elution buffer (Thermo). The following antigens and catalog #s from Acro Biosystems were used for serial analysis at the specified concentration ranges:

[0377] (1) SARS-CoV-2 S protein, His Tag, Super stable trimer (MALS & NS-EM verified), SPN-C52H9; 0 - 100 nM.

[0378] (2) SARS-CoV-2 S protein (D614G), His Tag, Super stable trimer (MALS verified), SPN-C52H3; 0 - 100 nM.

[0379] (3) SARS-CoV-2 (COVID-19) S protein RBD (triple mutant K417N, E484K, N501Y), His Tag (MALS verified), SPD-C52Hp; 0 - 500 nM.

[0380] (4) SARS-CoV-2 (COVID-19) S1 protein NTD, His Tag, S1D-C52H6; 0 - 500 nM.

[0381] (5) SARS-CoV-2 (COVID-19) S2 protein, His Tag, S2N-C52H5; 0 - 500 nM.

[0382] (6) MERS S1 protein, His Tag, S1N-M52H5; 0 - 500 nM.

[0383] (7) HCoV-HKU1 (isolate N5) S1 protein, His Tag, SIN-V52H6; 0 - 500 nM.

[0384] Traces were analyzed and fit using Carterra's Kinetics Tool software, fit to a 1:1 receptor-ligand binding model.

[0385] Table 4 below provides a summary of the binding affinity of the exemplary antibodies to the following antigens: (1) a trimerized wild-type SARS-CoV-2 S protein (**FIG. 15A** and SEQ ID NO: 3045), (2) a SARS-CoV-2 S protein variant with D614G substitution (**FIG. 15B** and SEQ ID NO: 3046). For comparative analysis, also included in this study were the four following FDA-approved therapeutic antibodies previously reported to bind SARS-CoV-2 S protein: (1) imdevimab (REGN-COV2), (2) bamlanivimab (Eli Lilly / AbCellera), (3) etesevimab (Eli Lilly / AbCellera), and sotrovimab (Vir / GlaxoSmithKline). It was observed that the majority of antibodies tested in this study could bind to both wild-type S protein and D614G

mutant in picomolar and nanomolar range. Remarkably, several antibodies described herein were found to have binding affinities as good as or superior to FDA-approved antibodies or antibodies in late clinical development. See also, **FIGS. 16A-16B** and **19**.

TABLE 4: Binding affinity of exemplary antibodies. CTRL-0005: Imdevimab. CTRL-0006: Bamlanivimab. CTRL-0007: Etesevimab. CTRL-0008: Sotrovimab. ND: not determined.

Antibody	Wild-type S Kon	Wild-type S Koff	Wild-type S KD	Mutant S Kon	Mutant S Koff	Mutant S KD
CTRL-0005	33480.66691	1.00E-05	8.16E-10	ND	ND	ND
CTRL-0006	575161.1799	0.000123288	2.16E-10	541074.4405	7.71E-05	1.43E-10
CTRL-0007	182141.3122	0.000643225	6.08E-09	86746.48391	0.000349403	1.46E-07
CTRL-0008	52645.53379	2.90E-05	6.33E-10	158662.6526	1.00E-06	6.30E-12
TXG-0001	285766.1865	1.00E-05	3.51E-11	233643.4491	7.96E-05	3.72E-10
TXG-0002	324236.6901	1.00E-05	3.19E-11	311498.381	1.00E-05	3.24E-11
TXG-0003	317582.6758	7.00E-06	2.20E-11	385492.0125	3.78E-05	1.06E-10
TXG-0004	317094.663	1.00E-05	3.18E-11	332487.9153	1.46E-05	4.35E-11
TXG-0005	259049.86	1.00E-05	3.87E-11	246682.2111	1.00E-05	4.06E-11
TXG-0006	393766.6837	1.07E-05	2.72E-11	349235.6381	1.15E-05	3.26E-11
TXG-0007	264165.6616	1.00E-05	3.85E-11	252729.0447	1.00E-05	4.05E-11
TXG-0008	265428.2103	1.00E-05	3.87E-11	253187.2882	1.35E-05	5.72E-11
TXG-0009	147738.3818	0.000472314	3.20E-09	206868.3514	0.000578988	2.76E-09
TXG-0010	451897.2342	0.000261191	5.80E-10	456379.2853	0.000114217	3.08E-10
TXG-0011	44016.88446	1.00E-05	7.29E-08	2603.539783	1.00E-05	3.40E-08
TXG-0013	381299.6487	1.00E-05	2.64E-11	273607.7368	1.00E-05	3.66E-11
TXG-0016	86207.35162	0.00106997	1.31E-08	18829.49894	0.000690207	2.23E-07
TXG-0017	123582.2445	1.00E-05	8.13E-11	112741.8322	1.00E-05	8.98E-11
TXG-0018	95724.90163	1.00E-05	1.21E-10	ND	ND	ND
TXG-0019	186435.9527	1.00E-05	5.62E-11	242350.7404	1.00E-05	4.22E-11
TXG-0022	51918.44826	0.000254493	4.58E-09	24667.42154	0.000395727	1.33E-06
TXG-0023	71109.38578	0.000325303	5.09E-09	301302.1993	0.00073614	4.39E-09
TXG-0024	331834.3971	4.54E-05	1.14E-10	274765.6338	8.80E-05	2.51E-10
TXG-0025	88755.07091	1.00E-05	1.15E-10	57617.50817	3.34E-05	5.71E-10
TXG-0026	193569.3447	1.00E-05	5.20E-11	118112.3405	1.07E-05	9.11E-11
TXG-0027	58232.71681	0.000210643	4.50E-09	77934.37599	0.000406092	6.33E-09
TXG-0029	286951.4325	6.08E-05	2.14E-10	299356.0559	5.55E-05	1.84E-10
TXG-0030	137012.1441	1.00E-05	7.48E-11	149135.744	1.00E-05	6.84E-11
TXG-0031	40896.26212	1.00E-05	8.59E-10	7262.491613	1.00E-05	2.81E-08
TXG-0032	123834.9045	3.83E-05	3.22E-10	99202.46931	7.66E-05	7.75E-10
TXG-0033	64014.37773	0.000228595	3.74E-09	12484.30024	0.00025265	6.39E-08
TXG-0034	368088.7832	3.59E-05	1.03E-10	371594.5579	2.30E-05	7.06E-11
TXG-0035	460154.3675	1.37E-05	3.00E-11	461103.9386	1.00E-05	2.17E-11
TXG-0038	563683.3852	1.00E-05	1.79E-11	534530.9279	1.00E-05	1.89E-11
TXG-0039	344637.347	3.17E-05	9.91E-11	345806.7879	3.22E-05	9.34E-11
TXG-0040	126865.0456	0.000556859	5.23E-09	217412.4803	0.000893651	7.95E-09
TXG-0044	148262.8818	0.000341469	2.38E-09	150685.878	0.000720289	4.87E-09
TXG-0045	1227224.797	0.001579333	1.32E-08	56952.13259	0.001817664	2.59E-06

TXG-0047	27991.3239	0.000929721	1.15E-06	8258.081646	0.000462127	2.70E-07
TXG-0048	27411.82023	2.57E-05	8.36E-10	15213.49968	1.00E-05	7.67E-09
TXG-0050	94809.36117	0.000755029	8.02E-09	13780.24925	0.000248122	2.63E-08
TXG-0052	21789.07369	1.00E-05	8.83E-10	4190.689191	1.00E-05	5.50E-09
TXG-0063	212361.8076	1.00E-05	4.75E-11	179584.3441	1.00E-05	5.62E-11
TXG-0064	77639.71908	1.61E-05	2.91E-10	-	-	-
TXG-0069	57977.25515	0.000618834	1.42E-08	32279.3224	0.000728655	3.84E-07
TXG-0074	133531.4967	0.001542719	1.17E-08	122178.4164	0.000998339	8.52E-09
TXG-0077	45964.68704	0.000417928	9.14E-07	251689.4962	0.000891283	2.01E-07
TXG-0084	673244.9221	0.00019921	3.02E-10	575151.3753	0.000143532	2.77E-10
TXG-0087	393354.1867	0.000386902	1.01E-09	334176.1246	0.000305042	9.02E-10
TXG-0091	276795.0945	0.00035805	1.40E-09	197651.2302	0.000124209	5.43E-10
TXG-0097	277106.5022	1.00E-05	3.62E-11	275274.1802	1.00E-05	3.71E-11
TXG-0120	264963.6181	0.000282927	1.14E-09	193926.0608	0.000136374	7.52E-10
TXG-0125	412046.6035	1.00E-05	2.45E-11	381651.5626	1.00E-05	2.85E-11
TXG-0151	291862.5721	0.000238067	8.44E-10	347129.5525	0.000131958	3.79E-10
TXG-0155	418540.4182	0.000431399	1.05E-09	315483.0498	0.000249738	7.90E-10
TXG-0166	202889.0038	1.00E-05	4.97E-11	118117.7014	1.00E-05	8.60E-11
TXG-0178	112460.2829	1.00E-05	8.98E-11	97507.52078	1.00E-05	1.03E-10
TXG-0180	129699.6492	0.00078585	6.25E-09	80225.80839	0.000147966	2.40E-09
TXG-0193	619611.179	2.41E-05	4.08E-11	634696.0542	3.36E-05	5.37E-11
TXG-0197	187244.6171	1.45E-05	8.39E-11	174629.1281	1.00E-05	5.76E-11
TXG-0199	27711.31745	1.00E-05	3.81E-10	29248.69151	1.00E-05	1.69E-09
TXG-0204	23144.94765	3.51E-05	9.68E-09	27097.44514	1.62E-05	2.31E-09
TXG-0206	334887.4683	0.000184403	5.52E-10	263740.5132	0.00015542	6.08E-10
TXG-0210	257744.784	1.00E-05	3.90E-11	248773.7553	1.00E-05	4.04E-11
TXG-0222	129961.5575	0.000713161	6.23E-09	99255.20883	0.000174759	1.81E-09
TXG-0224	211252.5782	1.00E-05	4.76E-11	188240.9459	2.86E-05	1.68E-10

[0386] Furthermore, as shown in Table 5 below, it was observed that several antibodies described herein demonstrated high binding affinity to a RBD fragment of SARS-CoV-2 S protein with triple amino acid substitutions K417N, E484K, and N501Y. For comparative analysis, also included in this study were two therapeutic antibodies previously reported to bind RBD of SARS-CoV-2 S protein (*i.e.*, etesevimab, and sotrovimab). It was observed that 21 antibodies tested in this study could bind to the triple mutant RBD in low to mid nanomolar range. In addition, several antibodies were found to bind the triple escape variant of RBD with binding affinities as good as or superior to FDA-approved antibodies or antibodies in late clinical development. See also, **FIGS. 17A-17B**.

TABLE 5: Binding affinity of exemplary antibodies to a RBD variant of SARS-CoV-2 S protein. Triple mutant RBD tested in this study contained a combination of three amino acid substitutions K417N, E484K, and N501Y. CTRL-0007: Etesevimab. CTRL-0008: Sotrovimab.

Antibody	Triple mutant RBD Kon	Triple mutant RBD Koff	Triple mutant RBD KD
CTRL-0007	74255.4904	4.27E+01	0.000575
CTRL-0008	77244.5795	5.70E-04	7.37E-09
TXG-0001	123478.738	1.81E-03	1.48E-08
TXG-0002	234264.918	2.48E-03	1.15E-08
TXG-0003	163921.762	2.09E-03	1.29E-08
TXG-0004	225534.355	3.75E-03	1.68E-08
TXG-0005	96345.0711	1.79E-03	2.28E-08
TXG-0006	232913.282	3.68E-03	1.70E-08
TXG-0007	39148.9439	1.53E-03	3.97E-08
TXG-0008	44157.2649	2.85E-03	1.01E-07
TXG-0011	79004.9431	3.55E-04	4.62E-09
TXG-0013	65791.1944	1.94E-04	3.21E-09
TXG-0017	33495.3107	2.27E-03	6.81E-08
TXG-0019	76021.0303	5.37E-03	7.40E-08
TXG-0030	94653.4207	1.08E-03	1.15E-08
TXG-0038	87063.0506	1.60E-04	1.85E-09
TXG-0064	228369.735	1.29E-04	2.90E-09
TXG-0097	816537.339	1.60E-04	2.35E-10
TXG-0125	207102.376	6.66E-04	4.62E-09
TXG-0166	142497.873	2.04E-03	1.54E-08
TXG-0199	239846.881	4.41E-04	1.84E-09
TXG-0204	156661.986	3.44E-04	2.40E-09

[0387] Remarkably, several antibodies (*e.g.*, TXG-0091, TXG-0112, TXG-0136, TXG-0192, TXG-228, and TXG-0230) were found to be pan-coronavirus antibodies that recognizes a conserved epitope in the S1 subunit and bind with high affinity to the S1 subunit of a new human coronavirus strain HCoV-HKU1. In particular, antibody TXG-0091 was found to be a pan-coronavirus antibody that recognizes a conserved epitope in the S1 subunit and bind with high affinity to the S1 subunit of a new human coronavirus strain HCoV-HKU1 (KD = 543 pM) (see, *e.g.*, Table 6). Accordingly, without being bound to any particular theory, this antibody could be particularly useful in therapeutic combination against SARS-CoV-2 and other coronaviruses and in combination with RBD-binding, NTD-binding, or non-S1 binding therapeutic antibodies.

[0388] As shown in Table 6, several antibodies (*e.g.*, TXG-0063, TXG-0072, TXG-0173, TXG-0174, and TXG-0230) were found to bind N-terminal domain of SARS-CoV-2 S protein with high affinity. In particular, antibody TXG-0063 was found to bind N-terminal domain of

SARS-CoV-2 S protein with high affinity ($K_D = 102$ nM). Accordingly, this antibody could be particularly useful in therapeutic combination against SARS-2 with RBD-binding and non-S1 binding therapeutic antibodies.

TABLE 6: Binding affinity of antibodies TXG-0063, TXG-0072, TXG-0091, TXG-0112, TXG-0136, TXG-0173, TXG-174, TXG-0192, TXG-228, and TXG-0230 to the N-terminal domain of SARS-CoV-2 S protein and/or the S1 subunit of HCoV-HKU1.

Antibody	NTD CoV-2 S K_{on}	NTD CoV-2 S K_{off}	NTD CoV-2 S K_D	HCoV-HKU1 K_{on}	HCoV-HKU1 K_{off}	HCoV-HKU1 K_D
TXG-0063	14800.36	1.53E-03	1.02E-07	ND	ND	ND
TXG-0072	50798.68	0.000922	1.81E-08	ND	ND	ND
TXG-0091	ND	ND	ND	257442	2.35E-04	9.06E-10
TXG-0112	ND	ND	ND	44045.58	0.00051411	1.17E-08
TXG-0136	ND	ND	ND	14774.41	0.00012629	8.55E-09
TXG-0173	28801.3	0.00078	2.71E-08	ND	ND	ND
TXG-0174	52925.25	0.002852	5.39E-08	ND	ND	ND
TXG-0192	ND	ND	ND	30640.36	0.00061101	1.99E-08
TXG-0228	ND	ND	ND	262421.1	0.00072991	2.78E-09
TXG-0230	35459.9	0.00081	2.29E-08	222367.6	0.00035694	1.61E-09

EXAMPLE 10

Identification of antibodies with desired kinetic profiles

[0389] Further analyses were performed using SPR binding curves to identify antibodies with particularly low K_{off} constants. As shown in Table 7 below, it was observed that antibodies could be stratified into two major classes: optimal binding kinetics and less optimal binding kinetics. For example, it was found that one could identify antibodies with visibly longer half-lives have a K_{off} lower than $4e-4$, with an additional subclass of antibodies that have exceptionally long half-lives and a K_{off} lower than $1e-4$ (see, *e.g.*, Table 7 and **FIGS. 18A-18D**). Antibody half-life values and mean-life values reported in Table 7 were calculated by using formula $\ln(2)/K_{off}$ and formula $1/K_{off}$, respectively.

[0390] A smaller number of antibodies have less optimal binding kinetics due to their higher K_{off} constants, which produce a less ideal K_D even given their acceptable K_{on} constants (see, *e.g.*, Table 7 and **FIGS. 18A-18D**). For comparative analysis, etesevimab and sotrovimab were also included in this study.

TABLE 7: Half-lives of exemplary antibodies. CTRL-0007: Etesevimab. CTRL-0008: Sotrovimab.

Antibody	Wild-type S Half-life	Mutant S Half-life	Triple mutant RBD Half-life
CTRL-0007	1077.612314	1983.80432	0.0162237
CTRL-0008	23901.62692	693147.181	1217.0555
TXG-0001	69314.71806	8707.87915	383.80328
TXG-0002	69314.71806	69314.7181	279.66026
TXG-0004	69314.71806	47475.8343	185.06053
TXG-0005	69314.71806	69314.7181	387.40296
TXG-0006	64780.11033	60273.6679	188.31351
TXG-0008	69314.71806	51344.2356	243.03455
TXG-0009	1467.555864	1197.1702	
TXG-0048	26970.70741	69314.7181	
TXG-0063	69314.71806	69314.7181	
TXG-0074	449.3022907	694.300414	
TXG-0087	1791.531655	2272.3008	
TXG-0091	1935.894932	5580.49079	
TXG-0120	2449.91528	5082.69304	
TXG-0180	882.0349692	4684.50307	
TXG-0197	47803.25383	69314.7181	
TXG-0204	19747.78292	42786.863	2017.8957
TXG-0210	69314.71806	69314.7181	

EXAMPLE 11

Functional characterization of antibodies

[0391] To further characterize the antibodies and antigen-binding fragments described in Examples 1-10 above, ligand-blocking assays are performed using GFP+ reporter cells expressing ACE2 and dose competition of pre-fusion D614G spike protein in dual-fluorescent format, where the antigens being competed are in tetrameric format. In these experiments, a relative K_D value for each mAb can be generated.

[0392] In addition, to determine whether the antibodies and antigen-binding fragments of the disclosure have a neutralizing activity (*e.g.*, antagonistic activity) against SARS-CoV-2, *e.g.*, able to bind to and neutralize the activity of SARS-CoV-S, additional live virus or pseudovirus neutralization assays are performed using these mAbs in a dose-dependent manner to generate an IC_{50} of neutralization activity. In some experiments, a neutralization activity IC_{50} value for each antibody can be determined in a quantitative focus reduction neutralization test (FRNT) described previously by Zost *et al.* (Nature, 584:443–449, 2020). In some experiments,

neutralization assays are used to determine infectivity of SARS-CoV-2 S protein-containing virus-like particles. In these experiments, a neutralizing or antagonistic CoV-S antibody or antigen-binding fragment can be identified based on its ability to inhibit an activity of CoV-S to any detectable degree, *e.g.*, inhibits or reduces the ability of CoV-S protein to bind to a receptor such as ACE2, to be cleaved by a protease such as TMPRSS2, or to mediate viral entry into a host cell or mediate viral reproduction in a host cell.

EXAMPLE 12

Additional surface plasmon resonance (SPR) analysis

[0393] This Example describes the results of an additional round of experiments performed to further characterize binding affinity of select antibodies described herein.

[0394] A new lot of all 239 antibodies identified in Example 6 were synthesized, cloned, expressed, and purified according to the methods described in Example 8.

[0395] A second SPR experiment was performed under the same experimental settings (flow times, antigen concentration, coupling method, buffer, etc.) with one set of measurements per antibody (in comparison to the triplicate measurements completed as part of the first SPR experiment). Trimeric forms of the SARS-CoV-2 Wuhan entry strain (WT), beta, gamma, and kappa pre-fusion spike, SARS-CoV-2 NTD, HcoV-HKU1 spike trimer, and human serum albumin were used as antigens to assess the affinity and reactivity of each antibody. The antigens used in these experiments were purchased from ACROBiosystems (His-tagged wild-type SARS-CoV-2: Cat# SPN-C52H9; His-tagged SARS-CoV-2 gamma variant: Cat# SPN-C52Hg; His-tagged SARS-CoV-2 kappa variant: Cat# SPN-C52Hr; His-tagged SARS-CoV-2 beta variant: Cat# SPN-C52Hk; His-tagged SARS-CoV-2 NTD: Cat# SPN-C52H6; and His-tagged HcoV-HKU1 (isolate N5) spike trimer: Cat# SPN-C52H5). In addition, His-tagged human serum albumin (HSA) was also purchased from ACROBiosystems (Cat# HSA-H5220). Mutations identified in the beta, gamma, and kappa variants are as follows.

[0396] Beta variant: L18F, D80A, D215G, 242-244del, R246I, **K417N**, **E484K**, **N501Y**, D614G, A701V.

[0397] Gamma variant: L18F, T20N, P26S, D138Y, R190S, **K417T**, **E484K**, **N501Y**, D614G, H655Y, T1027I, and V1176F.

[0398] Kappa variant: T95I, G142D, E154K, **L452R**, **E484Q**, D614G, P681R, and Q1071H.

[0399] It should be noted that the delta and kappa variants share two mutations E484Q and L452R. They were identified in India's second COVID-19 wave, and have been reported to share significant similarity, presumably due to the fact that they are from the same lineage.

[0400] As shown in Tables 8A-8B below, it was observed that several antibodies described herein demonstrated high binding affinity to various spike variants of interest (VoC), *e.g.*, beta, gamma, and kappa variants. For comparative analysis, also included in this study were several control antibodies (denoted as CTRL) that had been previously described as having binding affinity for SARS-CoV-2 S protein. It was observed that several antibodies tested in this experiment could bind to one or more spike variants in low to mid nanomolar range. In addition, several antibodies were found to bind beta, gamma, and/or kappa variants with binding affinities as good as or superior to FDA-approved antibodies or antibodies in late clinical development.

TABLES 8A AND 8B: Binding affinity of exemplary antibodies to beta, gamma, and kappa spike variants. A total of 51 control antibodies (CTRL) were included in these experiments, including: CTRL-0004: Casirivimab; CTRL-0005: Imdevimab; CTRL-0006: Bamlanivimab; CTRL-0007: Etesevimab; CTRL-0008: Sotrovimab; and CTRL-0009: Tixagevimab; (-): not determined.

TABLE 8A												
Antibody	WT S Kon	WT S Koff	WT S KD	beta Kon	beta Koff	beta KD	gamma Kon	gamma Koff	gamma KD	kappa Kon	kappa Koff	kappa KD
C ^{TRL} -0003	168409.3858	4.06E-05	2.41E-10									
C ^{TRL} -0004	780111.1	0.00001	1.28E-11	719344.14	0.00001	1.39E-11	690920.7	0.00001	1.45E-11	787567.5	0.00001	1.27E-11
C ^{TRL} -0005	425853.7	0.00001	2.35E-11	685071.11	0.00001	1.46E-11	397093.6	0.00001	2.52E-11	277653.7	0.00001	3.60E-11
C ^{TRL} -0006	376757.3	0.00001	2.65E-11									
C ^{TRL} -0007	280361.6	0.00001	3.57E-11				145069.5	0.000151	1.04E-09	288148	0.00001	3.47E-11
C ^{TRL} -0008	69055.65	2.41E-05	3.49E-10	67282.657	0.00001	1.49E-10	73180.24	0.00001	1.37E-10	114028.4	0.00001	8.77E-11
C ^{TRL} -0009	245014.7	0.00001	4.08E-11	396880.9	0.00001	2.52E-11	434878.3	0.00001	2.30E-11	534970.6	0.00001	1.87E-11
C ^{TRL} -0010	124581.1	2.67E-05	2.15E-10							174586.4	3.26E-05	1.87E-10
C ^{TRL} -0011	67315.18	0.000244	3.63E-09	92570.575	0.001055	1.14E-08	70861.33	0.00043	6.07E-09	138522.4	0.000144	1.04E-09
C ^{TRL} -0012	85130.28	5.00E-05	5.87E-10							148498	4.80E-05	3.23E-10
C ^{TRL} -0013	41993.52	0.00001	2.38E-10				2367.705	0.00063	2.66E-07	96040.55	0.00001	1.04E-10
C ^{TRL} -0014	318910.3	0.00001	3.14E-11	505162.26	0.00001	1.98E-11	430070.9	0.00001	2.33E-11	152031.7	0.000291	1.91E-09
C ^{TRL} -0015	16584	0.000274	1.65E-08	1509465.2	0.108929	7.22E-08				81269.48	6.01E-05	7.39E-10
C ^{TRL} -0016	58990.59	0.00001	1.70E-10	109857.57	0.000112	1.02E-09	107226	4.30E-05	4.01E-10	85218.62	0.00001	1.17E-10
C ^{TRL} -0017	185065.6	0.000355	1.92E-09	249966.16	0.000549	2.20E-09						
C ^{TRL} -0018	26750.32	0.00001	3.74E-10	69658.331	0.00001	1.44E-10	16313.45	1.38E-05	8.49E-10	28622.92	0.00001	3.49E-10
C ^{TRL} -0021	24080.72	2.11E-05	8.78E-10	130877.47	0.00001	7.64E-11	95747.46	0.00001	1.04E-10	150071.6	0.00001	6.66E-11
C ^{TRL} -0023	74396	0.000217	2.91E-09	154813.09	0.000251	1.62E-09	97270.21	0.000279	2.87E-09			
C ^{TRL} -0024	2444.646	0.000404	1.65E-07							28055.16	0.000381	1.36E-08
C ^{TRL} -0025	340585.7	7.92E-05	2.32E-10	201331.02	0.000131	6.50E-10	152226.8	0.000151	9.95E-10	362152.7	0.000163	4.49E-10
C ^{TRL} -0026	139713	2.86E-05	2.05E-10	71329.098	0.000387	5.42E-09	48055.96	0.000413	8.59E-09	88296.64	0.000271	3.07E-09
C ^{TRL} -0027	162664.2	0.00001	6.15E-11	254775.18	0.00001	3.93E-11	247821.6	0.00001	4.04E-11	213373	0.00001	4.69E-11
C ^{TRL} -0029	229485.4	4.46E-05	1.94E-10	282036.78	9.58E-05	3.40E-10	216032.8	0.000116	5.39E-10	49049.53	0.000289	5.90E-09
C ^{TRL} -0030	1007982	0.000482	4.78E-10									
C ^{TRL} -0031	333733.6	6.26E-05	1.88E-10	446901.56	0.000108	2.42E-10	336627.9	0.000126	3.74E-10	177884.6	0.000313	1.76E-09
C ^{TRL} -0033	248246.4	0.000525	2.11E-09				937.1916	0.034496	3.68E-05			
C ^{TRL} -0034	130018.6	0.000161	1.24E-09				109741.9	0.0004	3.65E-09			
C ^{TRL} -0035	47590.2	0.00001	2.10E-10	93172.211	0.00001	1.07E-10	59823.52	1.08E-05	1.81E-10	155822.9	0.00001	6.42E-11
C ^{TRL} -0036	1011121	4.36E-05	4.31E-08	35379.486	0.00001	2.83E-10	20646.69	1.16E-05	5.61E-10	40592.63	0.00001	2.46E-10
C ^{TRL} -0037	283158.2	0.00001	3.53E-11									

[illegible]

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TXG-0026	91710.93	0.000159	1.73E-09	86982.241	0.00001	1.15E-10	60649.31	1.70E-05	2.80E-10	84224.4	0.00001	1.19E-10
TXG-0029	92004.71	0.00001	1.09E-10	143423.62	0.000699	4.88E-09	90399.75	0.000644	7.12E-09	76970.55	0.000297	3.86E-09
TXG-0030	52190.23	0.000368	7.05E-09									
TXG-0031	14663.3	0.000205	1.40E-08									
TXG-0032	28217.51	0.000155	5.50E-09									
TXG-0033	7453.19	0.000224	3.01E-08									
TXG-0035	199186.9	0.000176	8.81E-10									
TXG-0036	222715.1	0.00014	6.30E-10									
TXG-0037	58.65976	0.00071	1.21E-05									
TXG-0038	102431.5	0.000154	1.51E-09									
TXG-0039	67197.52	0.000412	6.13E-09							220339	0.000263	1.19E-09
TXG-0040	130771	0.000173	1.32E-09							233936.9	0.000154	6.60E-10
TXG-0042	26871.42	0.000305	1.13E-08									
TXG-0044	154285.6	0.000188	1.22E-09				103026.4	0.000797	7.74E-09	168002.6	0.000162	9.62E-10
TXG-0045	701589.8	0.000144	2.05E-10									
TXG-0046	104217.9	0.00001	9.60E-11	188719.4	0.00001	5.30E-11	157681.1	1.16E-05	7.34E-11	200105.2	0.00001	5.00E-11
TXG-0047	169016.1	0.00001	5.92E-11	192154.86	0.00001	5.20E-11	138723.9	0.00001	7.21E-11	237583.5	0.00001	4.21E-11
TXG-0048	352315.6	8.96E-05	2.54E-10	336848.75	0.000117	3.47E-10	189058.6	0.000126	6.64E-10	53255.16	0.000194	3.65E-09
TXG-0050	328825.5	2.39E-05	7.27E-11							433725.1	4.95E-05	1.14E-10
TXG-0052	39889.46	0.000326	8.18E-09									
TXG-0053	98231.92	0.000476	4.84E-09	245247.88	0.00026	1.06E-09	204317.2	0.000238	1.16E-09	203079	0.000239	1.18E-09
TXG-0054	203382.5	0.00022	1.08E-09	371492.07	0.000171	4.61E-10	347157.9	0.000156	4.48E-10	365026.5	0.000151	4.14E-10
TXG-0055	73671.21	0.000291	3.96E-09	97945.439	0.00057	5.82E-09	39399.2	0.000561	1.42E-08			
TXG-0057	55653.7	0.00001	1.80E-10	12596.991	1.78E-05	1.41E-09	19437.86	3.84E-05	1.98E-09	62055.84	0.000303	4.89E-09
TXG-0058	295225.9	6.09E-05	2.06E-10	41234.78	0.000552	1.34E-08	195127	5.12E-05	2.62E-10	153799.3	0.000228	1.48E-09
TXG-0059	81275.01	0.000239	2.94E-09									
TXG-0060	192587.4	0.00001	5.19E-11	229389.14	0.00049	2.13E-09	158571.6	3.35E-05	2.11E-10	136230.1	0.00001	7.34E-11
TXG-0063	446499.9	0.00001	2.24E-11	809696.78	0.00001	1.24E-11	698943.3	0.00001	1.43E-11	573652.8	0.00001	1.74E-11
TXG-0064	219863.1	5.51E-05	2.50E-10							469086.5	1.36E-05	2.89E-11
TXG-0065	387729.2	4.53E-05	1.17E-10	219030.9	0.000243	1.11E-09	308014.3	0.00024	7.79E-10	349877	5.96E-05	1.70E-10
TXG-0066	240599	0.00001	4.16E-11				173908.5	0.00001	5.75E-11	145050	2.74E-05	1.89E-10
TXG-0069	8317052	0.00001	1.20E-12				107383.6	0.00001	9.31E-11			
TXG-0070	110689.5	1.30E-05	1.18E-10	273088.64	0.00001	3.66E-11	196229.8	0.00001	5.10E-11	293084.6	0.00001	3.41E-11
TXG-0071	498568.6	0.00001	2.01E-11	187789.44	0.00001	5.33E-11	268325	0.00001	3.73E-11	237093.6	0.00001	4.22E-11
TXG-0073	35730.14	0.000283	7.93E-09									

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TXG-0074	212871.8	2.20E-05	1.03E-10						210466.8	3.36E-05	1.60E-10	52258.05	0.000251	4.80E-09
TXG-0075	670.8758	3.06E-05	4.56E-08		0.00001	1.85E-10			24805.13	3.41E-05	1.37E-09	38024.91	2.64E-05	6.94E-10
TXG-0076	240008.1	5.93E-06	2.47E-11						182375.6	1.40E-05	7.66E-11	146530	1.65E-05	1.12E-10
TXG-0077	502833.1	0.00001	1.99E-11						185247.8	1.55E-05	8.37E-11	331733.3	0.00001	3.01E-11
TXG-0078	816671.8	0.00001	1.22E-11						725849.2	0.00001	1.38E-11	748059	0.00001	1.34E-11
TXG-0079	484917.7	0.00001	2.06E-11						409089.9	0.00001	2.44E-11	509423.3	1.29E-05	2.53E-11
TXG-0080	469444	0.00001	2.13E-11											
TXG-0081	307230.2	0.00001	3.25E-11											
TXG-0082	22678.11	0.00034	1.50E-08											
TXG-0084	561557.5	0.000138	2.46E-10											
TXG-0086	172085.6	0.00001	5.81E-11									46608.6	0.000315	6.76E-09
TXG-0087	109055.3	0.000407	3.73E-09						66598.4	0.000425	6.37E-09			
TXG-0088	358383.4	0.00001	2.79E-11						136400.5	8.43E-05	6.18E-10			
TXG-0091	483132.3	0.00001	2.07E-11						123741.5	0.00001	8.08E-11	45403.59	0.00001	2.20E-10
TXG-0093	603636.9	0.00001	1.66E-11						550911.8	0.00001	1.82E-11	588997.6	0.00001	1.70E-11
TXG-0094	255560.7	0.00001	3.91E-11						142433.9	0.00001	7.02E-11	127616.6	0.00001	7.84E-11
TXG-0097	190700.8	0.000174	9.15E-10											
TXG-0099	135348.4	0.00001	7.39E-11						71597.12	2.79E-05	3.90E-10	153610.9	0.00001	6.51E-11
TXG-0100	390105.2	1.47E-05	3.76E-11											
TXG-0101	350249.2	0.000124	3.54E-10									3412.061	0.000326	9.55E-08
TXG-0102	218013.6	9.03E-05	4.14E-10											
TXG-0103	562131.4	5.79E-05	1.03E-10											
TXG-0104	423299.2	0.00001	2.36E-11						300118.8	0.00001	3.33E-11	199123.2	7.38E-05	3.71E-10
TXG-0107	25951.13	0.00043	1.66E-08											
TXG-0109	785093.1	0.00001	1.27E-11						143755.1	0.00001	6.96E-11	208632.3	0.00001	4.79E-11
TXG-0114	604283.2	0.000126	2.08E-10						374594.4	0.000116	3.10E-10	309009.2	0.000176	5.70E-10
TXG-0116	435374.9	0.00001	2.30E-11						304760	0.00001	3.28E-11	275695.6	0.00001	3.63E-11
TXG-0117	108494.5	0.00001	9.22E-11						138269.1	0.00001	7.23E-11	175677.9	0.00001	5.69E-11
TXG-0119	496956.7	0.00001	2.01E-11						410817.1	0.00001	2.43E-11	375789.1	2.40E-05	6.39E-11
TXG-0120	1811915	0.00001	5.52E-12						144177	1.20E-05	8.34E-11	126446.9	2.34E-05	1.85E-10
TXG-0122	175708.7	0.00023	1.31E-09						101826.4	0.00027	2.65E-09	26571.5	0.000324	1.22E-08
TXG-0125	565476.5	0.000543	9.60E-10						313325	0.000535	1.71E-09	130512.1	0.00034	2.61E-09
TXG-0126	540451.1	0.00001	1.85E-11									249621.7	0.00001	4.01E-11
TXG-0127	75907.68	0.00001	1.32E-10						106302.5	0.00001	9.41E-11	177959.2	0.00001	5.62E-11
TXG-0128	729652.8	0.00001	1.37E-11									147872.6	0.00001	6.76E-11

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TXG-0129	881598.8	0.00001	1.13E-11				89445.31	6.47E-05	7.24E-10	138530	0.00001	7.22E-11
TXG-0131	189578	0.00001	5.27E-11				158774.7	0.00001	6.30E-11	130537.6	6.89E-05	5.28E-10
TXG-0132	251649.1	1.23E-05	4.90E-11							117984.2	0.00001	8.48E-11
TXG-0133	85657.09	0.00001	1.17E-10	202502.16	0.00001	4.94E-11	142898.4	0.00001	7.00E-11	224888.5	0.00001	4.45E-11
TXG-0141	425851.5	0.00001	2.35E-11	141627.36	8.61E-05	6.08E-10	106651	6.09E-05	5.71E-10	192762.1	1.47E-05	7.65E-11
TXG-0142	155175.9	0.00001	6.44E-11	147676.13	0.00001	6.77E-11	112965.9	0.00001	8.85E-11	20559.56	0.000703	3.42E-08
TXG-0143	160.3616	0.000363	2.26E-06							12863.36	0.000812	6.31E-08
TXG-0144	496160.8	0.00001	2.02E-11	681513.87	8.13E-05	1.19E-10	594557.8	8.07E-05	1.36E-10	596834.4	0.00001	1.68E-11
TXG-0146	502909.3	2.39E-05	4.76E-11	865028.08	0.000233	2.69E-10	328245.3	0.000125	3.81E-10	498594.3	0.000133	2.66E-10
TXG-0148	11889.43	0.000379	3.19E-08									
TXG-0149	1678.128	0.000392	2.33E-07									
TXG-0151	58206.41	0.00001	1.72E-10	29454.934	0.000544	1.85E-08	21124.77	0.000495	2.34E-08			
TXG-0156	69420.9	3.89E-05	5.60E-10	112533.1	0.00001	8.89E-11	78954.29	3.96E-05	5.02E-10	109736.6	0.00001	9.11E-11
TXG-0157	250330.5	0.00001	3.99E-11				197760.5	0.00001	5.06E-11	197792.7	0.000101	5.09E-10
TXG-0158	181.9377	0.000347	1.91E-06									
TXG-0161	172314.1	0.000148	8.61E-10									
TXG-0162	185611.9	0.00001	5.39E-11				126571.3	1.01E-05	8.01E-11	66540.24	0.000398	5.98E-09
TXG-0163	746725	0.00001	1.34E-11	202292.07	0.000303	1.50E-09	699220.8	0.00001	1.43E-11	664687.6	0.00001	1.50E-11
TXG-0164	476410.7	0.00001	2.10E-11				363869.1	0.00001	2.75E-11	236376.5	6.56E-05	2.78E-10
TXG-0166	5355.587	0.000302	5.63E-08	32880.786	0.001704	5.18E-08	13699.51	0.001575	1.15E-07	51627.55	0.000395	7.66E-09
TXG-0168	593680.4	0.00001	1.68E-11				467332.9	0.00001	2.14E-11	269659.7	6.57E-05	2.44E-10
TXG-0170	578040.4	0.00001	1.73E-11				496564.5	0.00001	2.01E-11	408671.2	0.00001	2.45E-11
TXG-0175	139662	0.00001	7.16E-11	292780.12	0.00001	3.42E-11	180570.4	0.00001	5.54E-11	79347.87	3.45E-05	4.35E-10
TXG-0176	67136.32	0.00001	1.49E-10	138813.21	0.00001	7.20E-11	107425.4	0.00001	9.31E-11	119409	1.37E-05	1.15E-10
TXG-0178	380021.5	0.00001	2.63E-11							54121.64	0.00001	1.85E-10
TXG-0180	225587.9	0.00001	4.43E-11	99282.622	0.000321	3.23E-09	104154.3	0.00024	2.30E-09	382467.9	0.00001	2.61E-11
TXG-0181	779763.9	0.00001	1.28E-11	1002845.8	0.00001	9.97E-12	937527.8	0.00001	1.07E-11	915434.1	0.00001	1.09E-11
TXG-0183	323560.7	0.00001	3.09E-11	228900.37	0.00001	4.37E-11	195255	0.00001	5.12E-11	103397.1	0.00001	9.67E-11
TXG-0184	345971.3	0.00001	2.89E-11				282684.3	0.00001	3.54E-11	222761.4	1.67E-05	7.49E-11
TXG-0185	38863.31	0.00001	2.57E-10	66683.389	0.00001	1.50E-10	40051.74	0.00001	2.50E-10	59487.2	0.00001	1.68E-10
TXG-0187	366158.2	0.000334	9.12E-10	247686.86	0.000337	1.36E-09	166893.2	0.000338	2.03E-09	186435.1	0.000463	2.48E-09
TXG-0188	702186.3	4.32E-05	6.15E-11				276497.1	0.000401	1.45E-09			
TXG-0189	197516.2	0.00001	5.06E-11									
TXG-0190	63092.81	8.64E-05	1.37E-09				3485478	0.185764	5.33E-08	13725.68	0.000365	2.66E-08
TXG-0197	473650.3	0.00001	2.11E-11				79304.61	0.000365	4.60E-09	673071.9	0.00001	1.49E-11

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TXG-0198	358355.6	0.00001	2.79E-11	162407.56	0.00001	6.16E-11	171013	1.71E-05	1.00E-10	535758.7	0.00001	1.87E-11
TXG-0199	330372.5	5.26E-05	1.59E-10									
TXG-0200	317928.7	0.00001	3.15E-11	77592.385	0.00001	1.29E-10	71861.13	2.42E-05	3.37E-10	96064.13	0.00001	1.04E-10
TXG-0201	86162.97	2.15E-05	2.50E-10	94.996938	0.003228	3.40E-05	2126.774	0.000648	3.05E-07	217994.9	0.00001	4.59E-11
TXG-0202	264368	0.00001	3.78E-11	187407.8	0.00001	5.34E-11	211577.7	0.00001	4.73E-11	160865.7	0.00001	6.22E-11
TXG-0203	432807.3	0.00034	7.87E-10	306131.43	0.000309	1.01E-09	236114.9	0.000314	1.33E-09	248521.1	0.00037	1.49E-09
TXG-0204	207477.5	0.00001	4.82E-11	254180.35	2.66E-05	1.05E-10	227636.4	0.00001	4.39E-11	323599.6	0.00001	3.09E-11
TXG-0206				15995.489	8.90E-05	5.57E-09						
TXG-0207	96602.3	2.11E-05	2.19E-10	124486.09	0.00021	1.68E-09	131217.3	7.30E-05	5.56E-10	126244.3	1.38E-05	1.09E-10
TXG-0209	102972.7	0.00001	9.71E-11	82882.265	0.000202	2.43E-09	76843.54	0.000117	1.53E-09	161684.2	0.00001	6.18E-11
TXG-0210	367920.2	1.03E-05	2.80E-11	227895.12	0.00001	4.39E-11	88096.28	0.00001	1.14E-10	98810.16	0.00001	1.01E-10
TXG-0221	187597	8.60E-05	4.58E-10									
TXG-0222	17033.57	0.00035	2.05E-08									
TXG-0223	63019.98	0.000455	7.22E-09									
TXG-0224	310857	0.000232	7.47E-10									
TXG-0225	549629	0.00001	1.82E-11									
TXG-0232	252644.5	0.00001	3.96E-11	379344.22	0.00017	4.48E-10	119739.5	1.71E-05	1.43E-10	253110.7	0.00001	3.95E-11
TXG-0234	39316.19	0.000228	5.81E-09				196415.6	0.00001	5.09E-11	272541.5	3.65E-05	1.34E-10
TXG-0236	346007	1.92E-05	5.54E-11									

TABLE 8B

Antibody	WT S Kon	WT S Koff	WT S KD	beta Kon	beta Koff	beta KD	gamma Kon	gamma Koff	gamma KD	kappa Kon	kappa Koff	kappa KD
CTRL-0003	168409.4	4.06E-05	2.41E-10	ND	ND	ND	ND	ND	ND	ND	ND	ND
CTRL-0004	780111.1	0.00001	1.28E-11	719344.14	0.00001	1.39E-11	690920.7	0.00001	1.45E-11	787567.5	0.00001	1.27E-11
CTRL-0005	425853.7	0.00001	2.35E-11	685071.11	0.00001	1.46E-11	397093.6	0.00001	2.52E-11	277653.7	0.00001	3.60E-11
CTRL-0006	376757.3	0.00001	2.65E-11	ND	ND	ND	ND	ND	ND	ND	ND	ND
CTRL-0007	280361.6	0.00001	3.57E-11	ND	ND	ND	145069.5	0.000151	1.04E-09	288148	0.00001	3.47E-11
CTRL-0008	69055.65	2.41E-05	3.49E-10	67282.657	0.00001	1.49E-10	73180.24	0.00001	1.37E-10	114028.4	0.00001	8.77E-11
CTRL-0009	245014.7	0.00001	4.08E-11	396880.9	0.00001	2.52E-11	434878.3	0.00001	2.30E-11	534970.6	0.00001	1.87E-11
CTRL-0010	124581.1	2.67E-05	2.15E-10	ND	ND	ND	ND	ND	ND	174586.4	3.26E-05	1.87E-10
CTRL-0011	67315.18	0.000244	3.63E-09	92570.575	0.001055	1.14E-08	70861.33	0.00043	6.07E-09	138522.4	0.000144	1.04E-09
CTRL-0012	85130.28	5.00E-05	5.87E-10	ND	ND	ND	ND	ND	ND	148498	4.80E-05	3.23E-10
CTRL-0013	41993.52	0.00001	2.38E-10	ND	ND	ND	2367.705	0.00063	2.66E-07	96040.55	0.00001	1.04E-10
CTRL-0014	318910.3	0.00001	3.14E-11	505162.26	0.00001	1.98E-11	430070.9	0.00001	2.33E-11	152031.7	0.000291	1.91E-09

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C ^{TRL} -0015	16584	0.000274	1.65E-08	1509465.2	0.108929	7.22E-08	ND	ND	ND	81269.48	6.01E-05	7.39E-10
C ^{TRL} -0016	58990.59	0.00001	1.70E-10	109857.57	0.000112	1.02E-09	107226	4.30E-05	4.01E-10	85218.62	0.00001	1.17E-10
C ^{TRL} -0017	185065.6	0.000355	1.92E-09	249966.16	0.000549	2.20E-09	ND	ND	ND	ND	ND	ND
C ^{TRL} -0018	26750.32	0.00001	3.74E-10	69658.331	0.00001	1.44E-10	16313.45	1.38E-05	8.49E-10	28622.92	0.00001	3.49E-10
C ^{TRL} -0021	24080.72	2.11E-05	8.78E-10	130877.47	0.00001	7.64E-11	95747.46	0.00001	1.04E-10	150071.6	0.00001	6.66E-11
C ^{TRL} -0023	74396	0.000217	2.91E-09	154813.09	0.000251	1.62E-09	97270.21	0.000279	2.87E-09	ND	ND	ND
C ^{TRL} -0024	2444.646	0.000404	1.65E-07	ND	ND	ND	ND	ND	ND	28055.16	0.000381	1.36E-08
C ^{TRL} -0025	340585.7	7.92E-05	2.32E-10	201331.02	0.000131	6.50E-10	152226.8	0.000151	9.95E-10	362152.7	0.000163	4.49E-10
C ^{TRL} -0026	139713	2.86E-05	2.05E-10	71329.098	0.000387	5.42E-09	48055.96	0.000413	8.59E-09	88296.64	0.000271	3.07E-09
C ^{TRL} -0027	162664.2	0.00001	6.15E-11	254775.18	0.00001	3.93E-11	247821.6	0.00001	4.04E-11	213373	0.00001	4.69E-11
C ^{TRL} -0029	229485.4	4.46E-05	1.94E-10	282036.78	9.58E-05	3.40E-10	216032.8	0.000116	5.39E-10	49049.53	0.000289	5.90E-09
C ^{TRL} -0030	1007982	0.000482	4.78E-10	ND	ND	ND	ND	ND	ND	ND	ND	ND
C ^{TRL} -0031	333733.6	6.26E-05	1.88E-10	446901.56	0.000108	2.42E-10	336627.9	0.000126	3.74E-10	177884.6	0.000313	1.76E-09
C ^{TRL} -0033	248246.4	0.000525	2.11E-09	ND	ND	ND	937.1916	0.034496	3.68E-05	ND	ND	ND
C ^{TRL} -0034	130018.6	0.000161	1.24E-09	ND	ND	ND	109741.9	0.0004	3.65E-09	ND	ND	ND
C ^{TRL} -0035	47590.2	0.00001	2.10E-10	93172.211	0.00001	1.07E-10	59823.52	1.08E-05	1.81E-10	155822.9	0.00001	6.42E-11
C ^{TRL} -0036	1011.121	4.36E-05	4.31E-08	35379.486	0.00001	2.83E-10	20646.69	1.16E-05	5.61E-10	40592.63	0.00001	2.46E-10
C ^{TRL} -0037	283158.2	0.00001	3.53E-11	ND	ND	ND	ND	ND	ND	ND	ND	ND
C ^{TRL} -0038	567188.5	0.00001	1.76E-11	ND	ND	ND	ND	ND	ND	531520.8	0.00001	1.88E-11
C ^{TRL} -0039	193867.8	0.00001	5.16E-11	ND	ND	ND	56494.62	0.00001	1.77E-10	75415.87	6.61E-05	8.76E-10
C ^{TRL} -0040	99948.55	0.00001	1.00E-10	140309.43	0.000102	7.27E-10	133195.6	4.47E-05	3.35E-10	123189.8	0.00001	8.12E-11
C ^{TRL} -0041	32453.98	0.00001	3.08E-10	ND	ND	ND	ND	ND	ND	40336.31	0.00001	2.48E-10
C ^{TRL} -0042	84356.91	0.001413	1.68E-08	ND	ND	ND	ND	ND	ND	ND	ND	ND
C ^{TRL} -0043	730049.9	0.000105	1.44E-10	ND	ND	ND	ND	ND	ND	ND	ND	ND
C ^{TRL} -0044	21110.2	0.00001	4.74E-10	54202.792	0.00001	1.84E-10	42983.85	0.00001	2.33E-10	72048.22	0.00001	1.39E-10
C ^{TRL} -0045	32822.46	3.71E-05	1.13E-09	56505.976	0.00001	1.77E-10	45808.39	0.00001	2.18E-10	46026.79	0.00001	2.17E-10
C ^{TRL} -0047	376730.5	0.00001	2.65E-11	ND	ND	ND	282873.4	0.00001	3.54E-11	62120.06	0.000253	4.07E-09
C ^{TRL} -0048	50725.55	0.000112	2.20E-09	ND	ND	ND	1996.237	0.000345	1.73E-07	ND	ND	ND
C ^{TRL} -0049	3423.314	0.000347	1.01E-07	325430.35	0.001889	5.80E-09	ND	ND	ND	45569.02	0.000896	1.97E-08
C ^{TRL} -0050	1481.382	0.000169	1.14E-07	ND	ND	ND	ND	ND	ND	ND	ND	ND
C ^{TRL} -0051	118529.8	0.000293	2.47E-09	119245.9	0.00041	3.44E-09	112418.1	0.000333	2.96E-09	ND	ND	ND
C ^{TRL} -0052	62024.63	0.000275	4.43E-09	47570.381	0.000266	5.59E-09	31967.12	0.000281	8.80E-09	68971.82	0.000175	2.53E-09
C ^{TRL} -0053	66049.93	0.00001	1.51E-10	134546.23	0.00001	7.43E-11	12480.41	2.83E-05	2.27E-09	30835.73	0.00001	3.24E-10
TXG-0021	58100.29	0.000702	1.21E-08	ND	ND	ND	ND	ND	ND	ND	ND	ND
TXG-0022	95715.25	0.000646	6.75E-09	ND	ND	ND	ND	ND	ND	ND	ND	ND

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TXG-0169	23442.35	0.000256	1.09E-08	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
TXG-0172	ND	ND	ND	56504.38	0.002193	3.88E-08	ND	2511.992	0.001847	7.35E-07	2861.962	ND	0.001611	5.63E-07					
TXG-0173	204634.4	0.00001	4.89E-11	ND	ND	ND	ND	176123.9	0.00001	5.68E-11	192552.8	4.75E-05	2.47E-10						
TXG-0174	63825.2	0.00001	1.53E-11	115353.74	0.000175	1.52E-09	610358.5	25409.73	0.000759	1.64E-11	523343.2	4.67E-05	8.93E-11						
TXG-0177	ND	ND	ND	ND	ND	ND	ND	147034.4	1.55E-05	2.99E-08	21365.33	0.000908	4.25E-08						
TXG-0182	130174.1	3.09E-05	2.37E-10	208806.99	0.00001	4.79E-11	10000	91208.85	0.000454	1.05E-10	31943.81	0.000278	8.71E-09						
TXG-0191	ND	ND	ND	ND	ND	ND	ND	10000	0.0001	1E-08	ND	ND	ND						
TXG-0192	179267.8	0.000496	2.77E-09	158967.97	0.000402	2.53E-09	91208.85	64843.99	0.00001	4.97E-09	128520.8	0.000592	4.60E-09						
TXG-0194	41416.06	0.00001	2.41E-10	79040.582	0.00001	1.27E-10	64843.99	ND	0.00001	1.54E-10	69322.61	0.00001	1.44E-10						
TXG-0195	54371.07	0.000198	3.65E-09	ND	ND	ND	ND	ND	ND	ND	55172.56	0.000268	4.85E-09						
TXG-0211	66441.78	0.000153	2.30E-09	6761664.9	0.299506	4.43E-08	67428.52	0.000169	0.000169	2.51E-09	93950.11	0.000186	1.98E-09						
TXG-0213	143359.5	0.000336	2.34E-09	156924.95	0.00034	2.16E-09	71268.46	0.000339	0.000339	4.76E-09	123788.4	0.000287	2.32E-09						
TXG-0215	71708.02	0.000228	3.18E-09	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND						
TXG-0216	43747.18	0.000995	2.27E-08	ND	ND	ND	ND	ND	ND	ND	276945.1	0.000857	3.09E-09						
TXG-0217	54611.04	0.00001	1.83E-10	71577.605	0.000227	3.17E-09	55140.78	0.000188	0.000188	3.42E-09	168458.3	3.96E-05	2.35E-10						
TXG-0218	105456.4	0.000138	1.30E-09	74037.374	0.000351	4.75E-09	ND	ND	ND	ND	ND	ND	ND						
TXG-0226	148097.7	0.00032	2.16E-09	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND						
TXG-0227	175242.9	0.000306	1.75E-09	279594.3	0.000341	1.22E-09	203744.8	0.000338	0.000338	1.66E-09	198083.4	0.000312	1.57E-09						
TXG-0228	147000.5	0.000338	2.30E-09	147785.36	0.000368	2.49E-09	150894.1	0.000337	0.000337	2.23E-09	144708	0.000316	2.18E-09						
TXG-0229	51842.91	0.000564	1.09E-08	135511.09	0.000352	2.60E-09	129558.1	0.000355	0.000355	2.74E-09	121189.8	0.000344	2.84E-09						
TXG-0230	93451.94	0.000182	1.94E-09	282891.09	0.00014	4.96E-10	291515.6	0.000147	0.000147	5.04E-10	247672.2	0.000158	6.37E-10						

[0401] An UpSet plot was generated (see, *e.g.*, **FIG. 25**) wherein antibodies are binned into antigen bins based on two rounds of SPR binding affinity data. For an antibody to be placed into a bin a detectable kinetic fit at all concentrations of antigen was required from at least one of the SPR experiments described in Examples 9 and 12, or orthogonal neutralization data. The results described in **FIG. 25** illustrate that the BEAM-seq process described in the present disclosure allows for rapid identification of many antibodies with broad and robust binding affinity against several coronavirus S antigens, including several variants of concern (VoC), *e.g.*, , beta, gamma, and kappa, as well as HKU1 (which is a different coronavirus).

[0402] A third SPR experiment was performed under the same experimental settings (flow times, antigen concentration, coupling method, buffer, etc.) where the antibodies were assessed at minimum in duplicate and up to sextuplicate. Trimeric forms of the human coronavirus HCoV-OC43 pre-fusion trimeric spike, HCoV-229E pre-fusion trimeric spike, SARS-CoV-2 omicron pre-fusion trimeric spike and SARS-CoV-2 NTD were used as antigens to assess the affinity and reactivity of each antibody. As shown in Table 9 below, it was observed that several antibodies described herein demonstrated high binding affinity to SARS-CoV-2 omicron spike as well as HCoV-OC43 spike and HCoV-229E spike. For comparative analysis, also included in this study were several control antibodies (denoted as CTRL) that had been previously described as having binding affinity for SARS-CoV-2 S protein.

[0403] In these experiments, it was observed that several antibodies tested in this experiment could bind to one or more spike variants in low to mid nanomolar range. In particular, thirty-seven (37) antibodies tested in this SPR experiment were found to exhibit binding affinity for the WT spike and the new SARS-CoV-2 strain omicron (see, *e.g.*, Tables 8-9 and FIG. 31). Of these 37 antibodies, at least 32 exhibit affinity for the beta variant, at least 34 exhibit affinity for the kappa variant, and at least 32 exhibit affinity for the gamma variants by SPR. In addition, at least 32 antibodies exhibit high affinity for the beta, gamma, and omicron variants by SPR, and at least antibodies exhibit high affinity for the gamma, kappa, and omicron variants by SPR. Exemplary antibodies exhibiting affinity for the gamma, kappa, and omicron variants include TXG-0057, TXG-0063, TXG-0070, TXG-0072, TXG-0091, TXG-0094, TXG-0098, TXG-0099, TXG-0109, TXG-0112, TXG-0114, TXG-0115, TXG-0120, TXG-0129, TXG-0141, TXG-0144, TXG-0174, TXG-0180, TXG-0183, TXG-0187, TXG-0192, TXG-0197,

TXG-0198, TXG-0200, TXG-0201, TXG-0202, TXG-0203, TXG-0204, TXG-0209, TXG-0210, TXG-0228, and TXG-0230.

[0404] Remarkably, at least 30 tested antibodies exhibit affinity for the WT spike and all four beta, gamma, kappa, and omicron variants. Exemplary antibodies exhibiting affinity for the WT spike and all four beta, gamma, kappa, and omicron variants include TXG-0057, TXG-0063, TXG-0070, TXG-0072, TXG-0091, TXG-0094, TXG-0098, TXG-0099, TXG-0109, TXG-0112, TXG-0114, TXG-0115, TXG-0120, TXG-0141, TXG-0144, TXG-0174, TXG-0180, TXG-0183, TXG-0187, TXG-0192, TXG-0198, TXG-0200, TXG-0201, TXG-0202, TXG-0203, TXG-0204, TXG-0209, TXG-0210, TXG-0228, and TXG-0230.

[0405] Furthermore, several antibodies were found to be pan-coronavirus antibodies that bind with high affinity to N-terminal domain of SARS-CoV-2 S protein (NTD) and/or to a spike protein of the new SARS-CoV-2 strain omicron (see, *e.g.*, TXG-0001, TXG-0002, TXG-0004, TXG-0005, TXG-0008, TXG-0009, TXG-0048, TXG-0057, TXG-0060, TXG-0063, TXG-0066, TXG-0070, TXG-0072, TXG-0074, TXG-0076, TXG-0078, TXG-0080, TXG-0081, TXG-0087, TXG-0088, TXG-0091, TXG-0094, TXG-0098, TXG-0099, TXG-0109, TXG-0114, TXG-0115, TXG-0120, TXG-0129, TXG-0136, TXG-0141, TXG-0144, TXG-0153, TXG-0170, TXG-0173, TXG-0174, TXG-0175, TXG-0180, TXG-0181, TXG-0183, TXG-0187, TXG-0189, TXG-0197, TXG-0198, TXG-0200, TXG-0201, TXG-0202, TXG-0203, TXG-0204, TXG-0209, TXG-0210, TXG-0228, and TXG-0230 of Table 9 and FIG. 31). Of these antibodies, at least five antibodies were found to have a high affinity to both (i) N-terminal domain of SARS-CoV-2 S protein (NTD) and (ii) a spike protein of the omicron variant. Exemplary antibodies having these binding characteristics include TXG-0072, TXG-0099, TXG-0114, TXG-0203, and TXG-0230.

[0406] In addition, several antibodies were found to be promising pan-coronavirus antibodies that bind with affinity to N-terminal domain of SARS-CoV-2 S protein (NTD) and to a spike protein of the endemic human coronavirus HCoV-OC43 (see, *e.g.*, TXG-0048, TXG-0078, TXG-0114, TXG-0136, TXG-0192, and TXG-0203) or HCoV-229E (*e.g.*, TXG-0078, TXG-0112, TXG-0114, TXG-0136, TXG-0192, TXG-0203, and TXG-0230).

[0407] At least 8 antibodies tested in this experiments exhibit binding high affinity for the endemic coronavirus HCoV-229E. Exemplary antibodies with high affinity for HCoV-229E include TXG-0078, TXG-0112, TXG-0114, TXG-0136, TXG-0192, TXG-0203, TXG-0228, and

TXG-0230. At least 10 tested antibodies exhibit binding affinity for the endemic coronavirus HCoV-OC43. Exemplary antibodies with affinity for HCoV-OC43 include TXG-0006, TXG-0048, TXG-0070, TXG-0078, TXG-0100, TXG-0114, TXG-0136, TXG-0154, TXG-0192, and TXG-0203. Of these 10 antibodies, at least five exhibit high affinity for HCoV-OC43 (see, e.g., TXG-0100, TXG-0114, TXG-0136, TXG-0192, and TXG-0203).

[0408] In addition, several antibodies were found to bind HCoV-OC43, HCoV-229E, SARS-CoV-2 omicron and SARS-CoV-2 NTD with binding affinities as good as or superior to FDA-approved antibodies or antibodies in late clinical development. Exemplary antibodies having this ultra-broad binding affinity include TXG-0114, TXG-0192, and TXG-0203. In particular, TXG-0114 and TXG-0203 were found to bind HCoV-OC43, HCoV-229E, SARS-CoV-2 omicron and SARS-CoV-2 NTD with high affinities.

[0409] Several antibodies were found to exhibit binding affinity for the WT spike, the spike protein of beta, gamma, and kappa variants as well as the endemic coronaviruses HCoV-OC43, HKU1, and HCoV-229E. Exemplary antibodies having this ultra-broad binding affinity include TXG-0078, TXG-0114, TXG-0136, TXG-0192, and TXG-0203.

[0410] Remarkably, at least three (3) antibodies tested in this experiment were found to exhibit binding affinity for the WT spike, all four variants (i.e., beta, gamma, kappa, and omicron) as well as the endemic coronaviruses HCoV-OC43 and HCoV-229E.

[0411] Additionally, several antibodies were found to be pan-coronavirus antibodies that recognizes a conserved epitope in the S1 subunit and bind with high affinity to N-terminal domain of SARS-CoV-2 S protein (NTD) (see, e.g., TXG-0048, TXG-0060, TXG-0066, TXG-0072, TXG-0074, TXG-0076, TXG-0078, TXG-0099, TXG-0114, TXG-0136, TXG-0170, TXG-0173, TXG-0181, TXG-0203, TXG-0230) and/or to the S1 subunit of a new human coronavirus strain HCoV-HKU1 (see, e.g., TXG-0078, TXG-0112, TXG-0114, TXG-0136, TXG-0187, TXG-0192, TXG-0203, and TXG-0230). Accordingly, without being bound to any particular theory, these antibodies could be particularly useful in therapeutic combination against SARS-CoV-2 and other coronaviruses and in combination with RBD-binding or non-S1 binding therapeutic antibodies.

TABLE 9: Binding affinity of exemplary antibodies to HCoV-OC43 Spike Trimer, HCoV-229E Spike Trimer, SARS-CoV-2 Spike Trimer (Omicron), and SARS-CoV-2 S1 N-terminal domain. Four control antibodies were included in these experiments, including: CTRL-0004: Casirivimab; CTRL-0005: Imdevimab; CTRL-0008: Sotrovimab; and CTRL-0054 (Cilgavimab); (-): not determined.

Antibody	HCoV-OC43 Spike Trimer				HCoV-229E Spike Trimer				SARS-CoV-2 Spike Trimer (Omicron)				SARS-CoV-2 S1 NTD			
	k_a (M-1 s-1)	k_d (s-1)	K_D (M)		k_a (M-1 s-1)	k_d (s-1)	K_D (M)		k_a (M-1 s-1)	k_d (s-1)	K_D (M)		k_a (M-1 s-1)	k_d (s-1)	K_D (M)	
CTRL-0004	4.79E+04	1.79E-04	3.82E-09		N/A	N/A	N/A		3.62E+05	1.15E-04	3.19E-10		N/A	N/A	N/A	
CTRL-0005	9.35E+03	2.27E-04	3.53E-08		8.01E+02	1.37E-04	6.42E-07		1.73E+05	3.86E-04	2.45E-09		7.21E+02	1.91E-05	2.49E-07	
CTRL-0008a	N/A	N/A	N/A		N/A	N/A	N/A		7.66E+04	1.00E-05	1.33E-10		N/A	N/A	N/A	
CTRL-0008c	N/A	N/A	N/A		N/A	N/A	N/A		5.99E+04	1.00E-05	1.68E-10		N/A	N/A	N/A	
CTRL-0054	N/A	N/A	N/A		N/A	N/A	N/A		2.69E+05	1.00E-05	3.72E-11		N/A	N/A	N/A	
TXG-0002	N/A	N/A	N/A		N/A	N/A	N/A		6.24E+04	1.00E-05	1.61E-10		N/A	N/A	N/A	
TXG-0006	2.87E+02	8.17E-04	3.35E-06		N/A	N/A	N/A		N/A	N/A	N/A		N/A	N/A	N/A	
TXG-0048	6.04E+02	4.42E-04	3.55E-06		N/A	N/A	N/A		N/A	N/A	N/A		3.07E+03	1.49E-04	5.09E-08	
TXG-0049	N/A	N/A	N/A		N/A	N/A	N/A		5.87E+05	3.69E-04	6.38E-10		N/A	N/A	N/A	
TXG-0057	N/A	N/A	N/A		N/A	N/A	N/A		4.86E+05	1.11E-05	2.30E-11		N/A	N/A	N/A	
TXG-0060	N/A	N/A	N/A		N/A	N/A	N/A		N/A	N/A	N/A		9.55E+03	1.80E-04	1.89E-08	
TXG-0063	N/A	N/A	N/A		N/A	N/A	N/A		2.88E+05	1.48E-05	5.12E-11		N/A	N/A	N/A	
TXG-0066	N/A	N/A	N/A		N/A	N/A	N/A		N/A	N/A	N/A		9.32E+03	5.26E-04	5.66E-08	
TXG-0070	4.47E+02	5.88E-04	1.45E-06		N/A	N/A	N/A		2.26E+05	1.00E-05	4.47E-11		N/A	N/A	N/A	
TXG-0072	N/A	N/A	N/A		N/A	N/A	N/A		3.64E+06	2.00E-01	5.48E-08		2.72E+04	3.00E-04	1.10E-08	
TXG-0074	N/A	N/A	N/A		N/A	N/A	N/A		N/A	N/A	N/A		1.33E+04	1.03E-03	7.86E-08	
TXG-0076	N/A	N/A	N/A		N/A	N/A	N/A		N/A	N/A	N/A		1.02E+04	3.95E-05	3.88E-09	
TXG-0078a	4.72E+02	5.10E-04	1.08E-06		1.53E+04	1.38E-04	9.02E-09		N/A	N/A	N/A		2.70E+04	1.90E-04	7.04E-09	
TXG-0078b	5.65E+02	5.38E-04	9.86E-07		2.14E+02	3.15E-04	1.91E-06		N/A	N/A	N/A		2.30E+04	1.80E-04	7.81E-09	
TXG-0078c	3.71E+02	4.66E-04	1.66E-06		3.31E+02	3.55E-04	1.10E-06		N/A	N/A	N/A		2.26E+04	1.82E-04	8.08E-09	
TXG-0080	N/A	N/A	N/A		N/A	N/A	N/A		8.77E+04	4.90E-04	6.42E-09		N/A	N/A	N/A	
TXG-0081	N/A	N/A	N/A		N/A	N/A	N/A		1.78E+05	2.86E-04	1.68E-09		N/A	N/A	N/A	

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TXG-0088	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	2.58E+05	1.29E-05	5.00E-11	N/A	N/A	N/A	N/A
TXG-0091a	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	3.41E+05	1.00E-05	2.94E-11	N/A	N/A	N/A	N/A
TXG-0091c	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	7.87E+04	1.00E-05	1.42E-10	N/A	N/A	N/A	N/A
TXG-0094	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	2.40E+05	7.94E-05	3.33E-10	N/A	N/A	N/A	N/A
TXG-0098	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	1.00E+05	2.29E-04	2.43E-09	N/A	N/A	N/A	N/A
TXG-0099	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	1.63E+05	1.53E-05	9.59E-11	1.26E+04	3.99E-04	3.17E-08	
TXG-0100	4.19E+04	1.33E-04	1.31E-08	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
TXG-0104	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	1.49E+04	2.69E-03	1.81E-07	
TXG-0109	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	4.81E+05	1.01E-05	2.09E-11	N/A	N/A	N/A	N/A
TXG-0112	N/A	N/A	N/A	1.31E+05	1.59E-04	1.23E-09	5.51E+04	1.39E-04	5.51E+04	1.39E-04	2.62E-09	FALSE	4.97E-04	2.54E-07	
TXG-0114	4.27E+04	2.33E-04	6.82E-09	4.08E+05	1.61E-04	4.11E-10	1.25E+05	2.94E-04	1.25E+05	2.94E-04	2.44E-09	4.31E+03	3.18E-04	7.50E-08	
TXG-0115	N/A	N/A	N/A	N/A	N/A	N/A	N/A	1.53E-05	2.75E+05	1.53E-05	5.88E-11	N/A	N/A	N/A	N/A
TXG-0120	N/A	N/A	N/A	N/A	N/A	N/A	N/A	1.00E-05	2.23E+05	1.00E-05	4.53E-11	N/A	N/A	N/A	N/A
TXG-0129	N/A	N/A	N/A	N/A	N/A	N/A	N/A	1.00E-05	8.87E+05	1.00E-05	1.13E-11	N/A	N/A	N/A	N/A
TXG-0136	2.71E+04	2.88E-04	1.08E-08	2.16E+04	2.67E-04	1.29E-08	N/A	N/A	N/A	N/A	N/A	3.44E+04	1.94E-03	5.64E-08	
TXG-0141	N/A	N/A	N/A	N/A	N/A	N/A	N/A	5.23E-04	9.09E+04	5.23E-04	5.98E-09	N/A	N/A	N/A	N/A
TXG-0144	N/A	N/A	N/A	N/A	N/A	N/A	N/A	3.68E-04	6.29E+04	3.68E-04	5.96E-09	N/A	N/A	N/A	N/A
TXG-0153	N/A	N/A	N/A	N/A	N/A	N/A	N/A	4.69E-05	8.32E+04	4.69E-05	5.74E-10	N/A	N/A	N/A	N/A
TXG-0154	8.45E+02	5.51E-04	7.33E-07	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
TXG-0170	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	2.13E+04	1.12E-04	5.28E-09	
TXG-0173	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	1.29E+04	1.57E-04	1.23E-08	
TXG-0174	N/A	N/A	N/A	N/A	N/A	N/A	N/A	1.91E-01	2.12E+06	1.91E-01	9.00E-08	N/A	N/A	N/A	N/A
TXG-0180	N/A	N/A	N/A	N/A	N/A	N/A	N/A	8.28E-04	1.06E+05	8.28E-04	7.80E-09	N/A	N/A	N/A	N/A
TXG-0181	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	2.08E+04	7.26E-04	3.50E-08	
TXG-0183	N/A	N/A	N/A	N/A	N/A	N/A	N/A	1.00E-05	3.08E+05	1.00E-05	3.25E-11	N/A	N/A	N/A	N/A
TXG-0187	N/A	N/A	N/A	N/A	N/A	N/A	N/A	1.39E-05	3.28E+05	1.39E-05	4.59E-11	N/A	N/A	N/A	N/A
TXG-0189	N/A	N/A	N/A	N/A	N/A	N/A	N/A	6.88E-04	1.27E+05	6.88E-04	5.41E-09	N/A	N/A	N/A	N/A
TXG-0192	2.49E+04	2.70E-04	1.82E-08	3.69E+05	2.42E-04	7.02E-10	4.30E+04	4.97E-04	4.30E+04	4.97E-04	4.19E-08	2.33E+03	4.53E-04	2.39E-07	
TXG-0197	N/A	N/A	N/A	N/A	N/A	N/A	N/A	9.39E-04	2.93E+04	9.39E-04	7.24E-08	N/A	N/A	N/A	N/A

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TXG-0198	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	1.58E+05	7.66E-05	4.96E-10	N/A	N/A	N/A	N/A
TXG-0200	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	4.45E+04	8.39E-04	2.21E-08	N/A	N/A	N/A	N/A
TXG-0201	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	3.45E+04	3.56E-04	1.76E-08	N/A	N/A	N/A	N/A
TXG-0202	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	8.69E+04	4.57E-04	5.51E-09	N/A	N/A	N/A	N/A
TXG-0203	2.30E+04	2.98E-04	1.64E-08	3.37E+05	1.13E-04	3.37E-10	6.83E+04	1.18E-04	6.83E+04	1.18E-04	1.73E-09	8.27E+03	2.42E-04	2.96E-08	
TXG-0204	N/A	N/A	N/A	N/A	N/A	N/A	4.61E+05	3.06E-05	4.61E+05	3.06E-05	6.65E-11	N/A	N/A	N/A	
TXG-0209	N/A	N/A	N/A	N/A	N/A	N/A	6.60E+04	4.47E-05	6.60E+04	4.47E-05	6.75E-10	N/A	N/A	N/A	
TXG-0210	N/A	N/A	N/A	N/A	N/A	N/A	1.31E+05	5.61E-05	1.31E+05	5.61E-05	4.36E-10	N/A	N/A	N/A	
TXG-0228	N/A	N/A	N/A	2.92E+04	7.81E-04	2.73E-08	1.74E+05	4.86E-04	1.74E+05	4.86E-04	2.81E-09	N/A	N/A	N/A	
TXG-0230	N/A	N/A	N/A	6.50E+04	4.11E-04	6.38E-09	3.03E+05	1.50E-04	3.03E+05	1.50E-04	4.95E-10	1.79E+04	6.30E-04	3.60E-08	

[0412] In addition, as shown in Table 10, several antibodies were found to be pan-coronavirus antibodies that recognizes a conserved epitope in the S1 subunit and bind with high affinity to the S1 subunit of a new human coronavirus strain HCoV-HKU1 (see, *e.g.*, TXG-0078, TXG-0091, TXG-0112, TXG-0114, TXG-0136, TXG-0187, TXG-0192, TXG-0203, TXG-0228, and TXG-0230 in Tables 6 and 10). It was observed that several antibodies tested in this experiment could bind to human coronavirus strain HCoV-HKU1 in low to mid nanomolar range. Accordingly, without being bound to any particular theory, these antibodies could be particularly useful in therapeutic combination against SARS-CoV-2 and other coronaviruses and in combination with RBD-binding, NTD-binding, or non-S1 binding therapeutic antibodies.

[0413] In addition, as shown in Table 10, several antibodies (*e.g.*, TXG-0060, TXG-0066, TXG-0072, TXG-0076, TXG-0078, TXG-0099, TXG-0104, TXG-0170, TXG-0173, TXG-0174, TXG-0175, and TXG-0230) were found to bind the N-terminal domain of SARS-CoV-2 S protein. Of these antibodies, at least 8 were found to bind the N-terminal domain of SARS-CoV-2 S protein with high affinity (*e.g.*, TXG-0072, TXG-0076, TXG-0078, TXG-0099, TXG-0170, TXG-0173, TXG-0174, TXG-0175, and TXG-0230). Accordingly, these antibodies could be particularly useful in therapeutic combination against SARS-2 with RBD-binding and non-S1 binding therapeutic antibodies.

TABLE 10: Binding affinity of exemplary antibodies to the NTD of SARS-CoV-2 S protein or the S1 subunit of HCoV-HKU1. (ND: not determined).

Antibody	NTD CoV-2 S Kon	NTD CoV-2 S Koff	NTD CoV-2 S KD	HCoV-HKU1 Kon	HCoV-HKU1 Koff	HCoV-HKU1 KD
CTRL-0047	13012.79	0.004982	3.83E-07	ND	ND	ND
CTRL-0053	52597.52	0.000391	7.44E-09	ND	ND	ND
TXG-0053	ND	ND	ND	243770.9	0.00084	3.44E-09
TXG-0054	ND	ND	ND	161075.5	0.00075	4.65E-09
TXG-0058	48648.2	0.002034	4.18E-08	ND	ND	ND
TXG-0060	22766.31	0.002982	1.31E-07	ND	ND	ND
TXG-0064	1154012	0.183146	1.59E-07	ND	ND	ND
TXG-0065	57306.22	0.004817	8.41E-08	ND	ND	ND
TXG-0066	27570.75	0.004265	1.55E-07	ND	ND	ND
TXG-0071	39108.56	7.30E-05	1.87E-09	ND	ND	ND
TXG-0076	27705.56	0.000328	1.18E-08	ND	ND	ND
TXG-0078	111996.1	0.000764	6.82E-09	8688.056	9.34E-05	1.08E-08
TXG-0079	71621.19	0.002013	2.81E-08	ND	ND	ND
TXG-0099	17637.52	0.000584	3.31E-08	ND	ND	ND

TXG-0104	43027.98	0.017182	3.99E-07	ND	ND	ND
TXG-0114	ND	ND	ND	68067.2	0.000592	8.70E-09
TXG-0116	60327.07	0.001364	2.26E-08	ND	ND	ND
TXG-0119	62184.39	0.001371	2.20E-08	ND	ND	ND
TXG-0131	33500.5	0.001244	3.71E-08	ND	ND	ND
TXG-0132	222323.2	0.318149	1.43E-06	ND	ND	ND
TXG-0146	58716.88	0.023037	3.92E-07	ND	ND	ND
TXG-0157	36876.01	0.000619	1.68E-08	ND	ND	ND
TXG-0162	23939.1	0.007035	2.94E-07	ND	ND	ND
TXG-0163	143575.5	0.000286	1.99E-09	ND	ND	ND
TXG-0164	53759.67	0.002474	4.60E-08	ND	ND	ND
TXG-0168	57502.47	0.002876	5.00E-08	ND	ND	ND
TXG-0170	80022.66	0.000666	8.33E-09	ND	ND	ND
TXG-0184	64845.78	0.000342	5.27E-09	ND	ND	ND
TXG-0187	ND	ND	ND	41458.2	0.000426	1.03E-08
TXG-0203	ND	ND	ND	73352.72	0.000346	4.71E-09
TXG-0206	ND	ND	ND	94.34697	0.000547	5.80E-06
TXG-0225	41245.74	4.31E-05	1.05E-09	ND	ND	ND
TXG-0232	28536.16	0.001196	4.19E-08	ND	ND	ND
TXG-0072	50798.68	0.000922	1.81E-08	ND	ND	ND
TXG-0085	ND	ND	ND	113390.6	0.00037552	3.31E-09
TXG-0112	ND	ND	ND	44045.58	0.00051411	1.17E-08
TXG-0136	ND	ND	ND	14774.41	0.00012629	8.55E-09
TXG-0137	42923.26	0.001742	4.06E-08	ND	ND	ND
TXG-0150	ND	ND	ND	152567.3	0.00138289	9.06E-09
TXG-0173	28801.3	0.00078	2.71E-08	ND	ND	ND
TXG-0174	52925.25	0.002852	5.39E-08	ND	ND	ND
TXG-0192	ND	ND	ND	30640.36	0.00061101	1.99E-08
TXG-0227	ND	ND	ND	395483	0.0004037	1.02E-09
TXG-0228	ND	ND	ND	262421.1	0.00072991	2.78E-09
TXG-0229	ND	ND	ND	179675.9	0.00055067	3.06E-09
TXG-0230	35459.9	0.00081	2.29E-08	222367.6	0.00035694	1.61E-09

EXAMPLE 13

Neutralization assays

[0414] All 239 antibodies identified in Example 6 above were screened in addition to 49 control antibodies of known SARS-2 and other viral binding. Assays were performed with a clinical isolate of the SARS-CoV-2 B.1 lineage (MEX-BC2/2020). This virus carries the D614G mutation in the spike protein (full sequence available at the GISAID/EpiCoV database ID: EPI_ISL_747242). The screen was performed with a microneutralization assay that utilizes prevention of the virus-induced cytopathic effect (CPE) in Vero E6 cells. All antibodies (*i.e.*, test-items) were provided at varying concentrations (0.06 to 0.23mg/mL), and they were stored at

4°C until use. The screen was performed in ten different experiments performed in ten days, each one assessing the activity of approximately 30 Abs in parallel. All plates included a positive control—plasma from a convalescent patient who had also received the first dose of the Pfizer/BioNTech mRNA vaccine (BNT162b2). Plasma was collected 21 days after vaccination.

[0415] For this screen, Vero E6 cells were used to evaluate the neutralization activity of the antibody test-items against a replication competent SARS-CoV-2 virus. Antibodies were pre-incubated first with the virus for 1 hour at 37°C before addition to cells. Following pre-incubation of Ab/virus samples, Vero E6 cells were challenged with the mixture. After addition to cells, antibodies were present in the cell culture for the duration of the infection (96 hours), at which time a “*Neutral Red*” uptake assay was performed to determine the extent of the virus-induced CPE. Prevention of the CPE was used as a surrogate marker to determine the neutralization activity of the test-items against SARS-CoV-2.

[0416] Eight dilutions of the antibodies were tested in duplicates for the neutralization assay using a five- fold dilution scheme starting at 1,000 ng/mL. Representative raw data from neutralization assay is shown in **FIGS. 21** and **22**. When possible, IC₅₀ values of the antibodies displaying neutralizing activity were determined using *GraphPad Prism* software. Plasma control was assessed on each plate using singlet data-points (8 two-fold dilutions throughout 1:20480). Representative neutralization curves (IC₅₀) for control antibodies and antibody test-items are shown in **FIGS. 23** and **24**.

Data analysis of CPE-based neutralization assay

[0417] The average absorbance at 540nm (A₅₄₀) observed in infected cells in the presence of vehicle alone was calculated first, and then subtracted from all samples to determine the inhibition of the virus induced CPE. Data points were then normalized to the average A₅₄₀ signal observed in uninfected cells (“mock”) after subtraction of the absorbance signal observed in infected cells.

[0418] In the neutral red CPE-based neutralization assay, uninfected cells remained viable and uptake the dye at higher levels than non-viable cells. In the absence of antibodies, the virus-induced CPE leads to cell death in infected cells and lowers the A₅₄₀ signal (this value equals 0% neutralization). By contrast, incubation with neutralizing antibodies prevents the virus induced CPE and leads to absorbance levels similar to those observed in uninfected cells. Full

recovery of cell viability in infected cells represents 100% neutralization of the virus. Each plate assessed 3 antibodies in triplicates (rows A-C and F-H) or duplicates (rows D and E). However, data analysis avoided samples located in rows A and H to minimize “edge effects.” Therefore, all antibodies were evaluated in duplicates. Uninfected cells and infected cells in the absence of antibodies were analyzed using six replica data-points of each. Control neutralizing plasma was run in singlet data-points (1:160 or 1:320 to 1:20480).

[0419] Every plate was analyzed during a QC step before data was selected for analysis. QC included signal to background values greater than 2.5, and percentage CV in uninfected lower than 20 (CV<20%). All plates passed QC and there was no need to perform repeats. In some instances, data-points identified as outliers may have been removed, or they were exchanged by an additional data-point of the extra row not used (the latter only for antibodies in A-C or F-H). However, these actions were rarely needed, and overall variation of the screen was excellent and within the ranges typically seen in the neutralization studies described herein.

Control inhibitors and quality controls in live SARS-CoV-2 assay

[0420] Quality controls for the infectivity assays were performed on every plate to determine: i) signal to background (S/B) values; ii) inhibition by plasma with neutralizing activity against SARS-CoV-2, and; iii) variation of the assay, as measured by the coefficient of variation (C.V.) of all data points. All controls worked as anticipated for the assay, and variation was within typical ranges seen in vendor laboratories.

[0421] The average of all C.V. (of all duplicate data-points) in each plate was below 10% (average CV 7.1% for the 10 plates, whereas the variation of uninfected controls (“mock”), which were repeated six times on each plate, was below 5% (average 3.2%) (see, *e.g.*, Table 11). The ratio of signal-to-background (S/B) for the neutralization assays, estimated by dividing the average signal in uninfected cells (A540nm) by the average signal in infected cells (vehicle alone), was 4.1-fold for the ten representative plates. When comparing the signal in uninfected cells to the signal in “no-cells” background wells, the S/B ratio of the assay was greater than 10 (data not shown). S/B values and variation for each of the plates are available in the accompanying excel file summary.

[0422] To evaluate the neutralization activity of 288 Abs against SARS-CoV-2, the clinical isolate (MEX- BC2/2020) carrying a D614G mutation in the viral spike protein was

used. Full sequence of this isolate is available at the GISAID/EpiCoV database with the identifier EPI_ISL_747242.

[0423] A CPE-based neutralization assay was performed by infecting Vero E6 cells in the presence or absence of antibodies. Infection of cells leads to significant cytopathic effect and cell death after 4 days of infection. In this screen, reduction of the virus CPE in the presence of antibodies was used as a surrogate marker to determine the neutralization activity of the tested items.

[0424] Vero E6 cells were maintained in DMEM with 10% fetal bovine serum (FBS), referred herein as DMEM10. Twenty-four hours after cell seeding, test samples were submitted to serial dilutions with DMEM with 2% FBS (DMEM2) in a different plate. Then, virus diluted in DMEM2 or DMEM2 alone was pre-incubated with antibody test-items for 1 hour at 37°C in a humidified incubator. Following incubation, media was removed from cells, and then cells were challenged with the SARS-CoV-2 / antibody pre-incubated mix. The amount of viral inoculum was previously titrated to result in a linear response inhibited by antibodies with known neutralizing activity against SARS-CoV-2. Cell culture media with the virus inoculum was not removed after virus adsorption, and antibodies and virus were maintained in the media for the duration of the assay (96 hours). After this period, the extent of cell viability was monitored with the *neutral red* (NR) uptake assay.

[0425] The virus-induced CPE was routinely monitored under the microscope after 3 days of infection, and after 4 days, cells were stained with neutral red to monitor cell viability. Viable cells incorporate neutral red in their lysosomes. The uptake of neutral red relies on the ability of live cells to maintain the pH inside the lysosomes lower than in the cytoplasm, a process that requires ATP. Inside the lysosome, the dye becomes charged and is retained. After a 3-h incubation with neutral red (0.017%), the extra dye is washed away, and the neutral red is extracted from lysosomes by incubating cells for 15 minutes with a solution containing 50% ethanol and 1% acetic acid. The amount of neutral red is estimated by measuring absorbance at 540nm in a plate reader. The general procedure followed to determine the anti-SARS-CoV-2 activity of antibody test-items is summarized in **FIG. 20**.

[0426] In these experiments, antibodies were evaluated in duplicates using five-fold serial dilutions starting at 1 µg/mL. Controls included uninfected cells (“mock-infected”), and

infected cells treated with vehicle alone. Some cells were treated with a positive control plasma derived from a convalescent patient who was also administered the first dose of Pfizer / BioNTech mRNA vaccine (BNT162b2). Plasma was collected 21 days after the vaccine injection.

Results

[0427] Of the antibodies tested against SARS-CoV-2 (lineage B.1, carrying the D614G mutation), approximately 40% of all antibodies displayed measurable neutralization activity. Exemplary antibodies that displayed measurable neutralization activity include TXG-0001, TXG-0002, TXG-0004, TXG-0005, TXG-0006, TXG-0008, TXG-0009, TXG-0048, TXG-0057, TXG-0060, TXG-0063, TXG-0066, TXG-0070, TXG-0072, TXG-0074, TXG-0076, TXG-0078, TXG-0080, TXG-0081, TXG-0088, TXG-0091, TXG-0094, TXG-0098, TXG-0099, TXG-0100, TXG-0104, TXG-0109, TXG-0120, TXG-0126, TXG-0129, TXG-0136, TXG-0141, TXG-0144, TXG-0153, TXG-0154, TXG-0170, TXG-0173, TXG-0174, TXG-0175, TXG-0180, TXG-0181, TXG-0183, TXG-0189, TXG-0197, TXG-0198, TXG-0200, TXG-0201, TXG-0202, TXG-0204, TXG-0209, and TXG-0210.

[0428] Table 11 below provides a summary of neutralization activity of 49 exemplary potentially neutralizing antibodies as determined by IC_{50} in live SARS-CoV-2 assays. Generally, an antibody is determined to potentially neutralize SARS-CoV 2 when its IC_{50} is 1,000 ng/mL or less.

TABLE 11: Neutralization activity of exemplary potentially neutralizing TXG antibodies as determined in testing against SARS-CoV-2 (lineage B.1, carrying the D614G mutation).

Antibody	IC ₅₀ (ng/mL)
CTRL-0003	13887
CTRL-0004	17.7
CTRL-0005	9.7
CTRL-0006	19.4
CTRL-0007	496.5
CTRL-0008	103.6
CTRL-0009	35
CTRL-0010	2460
CTRL-0011	2270
CTRL-0012	630,000
CTRL-0013	666
CTRL-0014	640.8

CTRL-0015	712
CTRL-0016	624.2
CTRL-0021	639,000
CTRL-0026	769.1
CTRL-0027	222.7
CTRL-0028	82034
CTRL-0033	1245
CTRL-0034	561.5
CTRL-0037	1508
CTRL-0038	23.8
CTRL-0039	60.4
CTRL-0040	281.8
CTRL-0041	87,000
CTRL-0043	42069
CTRL-0046	888.9
CTRL-0047	22168
CTRL-0048	798.2
TXG-0001	43.46
TXG-0002	152.7
TXG-0004	89.79
TXG-0005	337.9
TXG-0006	10.99
TXG-0008	457.5
TXG-0009	97.03
TXG-0057	239.5
TXG-0063	88.6
TXG-0066	851
TXG-0069	8.5
TXG-0076	221.1
TXG-0078	170.9
TXG-0080	42.1
TXG-0081	119.7
TXG-0088	65.1
TXG-0091	503.4
TXG-0094	305.8
TXG-0099	572
TXG-0100	141.5
TXG-0104	326.1
TXG-0109	31.8
TXG-0115	159

TXG-0116	452.6
TXG-0120	39
TXG-0126	35.2
TXG-0128	114.2
TXG-0129	14.5
TXG-0132	253.4
TXG-0140	40.2
TXG-0141	602.6
TXG-0144	674.7
TXG-0153	709.9
TXG-0154	21.9
TXG-0170	711.8
TXG-0173	363
TXG-0174	696.5
TXG-0178	19.5
TXG-0180	380.6
TXG-0181	185.7
TXG-0183	658.4
TXG-0189	52.8
TXG-0197	78.7
TXG-0198	350.9
TXG-0200	42
TXG-0201	251.6
TXG-0202	45
TXG-0204	46.6
TXG-0207	499.9
TXG-0209	50
TXG-0210	41.3

[0429] Excluding the 29 control antibodies, at least eighteen (18) of the hits displayed IC₅₀ values below 100 ng/mL, including TXG-0001 (44 ng/mL), TXG-0004 (90 ng/mL), TXG-0006 (11 ng/mL), TXG-0009 (97 ng/mL), TXG-0063 (89 ng/mL), TXG-0080 (42 ng/mL), TXG-0088 (65 ng/mL), TXG-0109 (32 ng/mL), TXG-0120 (39 ng/mL), TXG-0129 (15 ng/mL), TXG-0154 (22 ng/mL), TXG-0189 (53 ng/mL), TXG-0197 (79 ng/mL), TXG-0200 (42 ng/mL), TXG-0202 (45 ng/mL), TXG-0204 (47 ng/mL), TXG-0209 (50 ng/mL), and TXG-0210 (41 ng/mL).

[0430] A summary of the antibodies' neutralization potency is also shown in **FIG. 28**. As indicated in Table 11, the most potent neutralizing antibodies (excluding those identifying as

controls) were TXG-0006, TXG-0129, and TXG-0154.

[0431] In these experiments, positive plasma controls (CS478 pi_vac_pf1, plasma of Pfizer vaccine) were run on every plate to determine the intra-plate and inter-day variation. The average NT50 value and standard deviation of all plates was $2,183 \pm 551$ (CV=25.2%), with lower variation when plates in the same day were evaluated. Of note, NT50 values for the plasma control were generated with dose-response curves using singlet data-points (as compared to duplicates), and that may have increased the variation observed in these controls.

[0432] Additionally, an UpSet plot of antibodies identified as having neutralization activity against live SARS-COV-2 was generated (see, *e.g.*, **FIG. 26**), wherein the antibodies are binned into antigen bins as described in **FIG. 25**. The data described in this figure illustrates that the BEAM-seq process described in the present disclosure allows for rapid identification of many antibodies with broad and robust neutralizing activity against several SARS-CoV-2 S variants of concern (VoC), *e.g.*, beta, gamma, and kappa, as well as HKU1 (which is a different coronavirus).

[0433] In addition, two UpSet plots of the potently ($IC_{50} \leq 1000$ ng / ml) neutralizing antibodies retrieved from the BEAM-seq workflow described herein were generated (see, *e.g.*, **FIGS. 27A and 27B**). **FIG. 27A** is an Upset plot of the potently neutralizing antibodies selected from 239 antibodies identified in Example 6. **FIG. 27B** is an Upset plot of the potently neutralizing antibodies selected from the antibodies of Table 3. In these UpSet plots, rows represent the binding of these neutralizing antibodies to pre-fusion spike trimers from major SARS-CoV-2 variants of concern, the endemic HKU1 coronavirus spike protein and the SARS-CoV-2 N terminal domain. It was also observed that the antibodies identified in these experiments were diverse in their VH, VL, and isotype/subclass (see Table 3). These antibodies were found to use 18 diverse VH genes and 46 unique VH:VL pairings. Taken together, the data described in these figures illustrate that the BEAM-seq process described in the present disclosure allows for rapid identification of many antibodies with potent and broad neutralizing activity against several SARS-CoV-2 S variants of concern (VoC).

EXAMPLE 14

Epitope binning assays

[0434] This Example describes the results of experiments performed to assess binding

characteristics of select antibodies described herein.

Methodology

[0435] 1) Antigens:

[0436] a) Pre-fusion trimerized spike protein from SARS-CoV-2 USA-WA1/2020 isolate, ACRO Biosystems.

[0437] b) Pre-fusion trimerized spike protein from SARS-CoV-2 delta variant, ACRO Biosystems.

[0438] c) SARS-CoV-2 NTD, ACRO Biosystems.

[0439] 2) Surface Plasmon Resonance (SPR) techniques:

[0440] a) Competition/sandwich.

[0441] b) Bidirectional/premix.

[0442] Epitope binning experiments were performed in a premix format using a Carterra LSA SPR biosensor equipped with a HC30M chip at 25°C in HBS-TE (10 mM HEPES pH 7.4, 150 mM NaCl, 3 mM EDTA, 0.05% Tween-20). First, antibodies were amine-coupled to the sensor chip by EDC/NHS activation, followed by ethanolamine HCl quenching. Antibodies and SARS-CoV-2 prefusion stabilized S trimers were combined and incubated for 1 hour in HBS-TE with 0.5 mg/ml BSA at 120 nM and 7.5 nM, respectively. This constituted a 5-molar excess relative to the S trimer antigens, accounting for three (3) binding sites for each molecule. Each premix sample was injected over the immobilized antibodies to determine blocking, partial blocking, or non-blocking activity. The sensor chip was regenerated between injections with Pierce IgG Elution Buffer (Thermo Fisher Scientific).

[0443] Data were analyzed using Carterra's Epitope Tool software. Briefly, blocking assignments were determined relative to the binding responses for S trimer alone (normalized to 1); premixes giving binding responses less than 0.5 were determined to be blocking, 0.5-0.7 were intermediate blocking, and above 0.7 were not blocking. Heat maps representing the competition results were generated where red, yellow, and green cells represent blocked, intermediate, and not blocked analyte/ligand pairs, respectively. A summary of binding characteristics of exemplary antibodies described herein is presented in **FIGS. 29-30** and Table 12 below.

TABLE 12: Epitope binning of exemplary antibodies as determined in testing against a pre-fusion trimerized spike protein from SARS-CoV-2 USA-WA1/2020 isolate (WA1) and/or

SARS-CoV-2 delta variant (Delta) by using SPR competition assay and bidirectional assay. A number of control antibodies (CTRL) were included in these experiments, including: CTRL-0004: Casirivimab; CTRL-0005 (Imdevimab), CTRL-0006: Bamlanivimab; CTRL-0007: (Etesevimab), CTRL-0008: Sotrovimab; and CTRL-0009: Tixagevimab. NA: not applicable.

Other: antibodies capable of binding to an epitope different that the antibodies in any other of the bins identified in the same column of Table 12.

Antibody	WA1	WA1 (bidirectional)	Delta	Delta (bidirectional)
CTRL-0004	4	4	4	4*
CTRL-0005	Bin 3/4	Bin 3/4	Bin 3/4	Bin 3/4
CTRL-0006	Bin 3/4	NA	Other	NA
CTRL-0007	4	4	4	4*
CTRL-0008	3	3	3	NA
CTRL-0009	4	4	4	4*
CTRL-0034	Other	NA	5	NA
CTRL-0038	Bin 3/4	Bin 3/4	Bin 3/4	Bin 3/4
CTRL-0039	Bin 3/4	NA	5	NA
TXG-0001	Bin 3/4	NA	Bin 3/4	NA
TXG-0002	Bin 3/4	NA	Bin 3/4	NA
TXG-0004	Bin 3/4	NA	Bin 3/4	NA
TXG-0005	Bin 3/4	Bin 3/4	Bin 3/4	Bin 3/4
TXG-0006	Bin 3/4	Bin 3/4	Bin 3/4	Bin 3/4
TXG-0008	Bin 3/4	Bin 3/4	Bin 3/4	Bin 3/4
TXG-0009	Bin 3/4	Bin 3/4	Bin 3/4	Bin 3/4
TXG-0057	3	NA	Other	NA
TXG-0060	2	NA	1	NA
TXG-0063	3	3	3	3
TXG-0066	1	1	Bin 1/2	Bin 1/2
TXG-0072	2	NA	Bin 1/2	NA
TXG-0076	Other	NA	Other	NA
TXG-0078	1	1	1	1
TXG-0080	Bin 3/4	NA	5	NA
TXG-0081	Bin 3/4	NA	Other	NA
TXG-0088	Bin 3/4	NA	Other	NA
TXG-0091	3	NA	2	NA
TXG-0094	3	3	3	3
TXG-0099	Other	NA	1	1
TXG-0100	Bin 3/4	NA	Bin 3/4	NA
TXG-0104	1	NA	Other	NA
TXG-0109	4	NA	Other	NA
TXG-0112	Other	NA	Other	NA
TXG-0114	Other	NA	Other	NA
TXG-0115	Bin 3/4	Bin 3/4	5	NA

TXG-0120	3	3	3	NA
TXG-0129	Bin 3/4	NA	Bin 3/4	NA
TXG-0136	1	1	5	NA
TXG-0141	4	NA	Bin 3/4	NA
TXG-0144	4	4	Other	NA
TXG-0153	3	3	Bin 2/3	Bin 2/3
TXG-0154	Bin 3/4	Bin 3/4	Bin 3/4	Bin 3/4
TXG-0170	1	1	2	2
TXG-0173	1	NA	Other	NA
TXG-0174	1	1	2	2
TXG-0175	3	NA	5	NA
TXG-0180	4	4	4	4*
TXG-0181	3	3	3	3
TXG-0183	3	3	Other	NA
TXG-0187	Other	NA	Other	NA
TXG-0189	Bin 3/4	NA	Other	NA
TXG-0192	Other	NA	5	NA
TXG-0197	4	4	4	4*
TXG-0198	4	4	4	4*
TXG-0200	4	4	4	4*
TXG-0201	4	4	4	4*
TXG-0202	4	4	4	4*
TXG-0203	Other	NA	Other	Other
TXG-0204	4	4	4	4*
TXG-0209	4	4	4	4*
TXG-0210	4	NA	Bin 3/4	4*
TXG-0228	Other	NA	Other	Other
TXG-0230	Other	NA	5	5

Data interpretation

[0444] In these experiments, antibodies that share an epitope bin are antibodies which compete for binding to the same epitopes in a dose-dependent manner.

[0445] As shown in the table above and further described below, the discovered antibodies group into five prominent epitope bins. Furthermore, a number of the discovered antibodies group into unique bins outside of the five prominent bins.

A. NTD targeting antibodies

[0446] As shown in Table 12, nine (9) antibodies tested in these epitope binning experiments grouped into WA1 trimer bins 1 or 2. These likely represent antibodies that target NTD of the spike protein from SARS-CoV-2 USA-WA1/2020 isolate (WA1), based on SPR data indicating that antibodies that group into bins 1 and 2 exhibit high (nM) affinity for the NTD of

SARS-CoV-2 S protein and the observation that they do not compete for binding with the antibodies in WA1 trimer bins 3, 4, or 3/4 (which include the FDA-authorized antibodies which have been shown to target RBD epitopes). Of these antibodies, as least fifteen antibodies were found to display measurable neutralization activity as determined by IC₅₀ in live SARS-CoV-2 assays. Examples of antibodies that target NTD of the WA1 isolate and potentially neutralize live SARS-CoV-2 include TXG-0066, TXG-0078, TXG-0104, TXG-0170, TXG-0173, and TXG-0174.

[0447] As shown in Table 12, seven (7) antibodies tested in these epitope binning experiments grouped into delta trimer bins 1, 1/2, or 2. These likely represent antibodies that target NTD of the spike protein from SARS-CoV-2 delta variant, based on SPR data indicating that antibodies that group into these bins exhibit high (nM) affinity for the NTD of SARS-CoV-2 S protein and the observation that they do not compete for binding with the antibodies in delta trimer bins 3, 4, or 3/4 (which include the FDA-authorized antibodies which have been shown to target RBD epitopes). All of these 7 antibodies were found to display measurable neutralization activity as determined by IC₅₀ in live SARS-CoV-2 assays. Examples of antibodies that target NTD of the WA1 isolate and potentially neutralize live SARS-CoV-2 include TXG-0078, TXG-0091, TXG-0099, TXG-0170, and TXG-0174.

[0448] *B. RBD targeting antibodies*

[0449] As shown in Table 12, 36 antibodies tested in these epitope binning experiments grouped into WA1 trimer bins 3, 4, or 3/4. These likely represent antibodies targeting primarily RBD of the spike protein from SARS-CoV-2 USA-WA1/2020 isolate (WA1), based on the observation that they compete for binding with FDA-authorized antibodies which have been shown to target RBD epitopes. All of these 36 antibodies were found to display measurable neutralization activity as determined by IC₅₀ in live SARS-CoV-2 assays. Examples of antibodies that target primarily RBD of the WA1 isolate and potentially neutralize live SARS-CoV-2 include TXG-0001, TXG-0002, TXG-0004, TXG-0005, TXG-0006, TXG-0008, TXG-0009, TXG-0057, TXG-0063, TXG-0080, TXG-0081, TXG-0088, TXG-0091, TXG-0094, TXG-0100, TXG-0109, TXG-0115, TXG-0120, TXG-0129, TXG-0141, TXG-0144, TXG-0153, TXG-0154, TXG-0180, TXG-0181, TXG-0183, TXG-0189, TXG-0197, TXG-0198, TXG-0200, TXG-0201, TXG-0202, TXG-0204, TXG-0209, and TXG-0210.

[0450] As shown in Table 12, eight (8) antibodies tested in these epitope binning experiments grouped into WA1 trimer bin 3, along with CTRL-0008 (sotrovimab). These likely represent antibodies that target a WA1 RBD epitope that is at least partially distinctive from those targeted by bins 3/4 or 4, *e.g.*, a distinctive RBD epitope from those targeted by the tested FDA-approved antibodies save for sotrovimab. All of these 8 antibodies were found to display measurable neutralization activity as determined by IC₅₀ in live SARS-CoV-2 assays. Examples of antibodies in WA1 trimer bin 3 and which potentially neutralize live SARS-CoV-2 include TXG-0057, TXG-0063, TXG-0091, TXG-0094, TXG-0120, TXG-0153, TXG-0181, and TXG-0183.

[0451] As shown in Table 12, 12 antibodies tested in these epitope binning experiments grouped into WA1 trimer bin 4, along with CTRL-0004 (Casirivimab), CTRL-0007 (Etesevimab), and CTRL-0009 (Tixagevimab). These likely represent antibodies that target a WA1 RBD epitope that is at least partially distinctive from those targeted by bins 3 or 3/4. All of these 12 antibodies were found to display potent neutralization activity as determined by IC₅₀ in live SARS-CoV-2 assays. Examples of antibodies in WA1 trimer bin 4 and which potentially neutralize live SARS-CoV-2 include TXG-0109, TXG-0115, TXG-0141, TXG-0144, TXG-0154, TXG-0180, TXG-0197, TXG-0198, TXG-0200, TXG-0201, TXG-0202, TXG-0204, TXG-0209, and TXG-0210.

[0452] Fifteen (15) antibodies tested in these epitope binning experiments grouped into WA1 trimer bin 3/4, along with CTRL-0005 (Imdevimab) and CTRL-0006 (Bamlanivimab). These likely represent antibodies that target a WA1 RBD epitope that is at least partially distinctive from those targeted by bin 3 or bin 4, in that they partially compete with antibodies such bins. All of these antibodies displayed potent neutralization activity as determined by IC₅₀ in live SARS-CoV-2 assays. These antibodies include TXG-0001, TXG-0002, TXG-0004, TXG-0005, TXG-0006, TXG-0008, TXG-0009, TXG-0080, TXG-0081, TXG-0088, TXG-0100, TXG-0115, TXG-0129, TXG-0154, and TXG-0189.

[0453] As shown in Table 12, 25 antibodies tested in these epitope binning experiments grouped into delta trimer bins 3, 4, or 3/4. These likely represent antibodies targeting primarily RBD of the spike protein from SARS-CoV-2 delta variant, based on the observation that they compete for binding with FDA-authorized antibodies which have been shown to target RBD

epitopes. Nearly all of these antibodies also grouped into WA1 trimer bins 3, 4, or 3/4. All of these 25 antibodies were found to display measurable neutralization activity as determined by IC_{50} in live SARS-CoV-2 assays. Examples of antibodies that target primarily RBD of the SARS-CoV-2 delta variant and potentially neutralize live SARS-CoV-2 include TXG-0001, TXG-0002, TXG-0004, TXG-0005, TXG-0006, TXG-0008, TXG-0009, TXG-0063, TXG-0066, TXG-0094, TXG-0100, TXG-0120, TXG-0129, TXG-0141, TXG-0154, TXG-0180, TXG-0181, TXG-0197, TXG-0198, TXG-0200, TXG-0201, TXG-0202, TXG-0204, TXG-0209, and TXG-0210.

[0454] As shown in Table 12, four (4) antibodies tested in these epitope binning experiments grouped into delta trimer bin 3, along with CTRL-0008 (sotrovimab). These likely represent antibodies that target a delta RBD epitope that is at least partially distinctive from those targeted by bins 3/4 or 4, *e.g.*, a distinctive delta RBD epitope from those targeted by the tested FDA-approved antibodies save for sotrovimab. These 4 antibodies also grouped into WAT1 trimer bin 3. All of these 4 antibodies were found to display potent neutralization activity as determined by IC_{50} in live SARS-CoV-2 assays. Antibodies that distinctively target RBD of the SARS-CoV-2 delta variant and potentially neutralize live SARS-CoV-2 include TXG-0063, TXG-0094, TXG-0120, and TXG-0181.

[0455] Eight (8) antibodies tested in these epitope binning experiments grouped into delta trimer bin 4, along with CTRL-0004 (Casirivimab), CTRL-0007 (Etesevimab), and CTRL-0009 (Tixagevimab). These likely represent antibodies that target a delta RBD epitope that is at least partially distinctive from those targeted by bins 3 or 3/4. All of these 8 antibodies were found to display potent neutralization activity as determined by IC_{50} in live SARS-CoV-2 assays. Examples of antibodies in delta trimer bin 4 and which potentially neutralize live SARS-CoV-2 include TXG-0180, TXG-0197, TXG-0198, TXG-0200, TXG-0201, TXG-0202, TXG-0204, and TXG-0209.

[0456] Thirteen (13) antibodies tested in these epitope binning experiments grouped into delta trimer bin 3/4, along with CTRL-0005 (Imdevimab). These likely represent antibodies that target a delta RBD epitope that is at least partially distinctive from those targeted by bin 3 or bin 4, in that they partially compete with antibodies such bins. Of these, 13 display potent neutralization activity as determined by live SARS-CoV-2 assays. Examples of antibodies in

delta trimer bin 3/4 and which potentially neutralize live SARS-CoV-2 include TXG-0001, TXG-0002, TXG-0004, TXG-0005, TXG-0006, TXG-0008, TXG-0009, TXG-0066, TXG-0100, TXG-0129, TXG-0141, TXG-0154, and TXG-0210.

[0457] C. Other epitopes

[0458] Nine (9) antibodies tested in these epitope binning experiments grouped into WA1 trimer bins “Other”. These likely represent antibodies that target epitopes that are distinctive from the epitopes targeted by any other of the WA1 trimer bins. Exemplary antibodies in these categories include TXG-0076, TXG-0099, TXG-0112, TXG-0114, TXG-0187, TXG-0192, TXG-0203, TXG-0228, and TXG-0230. Of these eleven antibodies, at least two are potent neutralizers. Example antibodies that belong in the WA1 trimer “Other” bin and potentially neutralize live SARS-CoV-2 include TXG-0076 and TXG-0099. Of these nine antibodies, at least TXG-0099 exhibits high (nM) affinity for WT spike and the gamma, kappa, and beta variants by SPR. Of these nine antibodies, at least eight exhibit nanomolar affinity for NTD. Example antibodies that belong in the WA1 trimer “Other” and exhibit high (nM) affinity for NTD include TXG-0076, TXG-0099, TXG-0112, TXG-0114, TXG-0187, TXG-0192, TXG-0203, and TXG-0230. Of these nine antibodies, at least seven exhibit nanomolar affinity for HKU. Example antibodies that belong in the WA1 trimer “Other” bin and exhibit nanomolar affinity for HKU include TXG-0112, TXG-0114, TXG-0187, TXG-0192, TXG-0203, TXG-0228, and TXG-0230.

[0459] Nine (9) antibodies tested in these epitope binning experiments grouped into delta trimer bin 5. These likely represent antibodies that target a distinct delta variant epitope from other binned groups, *e.g.*, distinct from any of the tested FDA approved antibodies. Exemplary antibodies in this category include TXG-0080, TXG-0115, TXG-0136, TXG-0175, TXG-0192, and TXG-0230. Of these, three display potent neutralization activity as determined by live SARS-CoV-2 assays. Examples of antibodies in delta trimer bin 5 and which potentially neutralize live SARS-CoV-2 include TXG-0080, TXG-0115, and TXG-0175.

[0460] Fifteen (15) antibodies tested in these epitope binning experiments grouped into delta trimer bins “Other”, along with CTRL-0006 (bamlanivimab). These likely represent antibodies that target epitopes that are distinctive from the epitopes targeted by any other of the delta trimer bins. Exemplary antibodies in these categories include TXG-0057, TXG-0076,

TXG-0081, TXG-0088, TXG-0104, TXG-0109, TXG-0112, TXG-0114, TXG-0144, TXG-0173, TXG-0183, TXG-0187, TXG-0189, TXG-0203, and TXG-0228. Of these 15 antibodies, 10 exhibit potent neutralization activity. Examples of antibodies in delta trimer bin “Other” and which potently neutralize live SARS-CoV 2 include TXG-0057, TXG-0076, TXG-0081, TXG-0088, TXG-0104, TXG-0109, TXG-0144, TXG-0173, TXG-0183, and TXG-0189. Of these 15 antibodies, at least 12 exhibit high (nM) affinity for WT spike and the kappa and gamma variants by SPR, and at least 9 exhibit high (nM) affinity for WT spike and the beta, gamma, and kappa variants by SPR. Exemplary antibodies that belong in the delta trimer “Other” bin and exhibit high (nM) affinity for WT spike and the gamma and kappa variants include TXG-0057, TXG-0076, TXG-0104, TXG-0109, TXG-0112, TXG-0114, TXG-0144, TXG-0173, TXG-0183, TXG-0187, TXG-0203, and TXG-0228. Exemplary antibodies that belong in the delta trimer “Other “ bin and exhibit high (nM) affinity for WT spike and the beta, gamma, and kappa variants include TXG-0057, TXG-0109, TXG-0112, TXG-0114, TXG-0144, TXG-0183, TXG-0187, TXG-0203, and TXG-0228.

[0461] Antibodies that group into different epitope bins can advantageously be used in a therapeutic antibody cocktail or combination therapy regimen. For example, a neutralizing antibody from bin A can thus be combined with a neutralizing antibody from bin B effectively as the two antibodies do not bind in the same location. Examples of such complementary bins that may be advantageously used in a combination therapy or antibody cocktail include:

[0462] NTD and RBD targeting combination:

- a. Antibody 1: an antibody from bin 1 or bin 2, both of which represent NTD-binding antibodies
- b. Antibody 2: an antibody from bin 3, 4, or 3/4, which represent antibodies targeting primarily RBD

[0463] RBD distinctive targeting combination:

- a. Antibody 1: an antibody from bin 3 (sotrovimab-like antibodies)
- b. Antibody 2: an antibody from bin 4

[0464] RBD partially distinctive targeting combination:

- a. Antibody 1: an antibody from bin 3 or 4
- b. Antibody 2: an antibody from bin 3/4 which partially competes with an antibody

from bin 3 or 4.

EXAMPLE 15

LNP and pharmacokinetic (pK) studies

[0465] This Example describes the results of experiments demonstrating that antibodies described in the present disclosure can be administered to subjects using lipid nanoparticles (LNP) as delivery vehicle and subsequently be detected in animal pK models. Some experiments described in this Example are performed to demonstrate that antibodies of defined affinities and antigen specificities can exert protective functions through non-neutralizing and neutralizing activities.

[0466] In these experiments, twenty (20) antibodies are selected based on their relevant binding affinity, functional information, nucleotide coding sequences, including the rearranged VDJ/VJ and constant region identities. This study includes both neutralizing (n=13) and non-neutralizing antibodies (n=7) with IgM, IgA, and IgG isotypes as indicated in Table 13 below.

TABLE 13: Twenty (20) antibodies selected for LNP and pharmacokinetic studies. O escape: broad recognition of SARS-CoV-2 variants but no recognition of omicron variant.

Antibody	Neutralizing activity	Bin	Isotype	Binding affinity	Pan
TXG-0048	No	Other	IgA1	$\alpha, \beta, \gamma, \kappa$	OC-43
TXG-0070	No	Other	IgG1	All	OC-43
TXG-0087	No	Other	IgG2	γ	None
TXG-0114	No	Other (NTD)	IgM	All	Ultra-broad
TXG-0175	No	RBD	IgG1	$\alpha, \beta, \gamma, \kappa$	None
TXG-0192	No	Other (NTD)	IgM	All	Ultra-broad
TXG-0203	No	Other (NTD)	IgM	All	Ultra-broad
TXG-0001	Yes	RBD	IgG1	O escape	None
TXG-0002	Yes	RBD	IgG1	O escape	None
TXG-0004	Yes	RBD	IgG1	O escape	None
TXG-0005	Yes	RBD	IgA1	O escape	None
TXG-0006	Yes	RBD	IgG1	O escape	OC-43

TXG-0008	Yes	RBD	IgG1	O escape	None
TXG-0009	Yes	RBD	IgG2	O escape	None
TXG-0078	Yes	NTD	IgG1	O escape	Ultra-broad
TXG-0081	Yes	RBD	IgA1	WA1, O	None
TXG-0115	Yes	RBD	IgM	All	None
TXG-0154	Yes	RBD	IgM	All	OC-43
TXG-0174	Yes	NTD	IgM	All	None
TXG-0180	Yes	RBD	IgG1	All	None

[0467] mRNA-containing LNPs of each candidate antibody are manufactured according to the methods described above. These LNPs are injected into mice for pK studies with a duration of 1 week, with a total of 5 mice per antibody candidate (100 mice total). At least 5 time-points are collected and measured, every 12 hours over the first 2 days and then minimally at least one more time point 96 hours after injection. It is expected that one or more of the antibodies are successfully detected via anti-human immunoglobulin secondary antibodies recognizing the corresponding human IgM, IgA, and IgG isotypes, *e.g.*, at a concentration of ≥ 100 ng/ml peak serum levels .

[0468] *In vivo functional studies*

[0469] Sufficient LNP for each antibody is used to passively immunize Syrian hamsters (5-8 hamsters are tested per antibody). These Syrian hamsters are then challenged with a lethal concentration of live SARS-CoV-2 virus (strain 2019nCoV/USA-WA01/2020). In these experiments, the primary endpoint is survival; the secondary endpoint is prevention of weight loss; and additional exploratory endpoints include detectable viral subgenomic RNAs and infectious plaque-forming units in lung and affected tissue. Hamsters in the control/comparator group (n=8) receive LNPs containing a non-translating Factor IX RNA (NTFIX). The experiments are completed over the course of 3 months' time. It is expected that at least one antibody shows differential protection from death or weight loss during the challenge studies, as measured by comparison to the sham-treated hamsters, of which a large number (50%) are expected to die and/or lose significant body weight.

EXAMPLE 16

Structural definition of a broadly conserved NTD neutralizing epitope

[0470] This Example describes the results of experiments performed to characterize structural features of the epitope to which TXG-0078 binds. It was noted that although a number of NTD-specific nAbs have been reported, none exhibited the breadth of TXG-0078, making the specific molecular interactions between the antibody and its target particularly important. Experiments were performed to obtain a 3.9Å cryo-EM reconstruction of TXG-0078 in complex with the WA1 SARS-CoV-2 Spike (see, e.g., **FIG. 32A**). It was observed that TXG-0078 has an angle of approach similar to that of 4A8, a previously reported (Chi et al. 2020) NTD-specific nAb (see, e.g., **FIG. 32B**), with binding interactions between all three heavy chain complementarity determining region (CDR) loops and the N3 and N5 loops of NTD (see, e.g., **FIG. 32C**). Separately, a separate 3Å negative-stain EM image of TXG-0078 Fab in complex with the spike trimer from SARS-CoV-2 Wuhan entry strain (WT) was also obtained to confirm the angle of approach (see, e.g., **FIG. 32D**).

[0471] The cryo-EM studies show that TXG-0078 is an NTD supersite-targeting antibody. Such NTD supersite-targeting antibodies arise in response to SARS-CoV-2 infection but have not been known to broadly target other human coronaviruses. However, as disclosed herein, TXG-0078 has picomolar affinity to the WA-1/2020, beta, kappa, and gamma variants of SARS-CoV-2, and micromolar affinity to the spike proteins of the OC-43, HKU1, and 229E endemic human coronaviruses. This result is surprising, and highlights TXG-0078 as a broadly neutralizing antibody that targets the NTD domain of the spike protein and that broadly target a large number of SARS-CoV2 variants as well as other endemic human coronaviruses.

EXAMPLE 17

In vivo studies in mouse model confirms prophylactic efficacy of TXG-0078

[0472] This Example describes the results of experiments performed in mouse models demonstrating that antibodies described in the present disclosure can prophylactically protect mice from *in vivo* SARS-CoV-2 challenge.

Animal challenge study

[0473] Each group (n=5) was passively immunized with 20 µg of each mAb through intraperitoneal injections 24 hours prior to infection. Mice were infected with 30,000 FFU of

SARS-CoV-2 (WA1/2020). Mice were weighed daily, and percent baseline weight was calculated relative to day 0 weight. On day 5, mice were euthanized and lung lobes were extracted for viral titer quantification.

[0474] In these experiments, 20 µg of prophylactic antibody was administered to a total of 15 ACE2 transgenic mice in 3 treatment groups: (i) TXG-0078, (ii) anti-RBD antibody, and (iii) Control antibody. In these experiments, the Control antibody was an antibody targeting a different virus species, Zika virus (ZIKV), and the anti-RBD antibody was a RBD-targeting pan-coronavirus antibody which was markedly broader and less potent than TXG-0078.

[0475] Each mouse was weighed at Day 0 (baseline), and weighed daily for another 5 days before sacrifice. It was observed that mice receiving TXG-0078 were protected from weight loss and showed reduced viral load in the lung (see, e.g., **FIGS. 33A-33B**). These results demonstrate a markedly superior prophylactic effect of the TXG-0078 antibody as compare to the reference anti-RBD antibody.

[0476] It was observed that although the anti-RBD antibody used in this experiment was markedly broader than TXG-0078, it was less potent; the IC₅₀ of TXG-0078 against SARS-CoV-2 in these experiments was 170 ng/ml. Without being bound to any particular theory, it is believed that the anti-RBD antibody used in this experiment and similar antibodies could arise easily given the correct immune stimuli.

EXAMPLE 18

In vivo studies assessing prophylactic efficacy of cocktails of antibodies targeting different epitopes

[0477] This Example describes experiments performed in mouse models to demonstrate that therapeutic cocktails of antibodies targeting different epitope regions of the spike protein can provide superior protection *in vivo* to SARS-CoV-2 challenge.

[0478] In these experiments, each group (n=10) is passively immunized with 20 µg of each antibody cocktail through intraperitoneal injections 24 hours prior to infection. Mice are infected with 30,000 FFU of SARS-CoV-2. The SARS-CoV-2 can be WA1/2020, a beta variant, a gamma variant, a kappa variant, a delta variant, or an omicron variant (e.g., BA.4 variant, BA.5 variant, BA.2 variant such as BA.2.75). Mice are weighed daily, and percent baseline weight is calculated relative to day 0 weight. On day 5, mice were euthanized and lung lobes were

extracted for viral titer quantification.

[0479] In these experiments, 20 µg of prophylactic antibody is administered to a total of 50 ACE2 transgenic mice in 5 treatment groups:

[0480] (1) Groups 1-3 are administered with antibody cocktail comprising:

[0481] (i) a potentially neutralizing NTD-targeting antibody with binding affinity for the omicron variant of SARS-CoV-2 or at least one endemic human coronaviruses (HCoV)(i.e., containing TXG-0078, TXG-0099, or TXG-0174 in Groups 1, 2, and 3, respectively), and

[0482] (ii) a neutralizing RBD antibody with binding affinity for the omicron variant of SARS-CoV-2 and at least one endemic human coronaviruses (HCoV): TXG-0091

[0483] (1) Group 4 is administered with Control 1 containing only anti-RBD antibody, and

[0484] (2) Group 5 is administered with Control 2 containing only potentially neutralizing NTD-targeting antibody.

[0485] Each mouse is weighed at Day 0 (baseline), and is weighed daily for another 5 days before sacrifice. It is predicted that mice of Groups 1-3 receiving an antibody cocktail are better protected from weight loss and show reduced viral load in the lung, to demonstrate a markedly superior prophylactic effect of the antibody cocktail as compared to Groups 4 and 5.

[0486] While particular alternatives of the present disclosure have been disclosed, it is to be understood that various modifications and combinations are possible and are contemplated within the true spirit and scope of the appended claims. There is no intention, therefore, of limitations to the exact abstract and disclosure herein presented.

CLAIMS

WHAT IS CLAIMED IS:

1. A composition comprising a nucleic acid encoding an antigen-binding molecule, or an antigen-binding fragment thereof, that binds to a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), wherein the antigen-binding molecule or antigen-binding fragment thereof comprises all six complementary determining regions (CDRs) from an antibody identified in Tables 1A-1B, and wherein optionally the composition is formulated in a lipid-based nanoparticle (LNP).
2. A composition comprising an antigen-binding molecule, or an antigen-binding fragment thereof, that binds to a SARS-CoV-2, wherein the antigen-binding molecule or antigen-binding fragment thereof comprises all six CDRs from an antibody identified in Tables 1A-1B, and wherein optionally the composition is formulated in a lipid-based nanoparticle (LNP).
3. The composition of any one of claims 1 to 2, wherein the antigen-binding molecule is any one of TXG-0001, TXG-0002, TXG-0004, TXG-0005, TXG-0006, TXG-0008, TXG-0009, TXG-0048, TXG-0057, TXG-0060, TXG-0063, TXG-0066, TXG-0070, TXG-0072, TXG-0074, TXG-0076, TXG-0078, TXG-0080, TXG-0081, TXG-0087, TXG-0088, TXG-0091, TXG-0094, TXG-0098, TXG-0099, TXG-0100, TXG-0104, TXG-0109, TXG-0112, TXG-0114, TXG-0115, TXG-0120, TXG-0129, TXG-0136, TXG-0141, TXG-0144, TXG-0153, TXG-0154, TXG-0170, TXG-0173, TXG-0174, TXG-0175, TXG-0180, TXG-0181, TXG-0183, TXG-0187, TXG-0189, TXG-0192, TXG-0197, TXG-0198, TXG-0200, TXG-0201, TXG-0202, TXG-0203, TXG-0204, TXG-0209, TXG-0210, TXG-0228, or TXG-0230.
4. The composition of any one of claims 1 to 3, wherein the antigen-binding molecule or antigen-binding fragment thereof comprises all six complementary determining regions (CDRs) from an antibody being any one of TXG-0001, TXG-0002, TXG-0004, TXG-0005, TXG-0006, TXG-0008, TXG-0009, TXG-0048, TXG-0070, TXG-0078, TXG-0081, TXG-0087, TXG-0114, TXG-0115, TXG-0154, TXG-0174, TXG-0175, TXG-0180, TXG-0192, or TXG-0203.
5. The composition of any one of claims 1 to 4, wherein the antigen-binding molecule or antigen-binding fragment thereof has a binding affinity for a spike (S) protein of SARS-CoV-2.

6. The composition of any one of claims 1 and 3-5, wherein the nucleic acid is a DNA molecule or an RNA molecule.
7. The composition of claim 5, wherein the RNA molecule is a messenger RNA (mRNA) molecule.
8. The composition of any one of claims 6 to 7, wherein the nucleic acid comprises one or more modified nucleosides.
9. The composition of claim 8, wherein the one or more modified nucleosides comprises pyridin-4-one ribonucleoside, 5-aza-uridine, 2-thio- 5-aza-uridine, 2-thiouridine, 4-thio-pseudouridine, 2-thio-pseudouridine, 5- hydroxyuridine, 3-methyluridine, 5-carboxymethyl-uridine, 1-carboxymethyl- pseudouridine, 5-propynyl-uridine, 1-propynyl-pseudouridine, 5-taurinomethyluridine, 1- taurinomethyl-pseudouridine, 5-taurinomethyl-2-thio-uridine, 1 -taurinomethyl-4-thio- uridine, 5-methyl-uridine, 1-methyl-pseudouridine, 4-thio-1-methyl-pseudouridine, 2- thio- 1 -methyl-pseudouridine, 1 -methyl- 1 -deaza-pseudouridine, 2-thio- 1 -methyl- 1 -deaza- pseudouridine, dihydrouridine, dihydropseudouridine, 2-thio-dihydrouridine, 2-thio- dihydropseudouridine, 2-methoxyuridine, 2-methoxy-4-thio-uridine, 4-methoxy-pseudouridine, 4-methoxy-2-thio-pseudouridine, 5-aza-cytidine, pseudoisocytidine, 3- methyl-cytidine, N4-acetylcytidine, 5-formylcytidine, N4-methylcytidine, 5- hydroxymethylcytidine, 1 -methyl-pseudoisocytidine, pyrrolo-cytidine, pyrrolo- pseudoisocytidine, 2-thio-cytidine, 2-thio-5-methyl-cytidine, 4-thio-pseudoisocytidine, 4- thio- 1 -methyl-pseudoisocytidine, 4-thio- 1 -methyl- 1 -deaza-pseudoisocytidine, 1 -methyl- 1 -deaza-pseudoisocytidine, zebularine, 5-aza-zebularine, 5-methyl-zebularine, 5-aza-2- thio-zebularine, 2-thio-zebularine, 2-methoxy-cytidine, 2-methoxy-5-methyl-cytidine, 4- methoxy-pseudoisocytidine, 4-methoxy- 1 -methyl-pseudoisocytidine, 2-aminopurine, 2, 6-diaminopurine, 7-deaza-adenine, 7-deaza-8-aza-adenine, 7-deaza-2-aminopurine, 7- deaza-8-aza-2-aminopurine, 7-deaza-2,6-diaminopurine, 7-deaza-8-aza-2,6- diaminopurine, 1 -methyladenosine, N6-methyladenosine, N6-isopentenyladenosine, N6- (cis-hydroxyisopentenyl)adenosine, 2-methylthio-N6-(cis-hydroxyisopentenyl) adenosine, N6-glycinylocarbamoyladenosine, N6-threonylocarbamoyladenosine, 2- methylthio-N6-threonyl carbamoyladenosine, N6,N6-dimethyladenosine, 7- methyladenine, 2-methylthio-adenine, and 2-methoxy-adenine, inosine, 1 -methyl-inosine, wyosine, wybutosine, 7-deaza-guanosine, 7-deaza-

8-aza-guanosine, 6-thio-guanosine, 6-thio-7-deaza-guanosine, 6-thio-7-deaza-8-aza-guanosine, 7-methyl-guanosine, 6-thio-7-methyl-guanosine, 7-methylinosine, 6-methoxy-guanosine, 1-methyl-guanosine, N2-methyl-guanosine, N2,N2-dimethyl-guanosine, 8-oxo-guanosine, 7-methyl-8-oxo-guanosine, 1-methyl-6-thio-guanosine, N2-methyl-6-thio-guanosine, and N2,N2-dimethyl-6-thio-guanosine, and combinations thereof.

10. The composition of any one of claims 1 to 9, wherein the lipid nanoparticle comprises an ionizable cationic lipid, a cationic lipid, an anionic lipid, a neutral lipid, a sterol, a PEG-modified lipid, or a combination of any thereof.

11. The composition of claim 10, wherein the lipid nanoparticle further comprises phosphatidyl choline.

12. The composition of claim 10, wherein the sterol is cholesterol.

13. The composition of any one of claims 1 to 12, wherein the mean ratio of lipid to nucleic acid (wt/wt) ranges from about 2:1 to about 100:1.

14. The composition of any one of claims 1 to 13, wherein the LNP has a mean diameter ranging from about 10 nm to about 200 nm.

15. The composition of any one of claims 1 to 14, wherein the antigen-binding molecule or antigen-binding fragment has a binding affinity for the spike (S) protein of two, three, four, five or more variants of SARS-CoV-2.

16. The composition of claim 15, wherein the SARS-CoV-2 variants comprise any one of alpha, beta, delta, gamma, kappa, omicron, or a combination thereof.

17. The composition of claim 16, wherein at least one of the SARS-CoV-2 variants is omicron.

18. The composition of any one of claims 1 to 17, wherein the antigen-binding molecule or antigen-binding fragment further has a binding affinity for one or more human coronaviruses (HCoV) being any one of HCoV-229E, HCoV-OC43, HCoV-HKU1, or a variant of any thereof, or a combination thereof.

19. The composition of claim 18, wherein the one or more HCoV is any one of HCoV-229E, HCoV-OC43, or a combination thereof.
20. The composition of any one of claims 1 to 18, wherein the antigen-binding molecule or antigen-binding fragment has a sub-nanomolar binding affinity for a spike (S) protein of SARS-CoV-2, a fragment thereof, or a multimeric form thereof.
21. The composition of any one of claims 1 to 20, wherein the antigen-binding molecule or antigen-binding fragment has a sub-picomolar binding affinity for a SARS-CoV-2 S protein, a fragment thereof, or a multimeric form thereof.
22. The composition of any one of claims 1 to 21, wherein the antigen-binding molecule or antigen-binding fragment thereof has a binding affinity for S1 subunit of the SARS-CoV-2 S protein.
23. The composition of claim 22, wherein the antigen-binding molecule or antigen-binding fragment thereof has a binding affinity for a receptor binding domain (RBD) and/or a N-terminal domain (NTD) of the S1 subunit.
24. The composition of claim 23, wherein the antigen-binding molecule or antigen-binding fragment has a binding affinity to the NTD of the S1 subunit.
25. The composition of any one of claims 1 to 24, wherein the antigen-binding molecule or antigen-binding fragment thereof has binding affinity for a trimeric form of the SARS-CoV-2 S protein.
26. The composition of any one of claims 1 to 25, wherein the antigen-binding molecule or antigen-binding fragment thereof comprises all framework regions (FWRs) from the antibody selected from Tables 1A-1B.
27. The composition of any one of claims 3 to 26, wherein the antigen-binding molecule or antigen-binding fragment thereof comprises all framework regions (FWRs) from the antibody being any one of TXG-0001, TXG-0002, TXG-0004, TXG-0005, TXG-0006, TXG-0008, TXG-0009, TXG-0048, TXG-0057, TXG-0060, TXG-0063, TXG-0066, TXG-0070, TXG-0072,

TXG-0074, TXG-0076, TXG-0078, TXG-0080, TXG-0081, TXG-0087, TXG-0088, TXG-0091, TXG-0094, TXG-0098, TXG-0099, TXG-0100, TXG-0104, TXG-0109, TXG-0112, TXG-0114, TXG-0115, TXG-0120, TXG-0129, TXG-0136, TXG-0141, TXG-0144, TXG-0153, TXG-0154, TXG-0170, TXG-0173, TXG-0174, TXG-0175, TXG-0180, TXG-0181, TXG-0183, TXG-0187, TXG-0189, TXG-0192, TXG-0197, TXG-0198, TXG-0200, TXG-0201, TXG-0202, TXG-0203, TXG-0204, TXG-0209, TXG-0210, TXG-0228, or TXG-0230.

28. The composition of any one of claims 1 to 27, wherein the antigen-binding molecule or antigen-binding fragment further comprises a heavy chain constant region.

29. The composition of claim 28, wherein the heavy chain constant region is an IgA, IgD, IgE, IgG, or IgM heavy chain constant region.

30. The composition of any one of claims 28 to 29, wherein the heavy chain constant region is of the same isotype and subclass as the antibody identified in Tables 1A-1B.

31. The composition of any one of claims 28 to 29, wherein the heavy chain constant region is of the same isotype and subclass as the antibody being any one of TXG-0001, TXG-0002, TXG-0004, TXG-0005, TXG-0006, TXG-0008, TXG-0009, TXG-0048, TXG-0057, TXG-0060, TXG-0063, TXG-0066, TXG-0070, TXG-0072, TXG-0074, TXG-0076, TXG-0078, TXG-0080, TXG-0081, TXG-0087, TXG-0088, TXG-0091, TXG-0094, TXG-0098, TXG-0099, TXG-0100, TXG-0104, TXG-0109, TXG-0112, TXG-0114, TXG-0115, TXG-0120, TXG-0129, TXG-0136, TXG-0141, TXG-0144, TXG-0153, TXG-0154, TXG-0170, TXG-0173, TXG-0174, TXG-0175, TXG-0180, TXG-0181, TXG-0183, TXG-0187, TXG-0189, TXG-0192, TXG-0197, TXG-0198, TXG-0200, TXG-0201, TXG-0202, TXG-0203, TXG-0204, TXG-0209, TXG-0210, TXG-0228, or TXG-0230.

32. The composition of any one of claims 1 to 31, wherein the antigen-binding molecule or antigen-binding fragment further comprises a light chain constant region.

33. The composition of claim 32, wherein the light chain constant region is a kappa type or lambda type light chain constant region.

34. The composition of any one of claims 32 to 33, wherein the light chain constant region is the same light chain constant region of the antibody identified in Tables 1A-1B.

35. The composition of any one of claims 32 to 33, wherein the light chain constant region is the same light chain constant region of the antibody being any one of TXG-0001, TXG-0002, TXG-0004, TXG-0005, TXG-0006, TXG-0008, TXG-0009, TXG-0048, TXG-0057, TXG-0060, TXG-0063, TXG-0066, TXG-0070, TXG-0072, TXG-0074, TXG-0076, TXG-0078, TXG-0080, TXG-0081, TXG-0087, TXG-0088, TXG-0091, TXG-0094, TXG-0098, TXG-0099, TXG-0100, TXG-0104, TXG-0109, TXG-0112, TXG-0114, TXG-0115, TXG-0120, TXG-0129, TXG-0136, TXG-0141, TXG-0144, TXG-0153, TXG-0154, TXG-0170, TXG-0173, TXG-0174, TXG-0175, TXG-0180, TXG-0181, TXG-0183, TXG-0187, TXG-0189, TXG-0192, TXG-0197, TXG-0198, TXG-0200, TXG-0201, TXG-0202, TXG-0203, TXG-0204, TXG-0209, TXG-0210, TXG-0228, or TXG-0230.

36. A method for reducing binding of a spike protein of a coronavirus (CoV-S) to a cell in a subject and/or reducing entry of the coronavirus into a cell of a subject, wherein the method comprising therapeutically or prophylactically administering to the subject:

(a) an antigen-binding molecule, or an antigen-binding fragment thereof, that binds to a spike (S) protein of SARS-CoV-2, wherein the antigen-binding molecule or antigen-binding fragment thereof comprises all six CDRs from an antibody being any one of TXG-0001, TXG-0002, TXG-0004, TXG-0005, TXG-0006, TXG-0008, TXG-0009, TXG-0048, TXG-0057, TXG-0060, TXG-0063, TXG-0066, TXG-0070, TXG-0072, TXG-0074, TXG-0076, TXG-0078, TXG-0080, TXG-0081, TXG-0087, TXG-0088, TXG-0091, TXG-0094, TXG-0098, TXG-0099, TXG-0100, TXG-0104, TXG-0109, TXG-0112, TXG-0114, TXG-0115, TXG-0120, TXG-0129, TXG-0136, TXG-0141, TXG-0144, TXG-0153, TXG-0154, TXG-0170, TXG-0173, TXG-0174, TXG-0175, TXG-0180, TXG-0181, TXG-0183, TXG-0187, TXG-0189, TXG-0192, TXG-0197, TXG-0198, TXG-0200, TXG-0201, TXG-0202, TXG-0203, TXG-0204, TXG-0209, TXG-0210, TXG-0228, or TXG-0230,

and wherein the antigen-binding molecule or antigen-binding fragment thereof has a binding affinity for the spike (S) protein of two, three, four, five or more variants of SARS-CoV-2, and/or for one or more human coronaviruses (HCoVs) is any one of HCoV-229E, HCoV-OC43, HCoV-HKU1, or a variant of any thereof, or a combination thereof; and/or

(b) a nucleic acid encoding the antigen-binding molecule or antigen-binding fragment thereof of (a).

37. A method for inducing an immune response in a subject, the method comprising therapeutically or prophylactically administering to the subject a composition according to any one of claims 1 to 35.

38. A method for aiding in the neutralization of two, three, four, five or more variants of SARS-CoV-2, wherein said aiding comprises providing:

(a) an antigen-binding molecule, or an antigen-binding fragment thereof, that binds to a spike (S) protein of SARS-CoV-2, wherein the antigen-binding molecule or antigen-binding fragment thereof comprises all six CDRs from an antibody being any one of TXG-0001, TXG-0002, TXG-0004, TXG-0005, TXG-0006, TXG-0008, TXG-0009, TXG-0048, TXG-0057, TXG-0060, TXG-0063, TXG-0066, TXG-0070, TXG-0072, TXG-0074, TXG-0076, TXG-0078, TXG-0080, TXG-0081, TXG-0087, TXG-0088, TXG-0091, TXG-0094, TXG-0098, TXG-0099, TXG-0100, TXG-0104, TXG-0109, TXG-0112, TXG-0114, TXG-0115, TXG-0120, TXG-0129, TXG-0136, TXG-0141, TXG-0144, TXG-0153, TXG-0154, TXG-0170, TXG-0173, TXG-0174, TXG-0175, TXG-0180, TXG-0181, TXG-0183, TXG-0187, TXG-0189, TXG-0192, TXG-0197, TXG-0198, TXG-0200, TXG-0201, TXG-0202, TXG-0203, TXG-0204, TXG-0209, TXG-0210, TXG-0228, or TXG-0230; and/or

(b) a nucleic acid encoding the antigen-binding molecule or antigen-binding fragment thereof of (a).

39. A method for aiding in the neutralization of two, three, four, five or more variants of SARS-CoV-2, wherein said aiding comprises providing a composition according to any one of claims 3 to 35.

40. A method for reducing a viral load of two, three, four, five or more variants of SARS-CoV-2, the method comprises providing:

(a) an antigen-binding molecule, or an antigen-binding fragment thereof, that binds to a spike (S) protein of SARS-CoV-2, wherein the antigen-binding molecule or antigen-binding fragment thereof comprises all six CDRs from an antibody being any one of TXG-0001, TXG-0002, TXG-0004, TXG-0005, TXG-0006, TXG-0008, TXG-0009, TXG-0048, TXG-0057, TXG-0060, TXG-

0063, TXG-0066, TXG-0070, TXG-0072, TXG-0074, TXG-0076, TXG-0078, TXG-0080, TXG-0081, TXG-0087, TXG-0088, TXG-0091, TXG-0094, TXG-0098, TXG-0099, TXG-0100, TXG-0104, TXG-0109, TXG-0112, TXG-0114, TXG-0115, TXG-0120, TXG-0129, TXG-0136, TXG-0141, TXG-0144, TXG-0153, TXG-0154, TXG-0170, TXG-0173, TXG-0174, TXG-0175, TXG-0180, TXG-0181, TXG-0183, TXG-0187, TXG-0189, TXG-0192, TXG-0197, TXG-0198, TXG-0200, TXG-0201, TXG-0202, TXG-0203, TXG-0204, TXG-0209, TXG-0210, TXG-0228, or TXG-0230; and/or

(b) a nucleic acid encoding the antigen-binding molecule or antigen-binding fragment thereof of (a).

41. A method for reducing the viral load of two, three, four, five or more variants of SARS-CoV-2, wherein said method comprises providing a composition according to any one of claims 3 to 35.

42. A method of any one of claims 36 to 41, wherein the antigen-binding molecule or antigen-binding fragment thereof comprises all six complementary determining regions (CDRs) from an antibody being any one of TXG-0001, TXG-0002, TXG-0004, TXG-0005, TXG-0006, TXG-0008, TXG-0009, TXG-0048, TXG-0070, TXG-0078, TXG-0081, TXG-0087, TXG-0114, TXG-0115, TXG-0154, TXG-0174, TXG-0175, TXG-0180, TXG-0192, or TXG-0203.

43. The method of any one of claims 36 to 42, wherein the subject is suspected of being infected with a coronavirus, has been infected with a coronavirus, has been vaccinated, or has been recovered from a coronavirus infection.

44. The method of any one of claims 36 to 43, wherein the subject is an immunocompromised subject or has been previously treated for coronavirus infection.

45. The method of any one of claims 36 to 44, wherein the subject is a mammalian subject.

46. The method of claim 45, wherein the mammalian subject is a human subject.

47. The method of any one of claims 36 to 46, wherein the coronavirus belongs to a genus being any one of alphacoronavirus, betacoronavirus, gammacoronavirus, or deltacoronavirus.

48. The method of claim 47, wherein the coronavirus belongs to a betacoronavirus lineage being any one of lineage A, lineage B, lineage C, or lineage D.
49. The method of claim 48, wherein the coronavirus is human coronavirus 229E, OC43, HKU1, NL63, SARS-CoV-1, SARS-CoV-2, MERS-CoV, or a variant of any thereof.
50. The method of claim 49, wherein the coronavirus is SARS-CoV-2 or a variant thereof is any one of alpha, beta, delta, gamma, kappa, and omicron.
51. The method of any one of claims 36 to 50, wherein one of the two, three, four, five or more variants of SARS-CoV-2 is omicron.
52. The method of any one of claims 36 to 51, wherein one of the one or more of the HCoV-229E, HCoV-OC43, or a combination thereof; and HCoV-HKU1 is HCoV-229E or HCoV-OC43.
53. The method of any one of claims 36 to 50, wherein the composition is administered at a total dose of about 0.0001 mg/kg to about 40 mg/kg.
54. The method of any one of claims 36 to 53, wherein the composition is administered on a schedule being any one of the following: three times a day, twice a day, once a day, every other day, every third day, weekly, biweekly, every three weeks, every four weeks, and monthly.
55. The method of any one of claims 36 to 54, wherein the total dose is administered by multiple administrations.
56. The method of claim 55, wherein the multiple administrations occur on a schedule being any one of the following: three times a day, twice a day, once a day, every other day, every third day, weekly, biweekly, every three weeks, every four weeks, and monthly.
57. The method of any one of claims 36 to 56, wherein the composition is administered by intravenous, intramuscular, subcutaneous, and/or local administration.
58. The method of any one of claims 36 to 57 wherein the administered composition reduces binding of the CoV-S protein to and/or reduces coronavirus entry into a cell of the subject.

59. The method of any one of claims 36 to 58, wherein the administered composition neutralizes against the coronavirus.
60. The method of any one of claims 36 to 59, wherein the administered composition treats, prevents, or ameliorates a health condition associated with a coronavirus infection in the subject.
61. The method of claim 60, wherein the administered composition reduces the viral load in the subject as compared to a reference subject who has not been administered with the composition.
62. The method of any one of claims 36 to 61, further comprising administering to the subject an additional therapy.
63. The method of claim 62, wherein the additional therapy comprises an anti-viral agent being any one of interferon, Remdesivir, Baricitinib, Azithromycin, Nirmatrelvir, Ritonavir, Molnupiravir, Casirivimab, Imdevimab, Bamlanivimab, Etesevimab, Sotrovimab, Cilgavimab, Bebtelovimab, Tocilizumab, Tixagevimab, or a combination thereof.
64. A method for detecting the presence of SARS-CoV-2 S protein and/or SARS-CoV-2 in a biological sample, the method comprising contacting a biological sample with an antigen-binding molecule having an amino acid sequence that is any one of TXG-0001, TXG-0002, TXG-0004, TXG-0005, TXG-0006, TXG-0008, TXG-0009, TXG-0048, TXG-0057, TXG-0060, TXG-0063, TXG-0066, TXG-0070, TXG-0072, TXG-0074, TXG-0076, TXG-0078, TXG-0080, TXG-0081, TXG-0087, TXG-0088, TXG-0091, TXG-0094, TXG-0098, TXG-0099, TXG-0100, TXG-0104, TXG-0109, TXG-0112, TXG-0114, TXG-0115, TXG-0120, TXG-0129, TXG-0136, TXG-0141, TXG-0144, TXG-0153, TXG-0154, TXG-0170, TXG-0173, TXG-0174, TXG-0175, TXG-0180, TXG-0181, TXG-0183, TXG-0187, TXG-0189, TXG-0192, TXG-0197, TXG-0198, TXG-0200, TXG-0201, TXG-0202, TXG-0203, TXG-0204, TXG-0209, TXG-0210, TXG-0228, or TXG-0230, or an antigen-binding fragment of any thereof, and wherein optionally the antigen-binding molecule or antigen-binding fragment has a binding affinity for the omicron variant of SARS-CoV-2 or one or more endemic HCoVs that is any one of 229E, OC43, HKU1, or a combination thereof.

65. The method of claim 64, wherein the antigen-binding molecule or antigen-binding fragment thereof comprises all six complementary determining regions (CDRs) from an antibody being any one of TXG-0001, TXG-0002, TXG-0004, TXG-0005, TXG-0006, TXG-0008, TXG-0009, TXG-0048, TXG-0070, TXG-0078, TXG-0081, TXG-0087, TXG-0114, TXG-0115, TXG-0154, TXG-0174, TXG-0175, TXG-0180, TXG-0192, or TXG-0203.

66. The method of any one of claims 64 to 65, wherein the biological sample is from a subject suspected of being infected with a coronavirus, has been infected with a coronavirus, has been vaccinated, or has been recovered from a coronavirus infection.

67. The method of any one of claims 64 to 66, further comprising detecting a complex formed between the antigen-binding molecule or antigen-binding fragment with an SARS-CoV-2 S antigen.

68. The method of claim 67, wherein said detecting comprises visualizing the complex by using an enzyme, a secondary antibody, a colored dye, a fluorescent dye, a chemiluminescent molecule, a molecule containing a radioactive atom, or a molecule containing a heavy metal.

69. A method for aiding in the diagnosis, prognosis, monitoring, and/or evaluation of a coronavirus infection and/or treatment thereof in a subject, wherein said aiding comprises providing:

an antigen-binding molecule having an amino acid sequence being any one of TXG-0001, TXG-0002, TXG-0004, TXG-0005, TXG-0006, TXG-0008, TXG-0009, TXG-0048, TXG-0057, TXG-0060, TXG-0063, TXG-0066, TXG-0070, TXG-0072, TXG-0074, TXG-0076, TXG-0078, TXG-0080, TXG-0081, TXG-0087, TXG-0088, TXG-0091, TXG-0094, TXG-0098, TXG-0099, TXG-0100, TXG-0104, TXG-0109, TXG-0112, TXG-0114, TXG-0115, TXG-0120, TXG-0129, TXG-0136, TXG-0141, TXG-0144, TXG-0153, TXG-0154, TXG-0170, TXG-0173, TXG-0174, TXG-0175, TXG-0180, TXG-0181, TXG-0183, TXG-0187, TXG-0189, TXG-0192, TXG-0197, TXG-0198, TXG-0200, TXG-0201, TXG-0202, TXG-0203, TXG-0204, TXG-0209, TXG-0210, TXG-0228, or TXG-0230; or an antigen-binding fragment of any thereof, wherein optionally the antigen-binding molecule or antigen-binding fragment thereof has a binding affinity for the omicron variant of SARS-CoV-2 or one or more endemic HCoVs that is any one of 229E, OC43, HKU1, or a combination thereof.

70. Kit for preventing, treating, diagnosing, or imaging a virus, a disease, a disorder, and/or a health condition, the kit comprising:

(a) an antigen-binding molecule, or an antigen-binding fragment of any thereof, comprising all 6 CDRs from an antibody being any one of TXG-0001, TXG-0002, TXG-0004, TXG-0005, TXG-0006, TXG-0008, TXG-0009, TXG-0048, TXG-0057, TXG-0060, TXG-0063, TXG-0066, TXG-0070, TXG-0072, TXG-0074, TXG-0076, TXG-0078, TXG-0080, TXG-0081, TXG-0087, TXG-0088, TXG-0091, TXG-0094, TXG-0098, TXG-0099, TXG-0100, TXG-0104, TXG-0109, TXG-0112, TXG-0114, TXG-0115, TXG-0120, TXG-0129, TXG-0136, TXG-0141, TXG-0144, TXG-0153, TXG-0154, TXG-0170, TXG-0173, TXG-0174, TXG-0175, TXG-0180, TXG-0181, TXG-0183, TXG-0187, TXG-0189, TXG-0192, TXG-0197, TXG-0198, TXG-0200, TXG-0201, TXG-0202, TXG-0203, TXG-0204, TXG-0209, TXG-0210, TXG-0228, or TXG-0230, wherein optionally the antigen-binding molecule or antigen-binding fragment thereof has a binding affinity for the omicron variant of SARS-CoV-2 or one or more endemic HCoVs that is any one of 229E, OC43, HKU1, or a combination thereof; and/or

(b) a nucleic acid encoding the antigen-binding molecule or antigen-binding fragment thereof of (a);

and instructions for performing the method of any one of claims 36 to 69.

71. A method of manufacturing a pharmaceutical composition, the method comprising:

(a) admixing a lipid solution with an aqueous buffer solution comprising a buffer agent thereby forming a lipid nanoparticle solution comprising a lipid nanoparticle (LNP); and

(b) adding to the lipid nanoparticle:

(i) an antigen-binding molecule, or an antigen-binding fragment of any thereof, comprising all 6 CDRs from an antibody being any one of TXG-0001, TXG-0002, TXG-0004, TXG-0005, TXG-0006, TXG-0008, TXG-0009, TXG-0048, TXG-0057, TXG-0060, TXG-0063, TXG-0066, TXG-0070, TXG-0072, TXG-0074, TXG-0076, TXG-0078, TXG-0080, TXG-0081, TXG-0087, TXG-0088, TXG-0091, TXG-0094, TXG-0098, TXG-0099, TXG-0100, TXG-0104, TXG-0109, TXG-0112, TXG-0114, TXG-0115, TXG-0120, TXG-0129, TXG-0136, TXG-0141, TXG-0144, TXG-0153, TXG-0154, TXG-0170, TXG-0173, TXG-0174, TXG-0175, TXG-0180, TXG-0181, TXG-0183, TXG-0187, TXG-0189, TXG-0192, TXG-0197, TXG-0198, TXG-0200, TXG-0201, TXG-0202, TXG-0203, TXG-0204, TXG-0209, TXG-0210, TXG-0228, or TXG-

0230, wherein optionally the antigen-binding molecule or antigen-binding fragment thereof has a binding affinity for the omicron variant of SARS-CoV-2 or one or more endemic HCoV-229E, HCoV-OC43, HCoV-NK61, or a combination thereof; and/or

(ii) a nucleic acid encoding the antigen-binding molecule or antigen-binding fragment thereof of (a),

thereby forming a LNP formulation comprising the LNP associated with the antigen-binding molecule or antigen-binding fragment thereof, and/or with the nucleic acid encoding the antigen-binding molecule or antigen-binding fragment thereof.

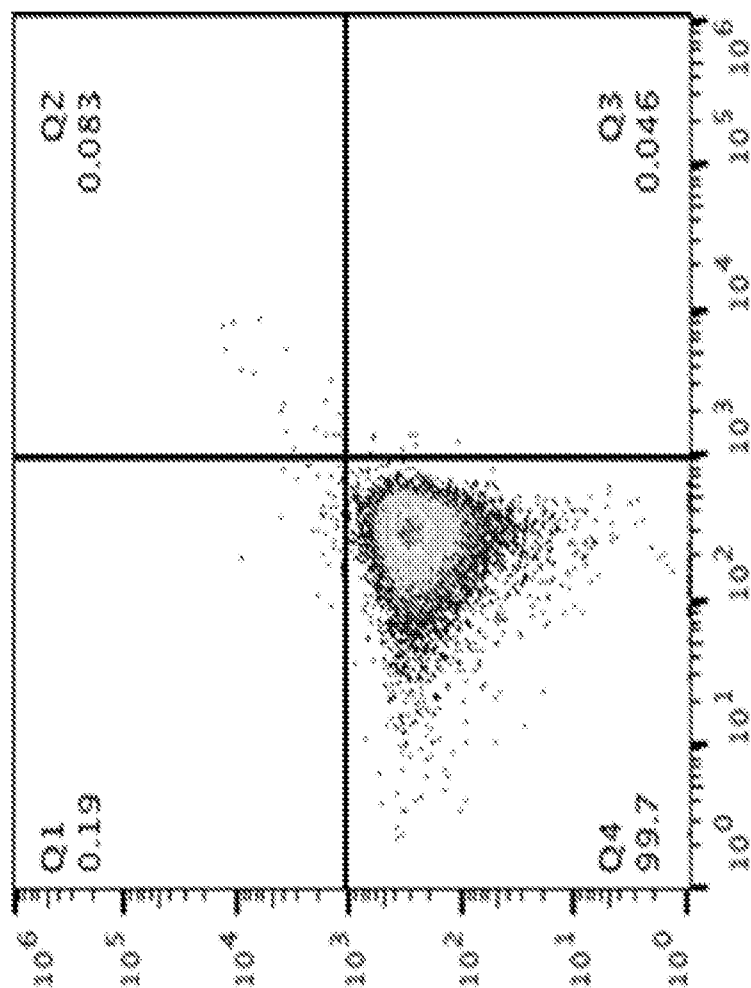


FIG. 1

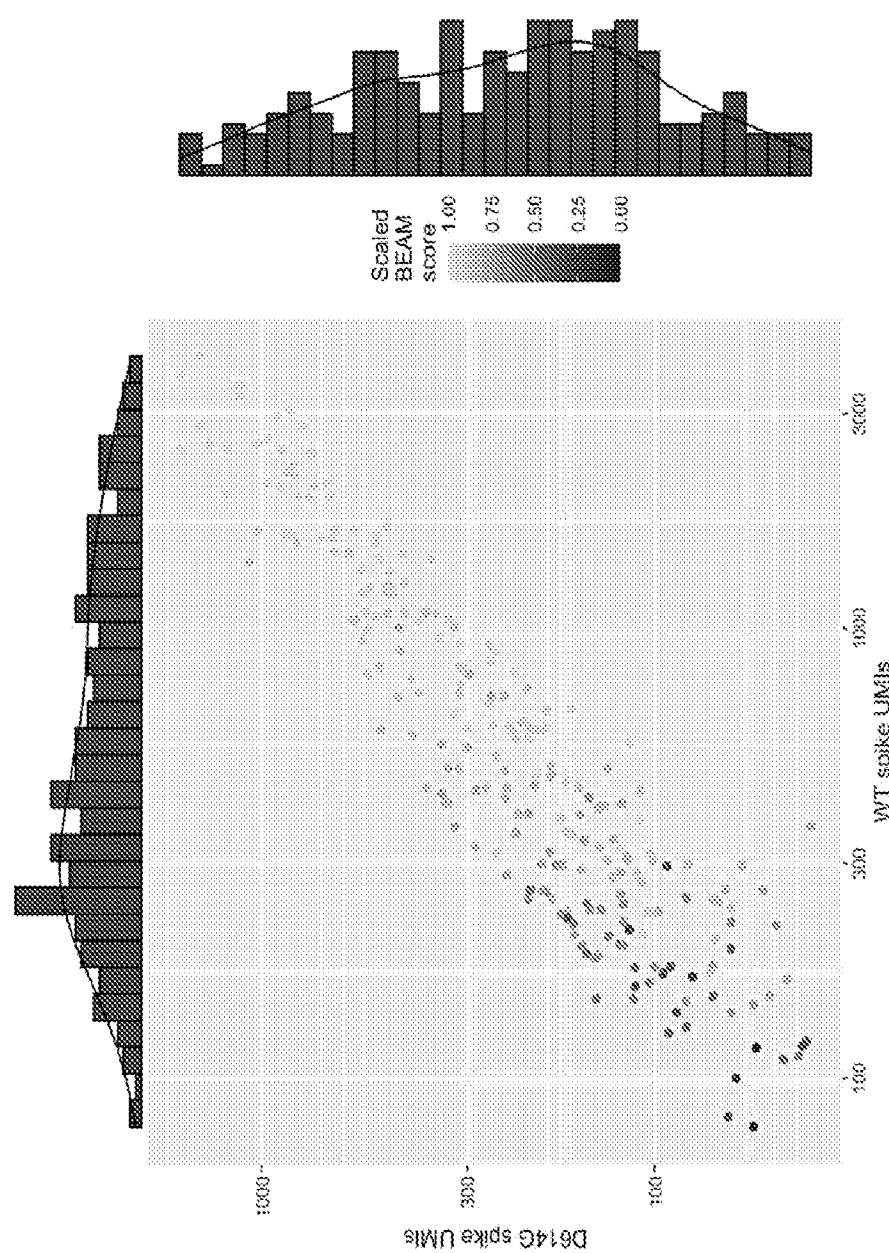


FIG. 2

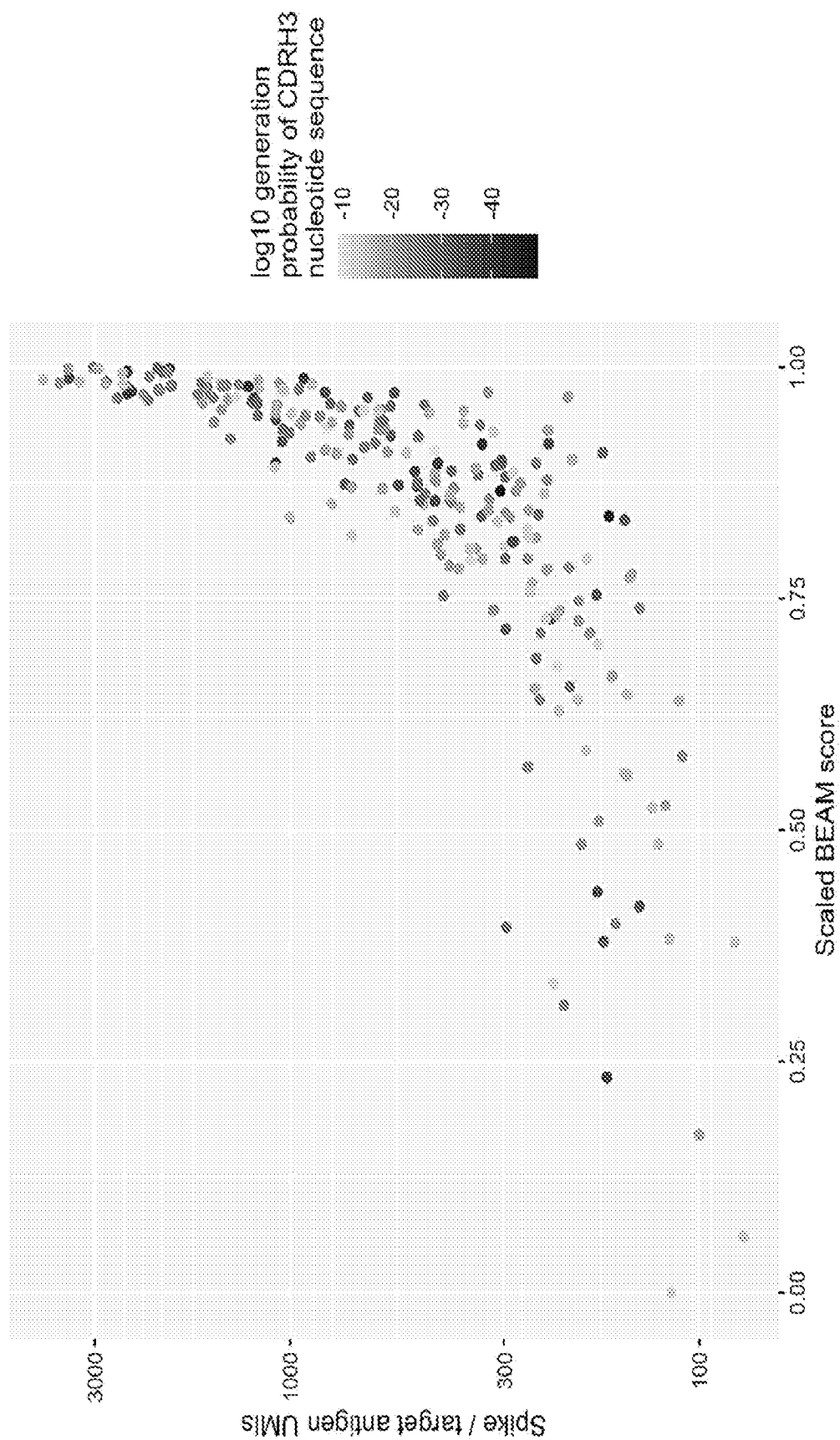


FIG. 3A

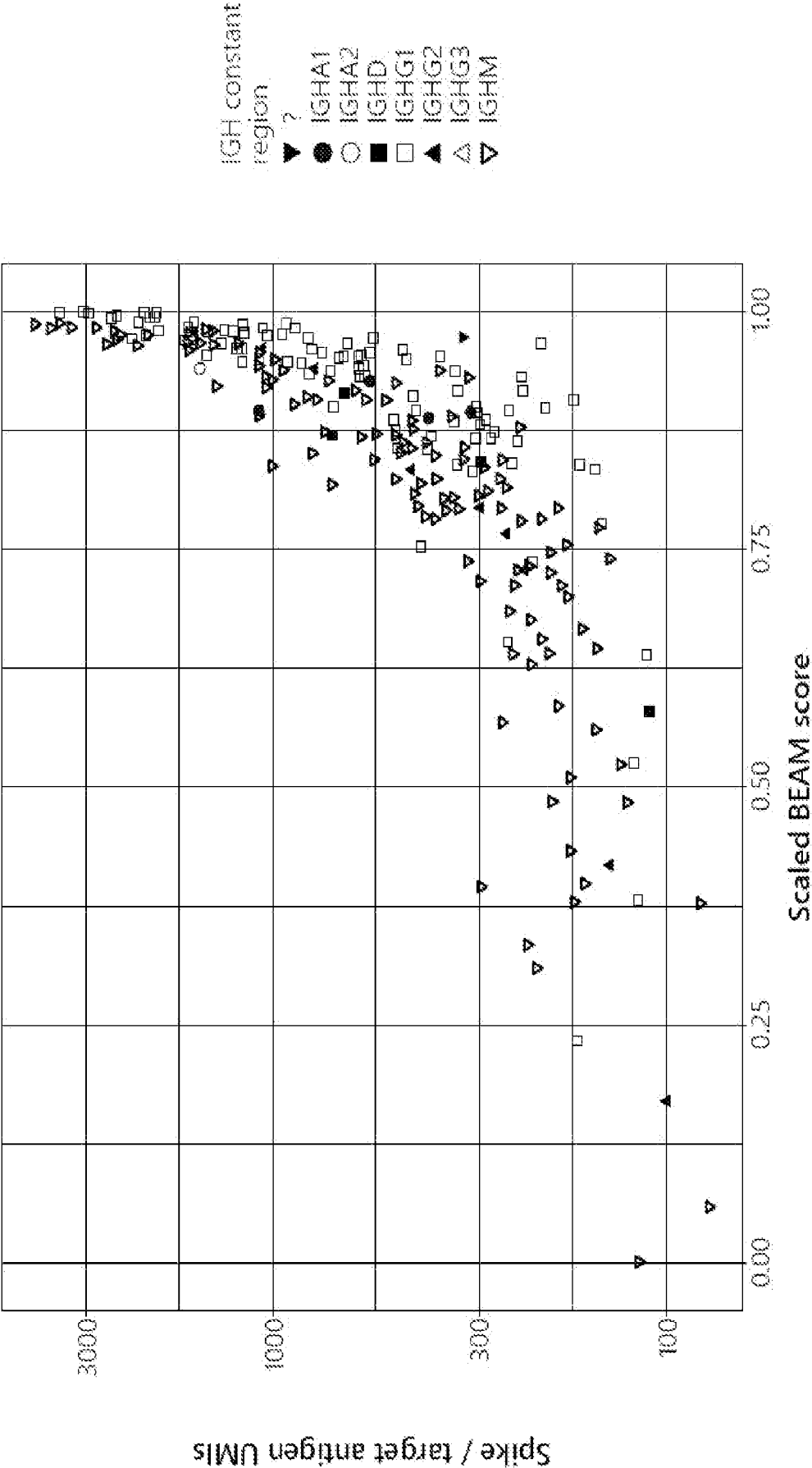
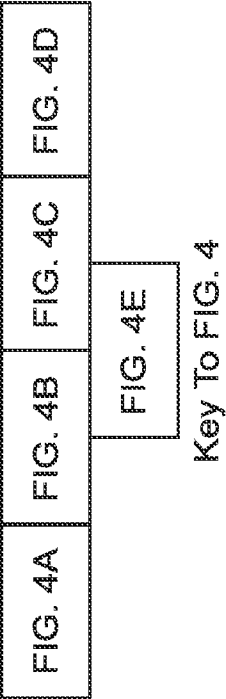


FIG. 3B

[1]GROUP = 1 CLONOTYPES = 9 CELLS

[1.1] CLONOTYPE = 9 CELLS



reference						
donor ref						
#	datasets	n	Spike	Alb1	MutSpike	Alb2
1	all	1	766	0	466	0
2	all	1	185	2	162	1
3	all	1	1451	0	833	4
4	all	1	762	0	478	1
5	all	1	212	0	103	0
6	Spike+Alb1	1	584	0	261	0
7	all	1	714	0	361	0
8	all	1	774	0	837	1
9	all	1	888	1	705	0

FIG. 4A

CHAIN 2		281 IGKV3-15 ◆ 213 IGKJ1	
1111222334	44444445555	55556666	
6789123462	34567890123	56780247	
=====CDR1=====			
DTTGIVMPEC	RASQSVSSNLA	YQOKGARI	
DTTGIVMPEC	RASQSVSSNLA	YQOKGARI	
LLLLLLLLLLLL	C.CCC..	FFFFFFF	
EIPGIVLPEC	RASQTVSTTLA	FQLKGARI	
DSTGIVMPEC	RASQTVSTILA	YQORGARI	
EIPGIVLPEC	RASQTVSTILA	FQOKGARI	
ETPGIVLPGC	RASQSVSTSLA	FQOKGTRI	
DTPAIVMPEC	RASQTVNSNLA	FQOKGARI	
EIPGIVLPEC	RASQTVSTSLA	FQOKGARI	
ETPGIALPGC	RASQTVSTNLA	FQOKGASI	
DTTGIVMPVC	RASQTVGSNLA	YLORGARV	
DTPGIVMPEC	RASQTVSNALA	FQOKGTRI	

FIG. 4C

11111 1111111111 11									
6777777	7788999	00000	0001111111	22					
9012345	6729568	12346	7890123456	45					
==CDR2==									
==CDR3==									
GASTRAT	GI	SESSQ	DEAVY	CQO*****	IK				
GASTRAT	GI	SESSQ	DEAVY	CQO*****	IK				
..... FFFFFFFF .CCCCC..CC FF									
GASTRAT	GVSASSR	DEAVY	CQOYHN	WWTF	VK	173	IGKC	173	IGKC 88.8
GASTRAT	GVRESSQ	DEGVY	CQQYNN	WWTF	VK	98	IGKC	98	IGKC 92.2
GASTRAT	GVSASSR	DEAVY	CQOYNN	WWTF	VK	121	IGKC	121	IGKC 90.5
GASTRAT	GVSASSR	DEFAIY	CQQYNN	WWTF	VN	69	IGKC	69	IGKC 87.9
GASTRAT	GVSASSQ	DEALF	CQOYEN	WWTF	IK	43	IGKC	43	IGKC 92.2
GASTRAT	GVSASSR	DEAVY	CQOYND	WWTF	VK	90	IGKC	90	IGKC 89.7
GASTRAT	GVSASGR	DEAVY	CQQYND	WWTF	VK	88	IGKC	88	IGKC 87.9
GASTRAT	GI	RESSQ	DEGVY	CQOYNN	WWTF	VK	71	IGKC	71 IGKC 92.2
GASTRAT	GVSASSQ	DDVAVY	CQOYNN	WWTF	IK	69	IGKC	69	IGKC 92.2

FIG. 4D

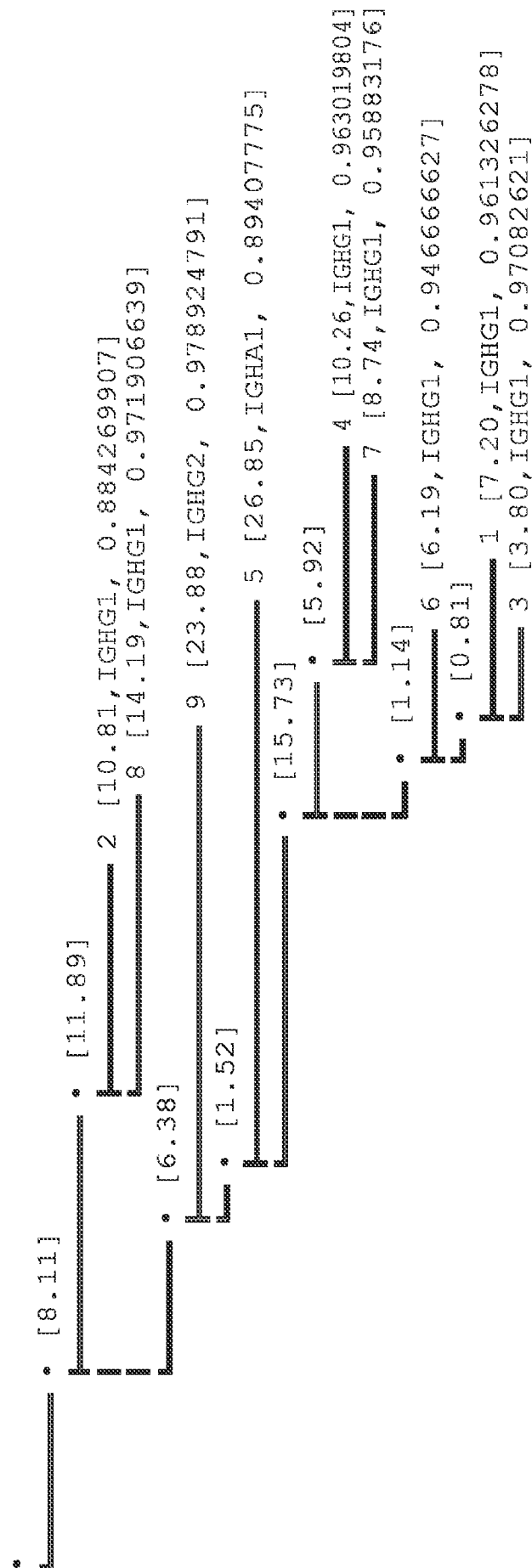


FIG. 4E

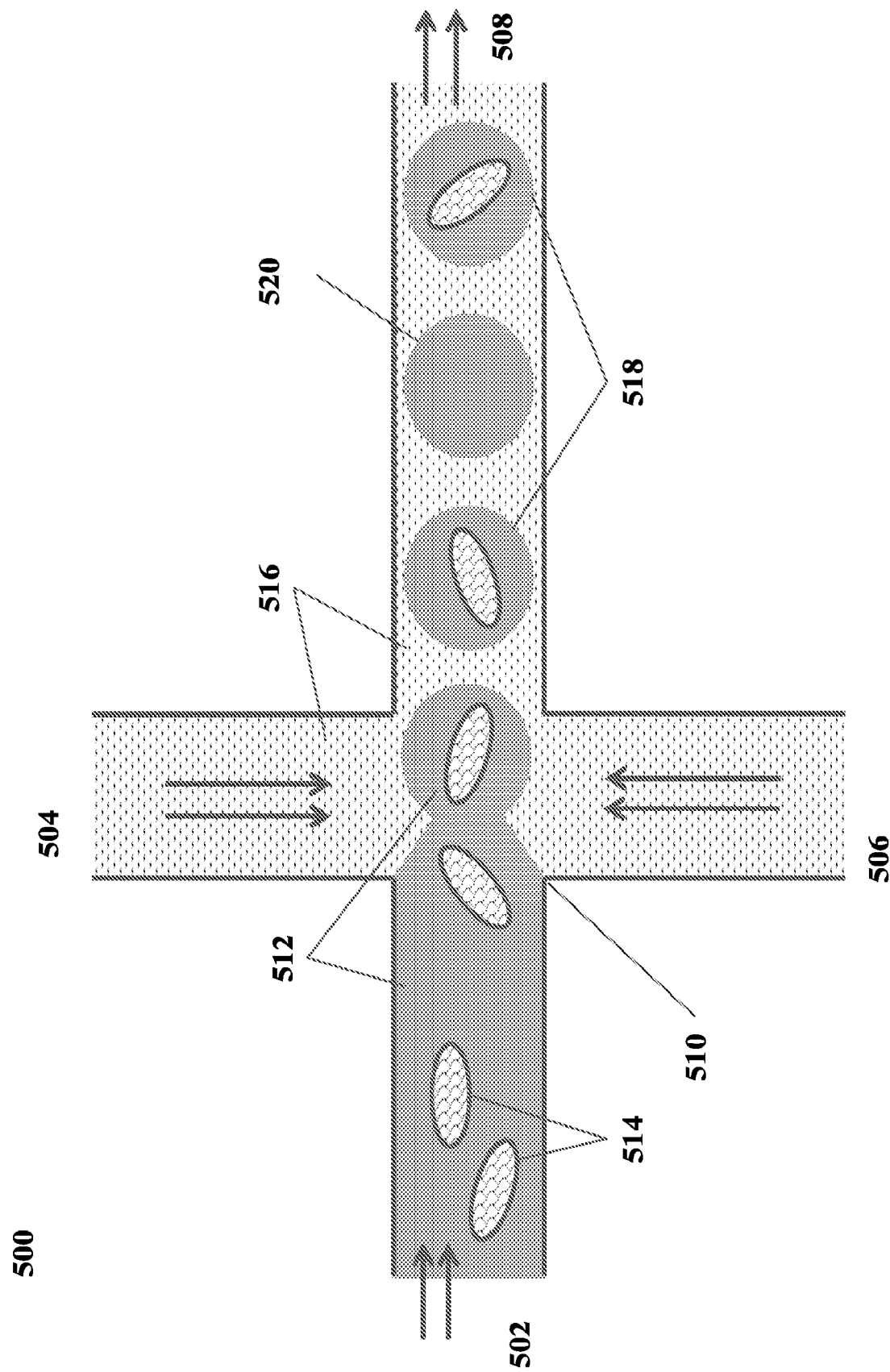


FIG. 5

600

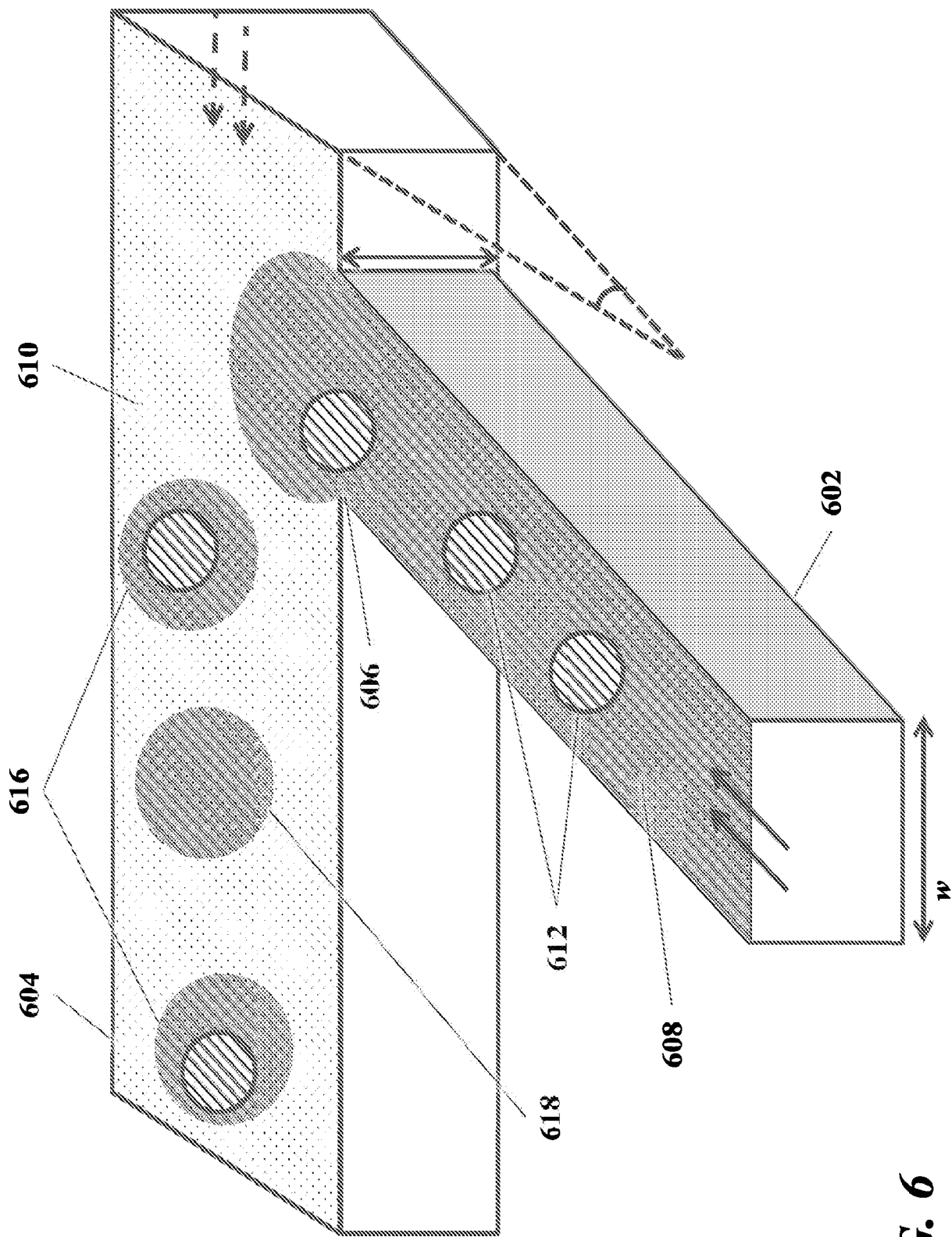


FIG. 6

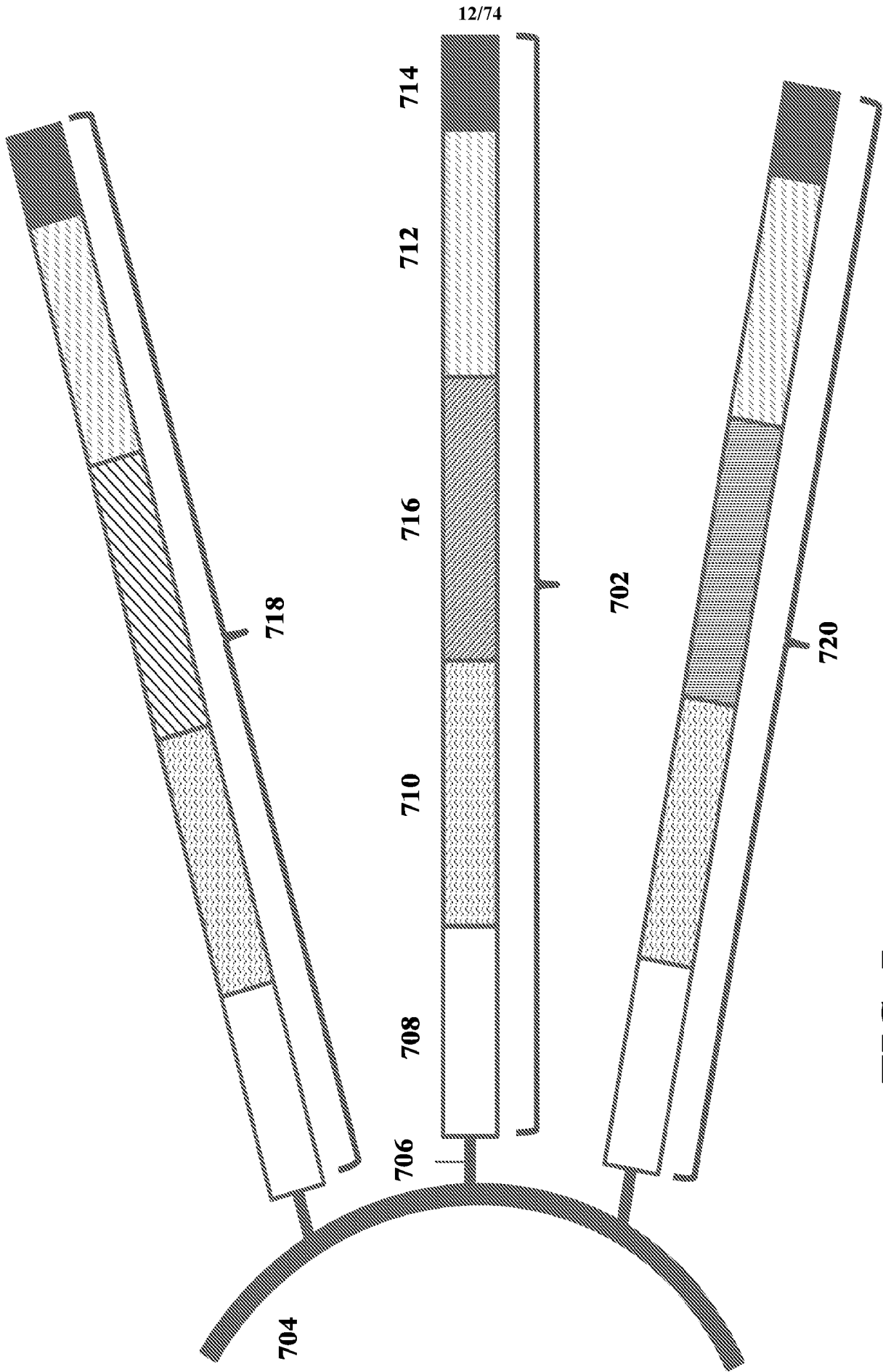


FIG. 7

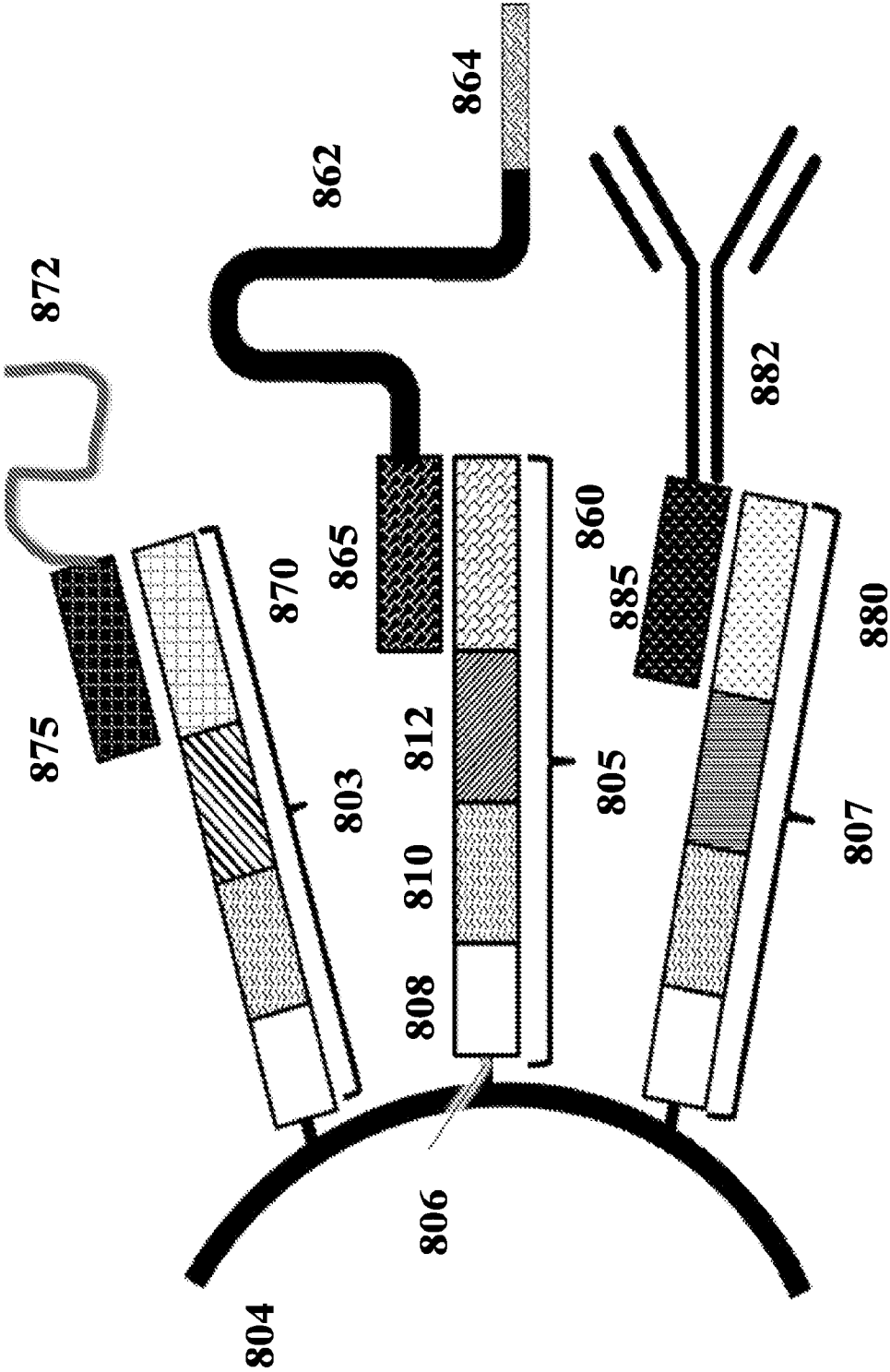


FIG. 8

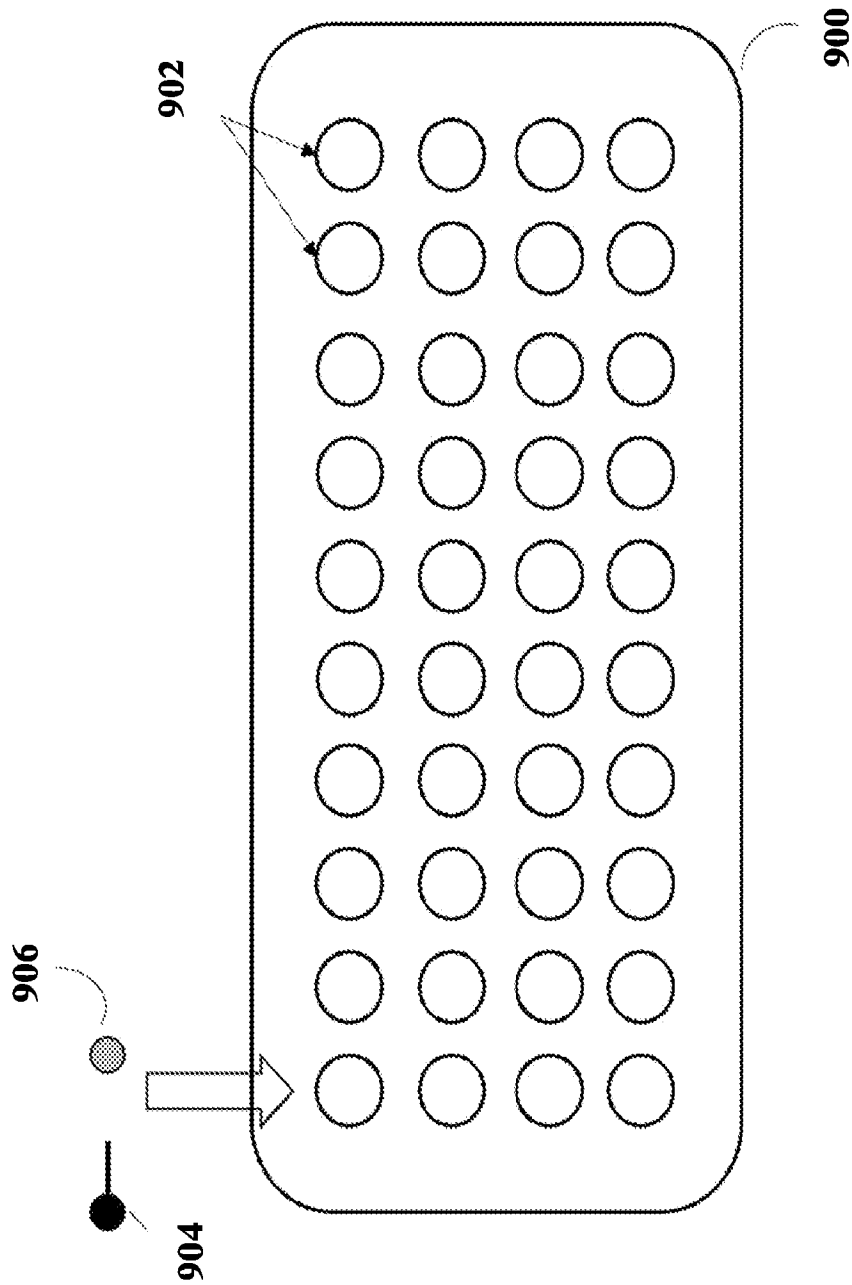


FIG. 9

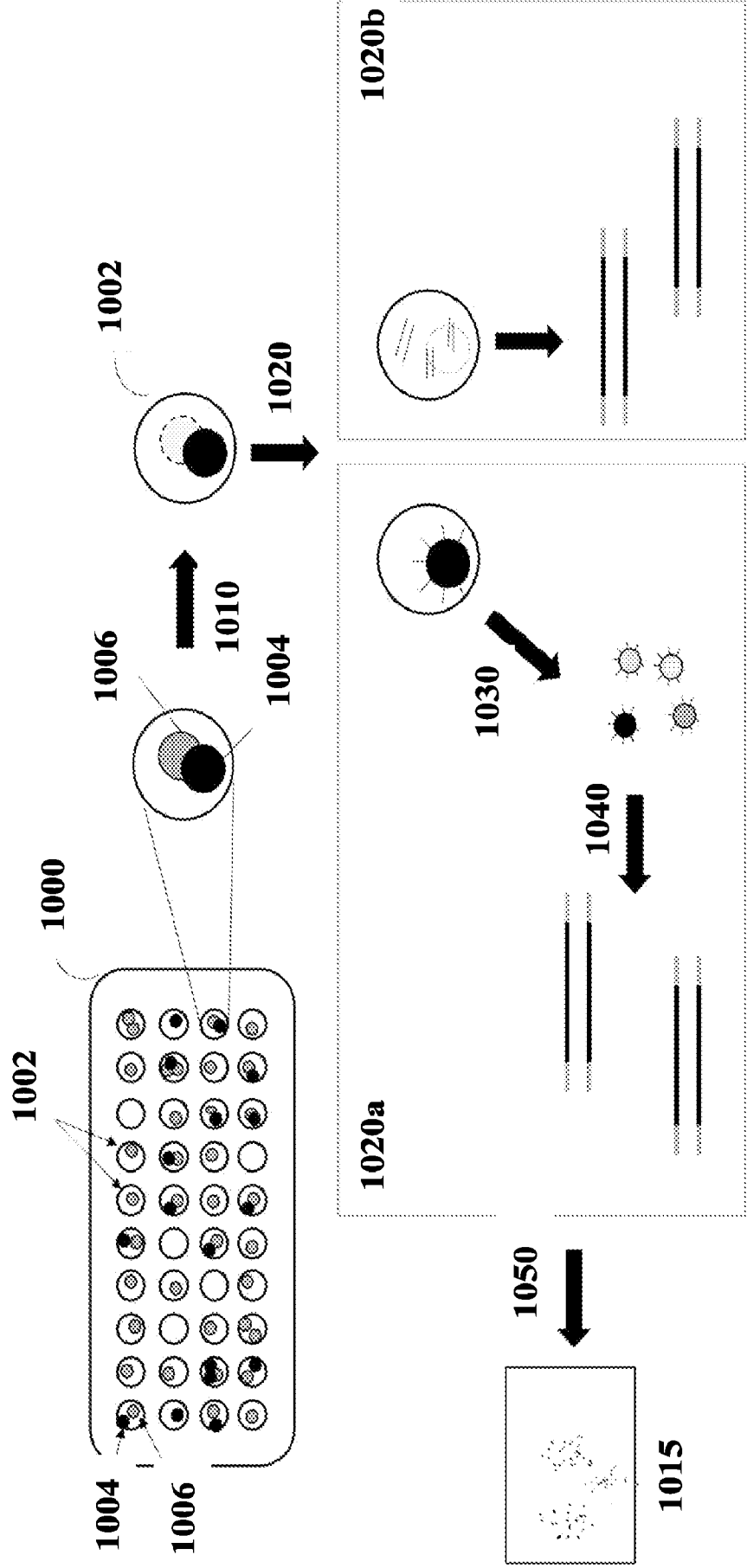


FIG. 10

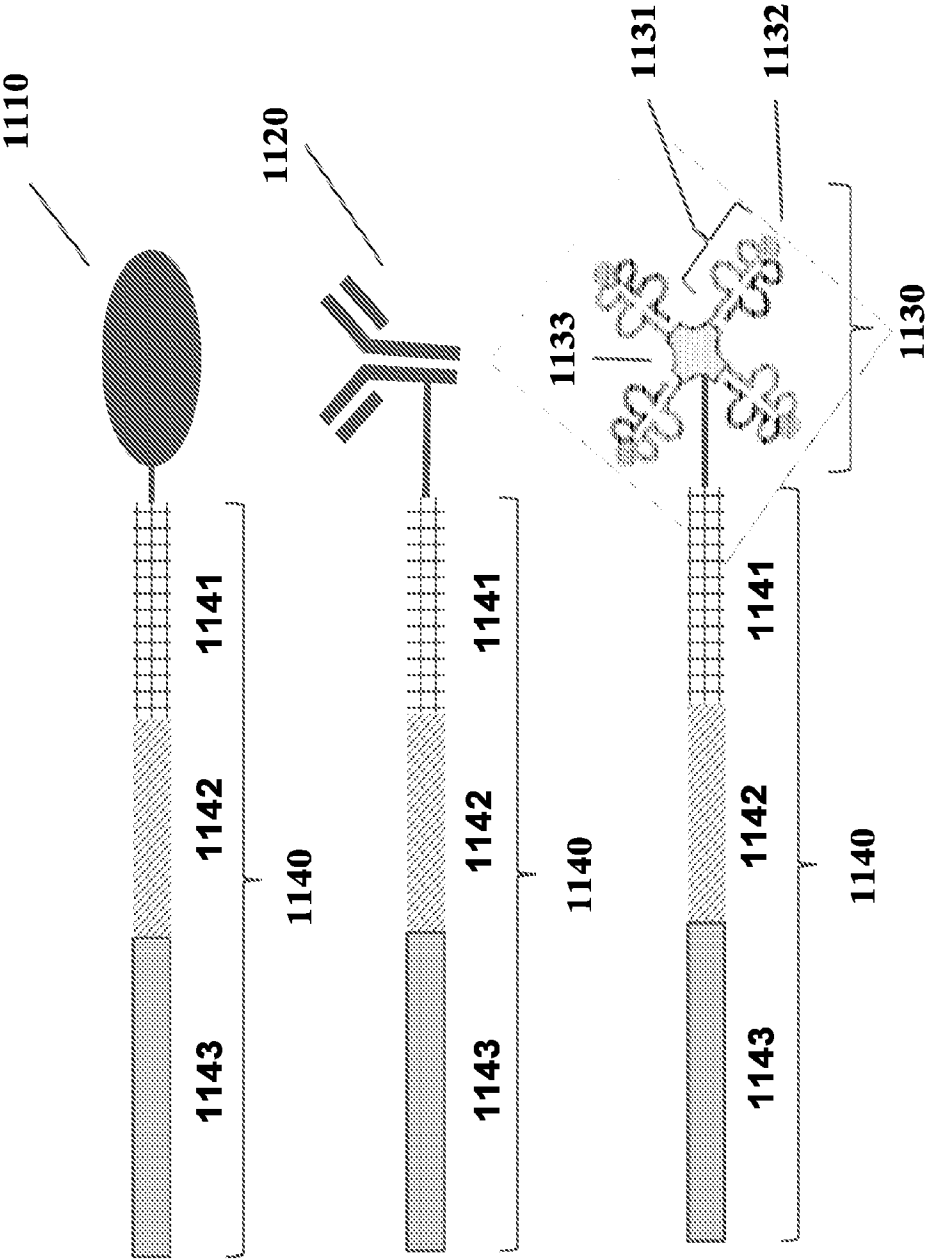


FIG. 11

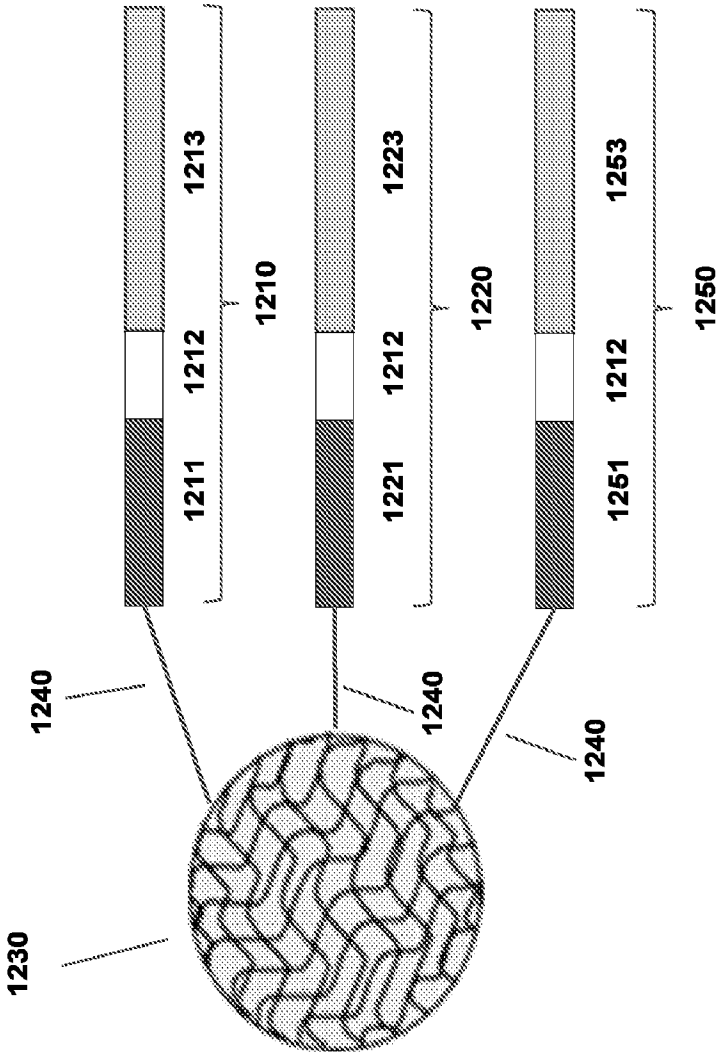
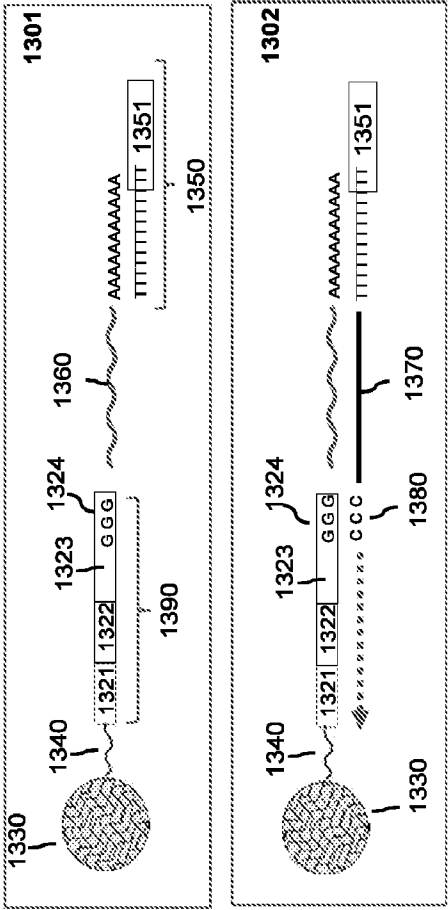
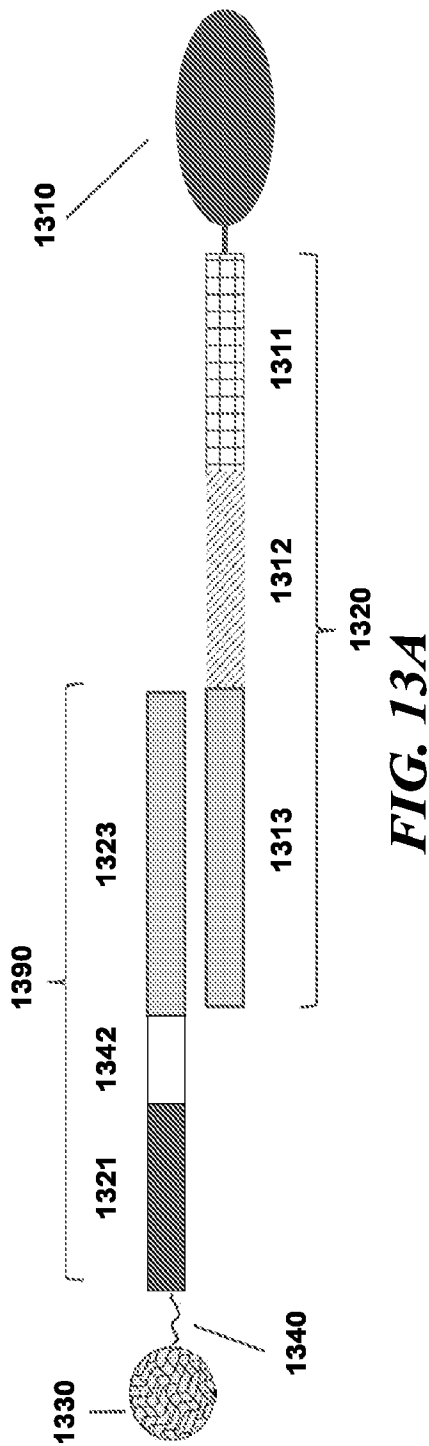


FIG. 12



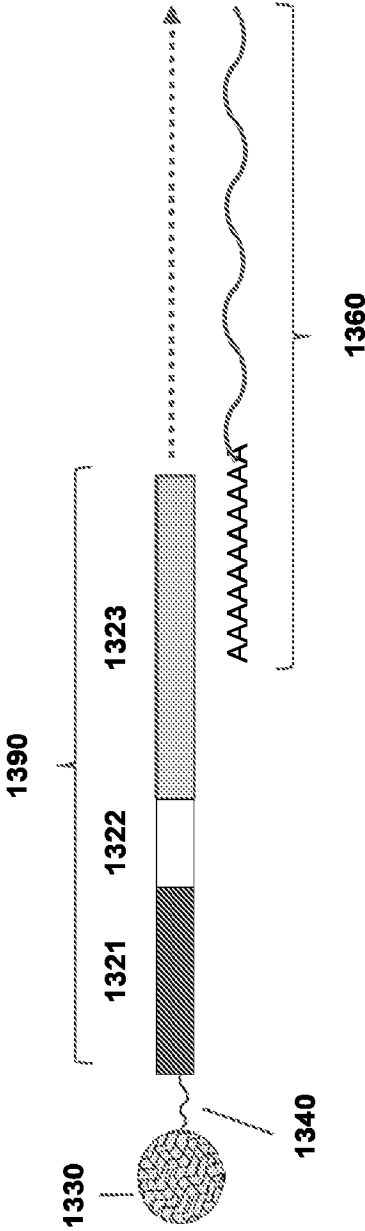


FIG. 13C

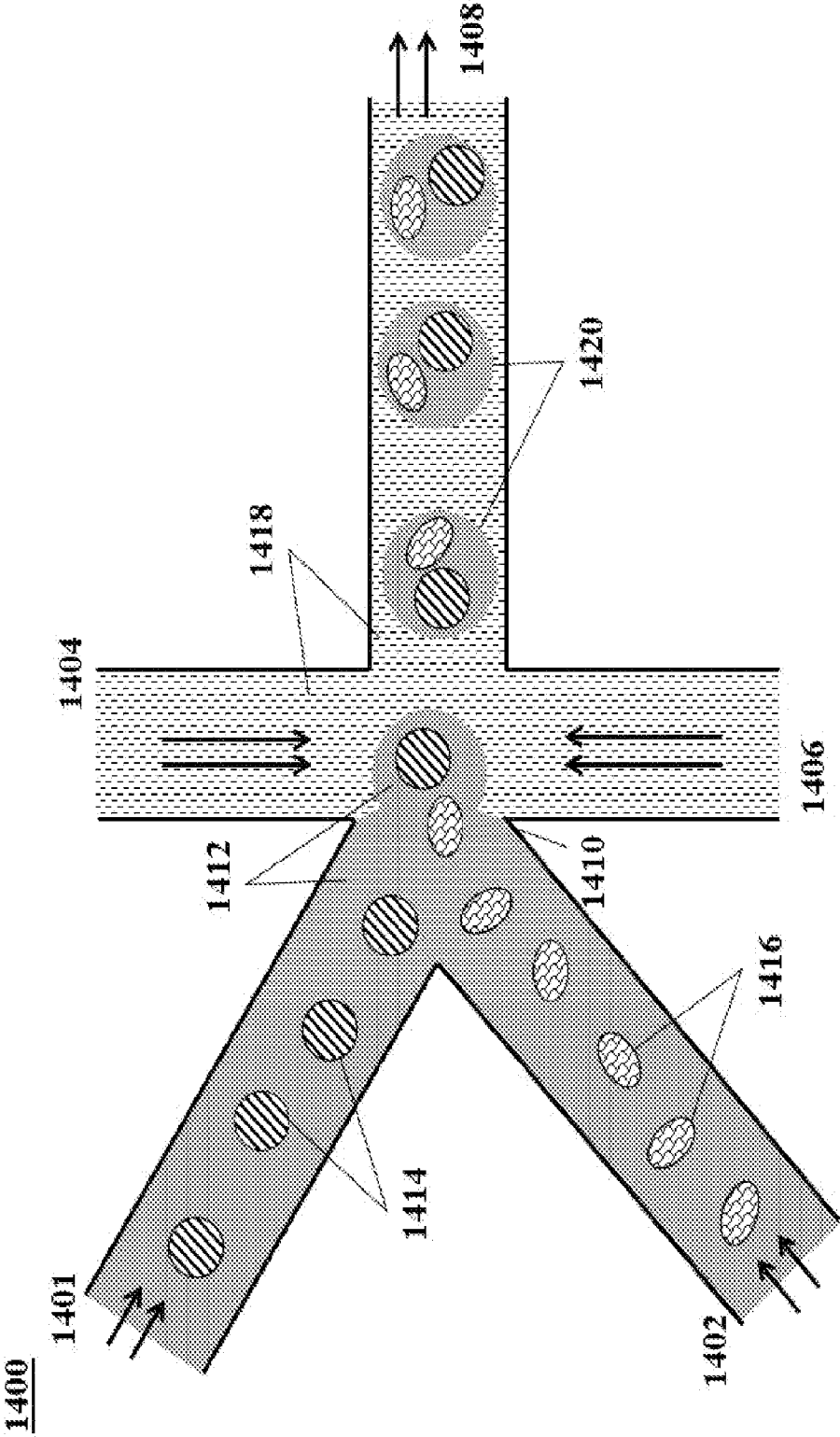


FIG. 14

10	20	30	40	50
NFVFLVLLPL	VSSQC*VNLTT	RTQLPPAYTN	SFTRGVVYPO	KVFRSSVLHS
60	70	80	90	100
TQDLFLPFFS	NVTWFHAIHV	SGTNGTKRFD	NPVLPPHOGV	YFASTERSTNI
110	120	130	140	150
IRGWIFGTTL	DSKTQSLIV	NNATNVVIKV	CEPQFCNDPF	LGVIYHNNK
160	170	180	190	200
SMNESEFRVY	SSANNCTFEY	VSQPFLMDLE	GKQGNFKNLR	EPVFKNIDGV
210	220	230	240	250
FKIYSEHTPI	NLVRDLPOGF	SALEPLVDLP	IGINITRFQT	LLALHRSYLT
260	270	280	290	300
PGDSSSGHTA	GAAAYVGYL	QPRTFLLKYN	ENGTITDAVD	CALDPLSETK
310	320	330	340	350
CTLKSFTVEK	GIYQTSNFRV	QPTESIVRFP	NITNLCPPGE	VFNATRFASV
360	370	380	390	400
YAWNRKRISH	CVAQSVLYN	SASFSTFKCY	GVSPTKLNDL	CFTNVYADSF
410	420	430	440	450
VIRGDEVROQ	APGQTKIAD	YNYKLPODFT	GCVIAMNSNN	LDKVGGNYN
460	470	480	490	500
YLYBLFRKSN	LKPFERDIST	EIVQAGSTPC	NGVEGFNCYF	PLQSYGFQPT
510	520	530	540	550
NGVGYQPYRV	VVLSFELLHA	PATVCGPKKS	TNLVKNKCVN	PNFNGLTGTG
560	570	580	590	600
VLTESNKKFL	PFQQFGRDIA	DTTDAVRDPQ	TLEILOITPC	SFGGVSVITP
610	620	630	640	650
GTNTSNQVAV	LYQDVNCTEV	PVAIHADQLT	PTWRVYSTGS	NVFQTRAGCL
660	670	680	690	700
		R R		
IGAETHVNSY	ECDIPIGAGI	CASYQTQTN	PRAAASVASQ	SIIAYTMSLG
710	720	730	740	750
AENSVAYSNN	SIAIPINFTI	SVTTEILPVS	MTKTSVQCTM	YICGDSIECS
760	770	780	790	800
NLLQYGSFC	TQLNRALTGI	AVEQDKNTQE	VFAQVKQIYK	TPPIKDFGGF
810	820	830	840	850
	F			
NFSQILPDPS	KPSKRSPIED	LLFNKVTIAD	AGFIKQYGDC	LGDIAARDLI
860	870	880	890	900
			A A	
CAQKFNGLTV	LPPLLTDEMI	AQYTSALLAG	TITSGWTFGA	GAPLQIPFPM
910	920	930	940	950
			A	
QNAYRFNGIG	VTQNVLYENQ	KLIANQFNSA	IGKIQDSLSS	TPSALGKLQD
960	970	980	990	1000
		KV		
VVNQNAQALN	TLVKQLSSNF	GAISSVLNDI	LSRLDPPEAE	VQIDRLITGR
1010	1020	1030	1040	1050
LQSLQTYVTQ	QLIRAAEIRA	SANLAATKMS	ECVLGQSKRV	DFCGKGYHLM
1060	1070	1080	1090	1100
SFPQSAPHGV	VFLHVTYVPA	QEKNFITAPA	ICHOGKAHFP	REGVFSNGT
1110	1120	1130	1140	1150
HWFVTQRNFP	EPQIITDNT	FVSGNCOVVI	GIVNNTVYDP	LQPELDSFKE
1160	1170	1180	1190	1200
ELOKYFKNHT	SPOVDLGDIS	GINASVVNIQ	KEIDRLNEVA	KNLNESLIDL
1210	1220	1230	1240	1250
QELGKYEQVI	KWP*WYIWLGF	IAGLIAIVNV	TIMLCOMTSC	CSCLKGCCSC
1260	1270			
GSCCKFOEDD	SEPVLKGVKL	HYT		

FIG. 15A

10	20	30	40	50
MFVFLVLLPL	VSSQC*VNLTT	RTQLPPAYTN	SFTRGVVYYPD	KVFRSSVLHS
60	70	80	90	100
TQDLFLPFFS	NVTWFHAIHV	SGTNGTKRFD	NPVLPFNDGV	YFASTEKSN
110	120	130	140	150
IRGWIFGTTL	DSKTQSLIIV	NNATNVVIKV	CEFQFCNDPF	LSVYYHKNHK
160	170	180	190	200
SWMESEFRVY	SSANNCTFEY	VSQPFLMDLE	GKQGNFKNLR	EFVFNIDGY
210	220	230	240	250
FKIYSKHTPI	NLVRDLPQGF	SALEPLVDLP	IGINITRFQT	LLALHRSYLT
260	270	280	290	300
PGDSSSGWTA	GAAAVYVGYL	QPRTELLKYN	ENGTITDAVD	CALDPLSETK
310	320	330	340	350
CTLKSFTVEK	GIYQTSNFRV	QPTESIVRFP	NITNLCPFGE	VFNATRFASV
360	370	380	390	400
YAMNRKRISH	CVADYSVLVN	SASFSTFKCY	GVSPTKLNDL	CFTNVYADSF
410	420	430	440	450
VIRGDEVQRQI	APGQTKIAD	YNYKLPDQFT	GCVIAMNSNN	LDSKVGGHYN
460	470	480	490	500
YLYRLFRRSN	LKPFERDIST	EIYQAGSTPC	NGVEGFNCYF	PLQSYGFQPT
510	520	530	540	550
NGVGYQPYRV	VVLSFELLHA	PATVCGPKKS	TNLVKNKCVN	FNFNGLTGTG
560	570	580	590	600
VLTESNKKFL	PFQQFGRDIA	DTTDAVRDPQ	TLEILDITPC	SFGGVSVITP
610	620	630	640	650
	D			
GTNTSNQVAV	LYQGVNCTEV	PVAIHADQLT	PTWRVYSTGS	NVFQTRAGCL
660	670	680	690	700
		R R		
IGAETHVNSY	ECDIPIGAGI	CASYQTQTN	PRAAASVASQ	STIAYTMSLG
710	720	730	740	750
AENSVAYSNN	SIAIPTNFTI	SVTTEILPVS	MTKTSVDCTM	VICGOSTECS
760	770	780	790	800
NLLLQYGSFC	TQLNRALTGI	AVEQDKNTQE	VFAQVKQIYK	TPPIKDFGGF
810	820	830	840	850
	F			
NFSQILPDPS	KPSKRSPIED	LLFNKVTLAD	AGFIKQYGDC	LGDIAARDLI
860	870	880	890	900
			A A	
CAQKFNGLTV	LPPLLTDEMI	AQYTSALLAG	TITSGWTFGA	GAPLQIPFPM
910	920	930	940	950
			A	
QMAYRFNGIG	VTQWVLYENQ	KLIANQFNSA	IGKIQDSLSS	TPSALGKLQD
960	970	980	990	1000
		KV		
VVNQNAQALN	TLVKQLSSNF	GATSSVLNDI	LSRLDPPEAE	VQIDRLITGR
1010	1020	1030	1040	1050
LQSLQTYVTQ	QLIRAAEIRA	SANLAATKMS	ECVLGQSKRV	DFCGKGYHLM
1060	1070	1080	1090	1100
SFPQSAPHGV	VFLHVTYVPA	QERNFTTAPA	ICHOCKAHFP	REGVFSVNGT
1110	1120	1130	1140	1150
HWFVTQANFY	EPQIITTDNT	FVSGNCOVVI	GIVNNTVYDP	LQPELDSFKE
1160	1170	1180	1190	1200
ELOCKYFKNHT	SPOVDLGDIS	GINASVVNIQ	KEIDRLNEVA	KNLNESLIDL
1210	1220	1230	1240	1250
QELGKYEQYI	KWP*WYINLGF	IAGLIAIVMV	TIMLCMTSC	CSCLKGCCSC
1260	1270			
GSCCKFOEDD	SEPVLKGVKL	HYT		

FIG. 15B

Pre-fusion trimeric spike kinetics – Wild-type spike protein

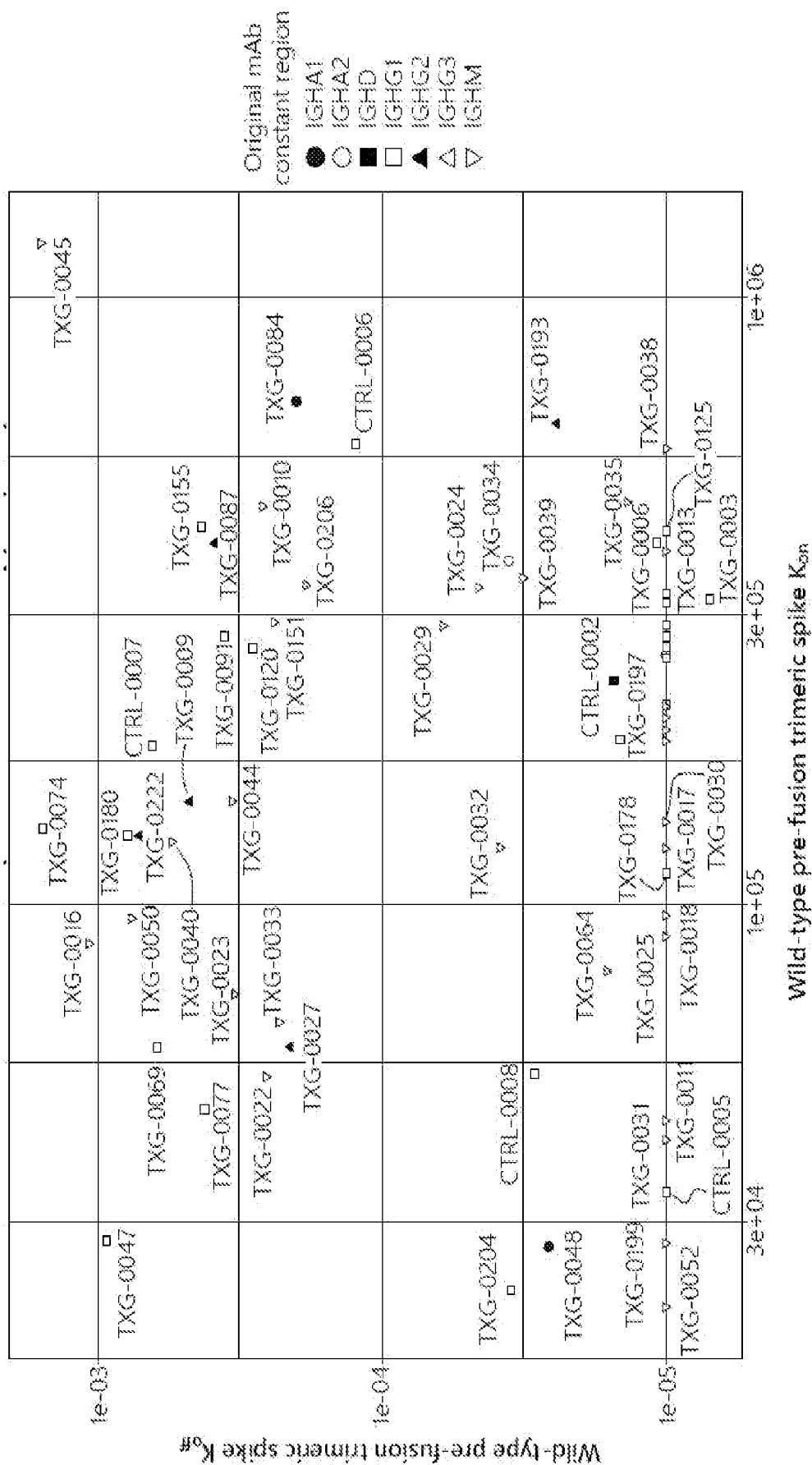


FIG. 16A

Pre-fusion trimeric spike kinetics – D614G spike protein

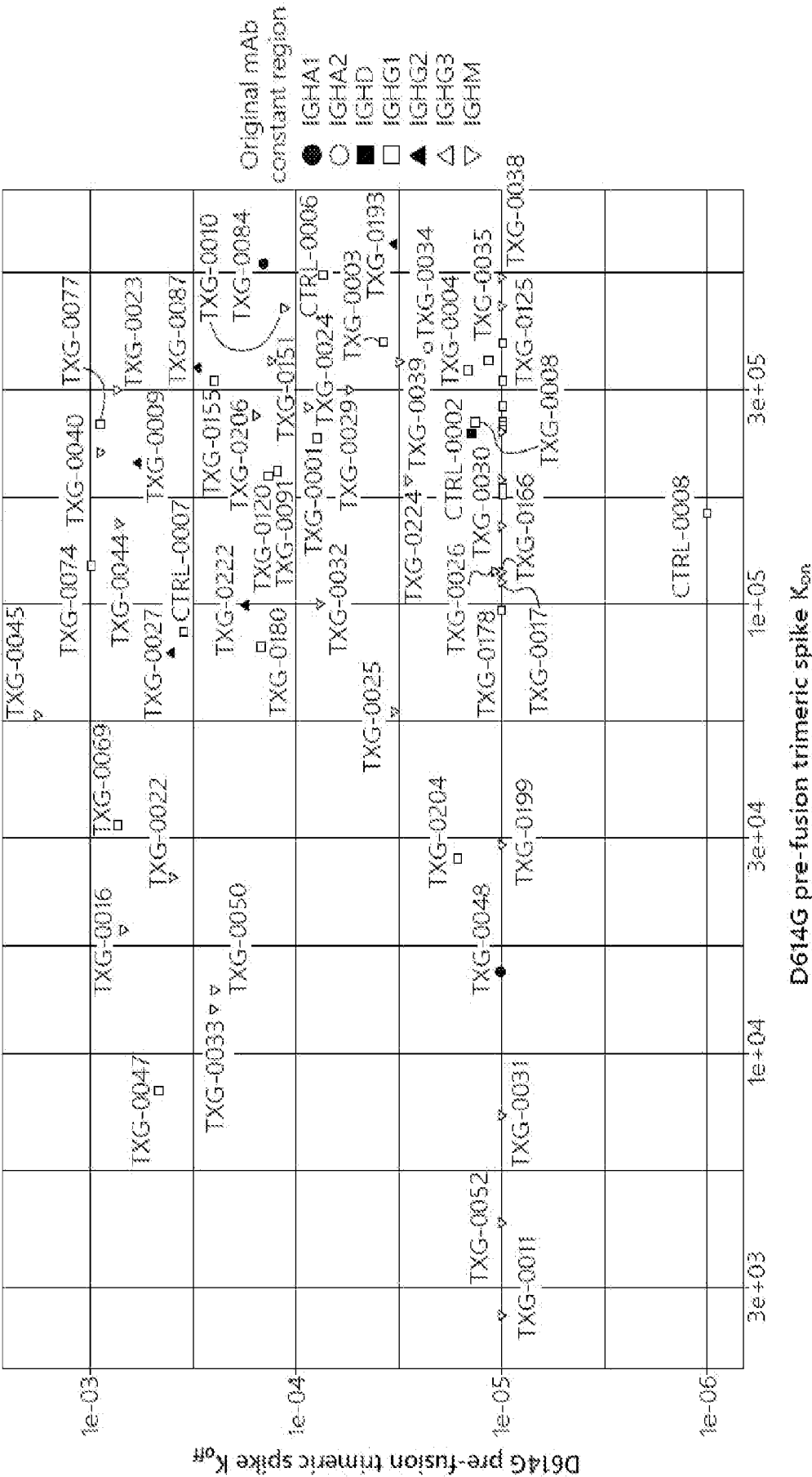


FIG. 16B

RBD kinetics: Triple escape variant K417N / E484K / N501Y

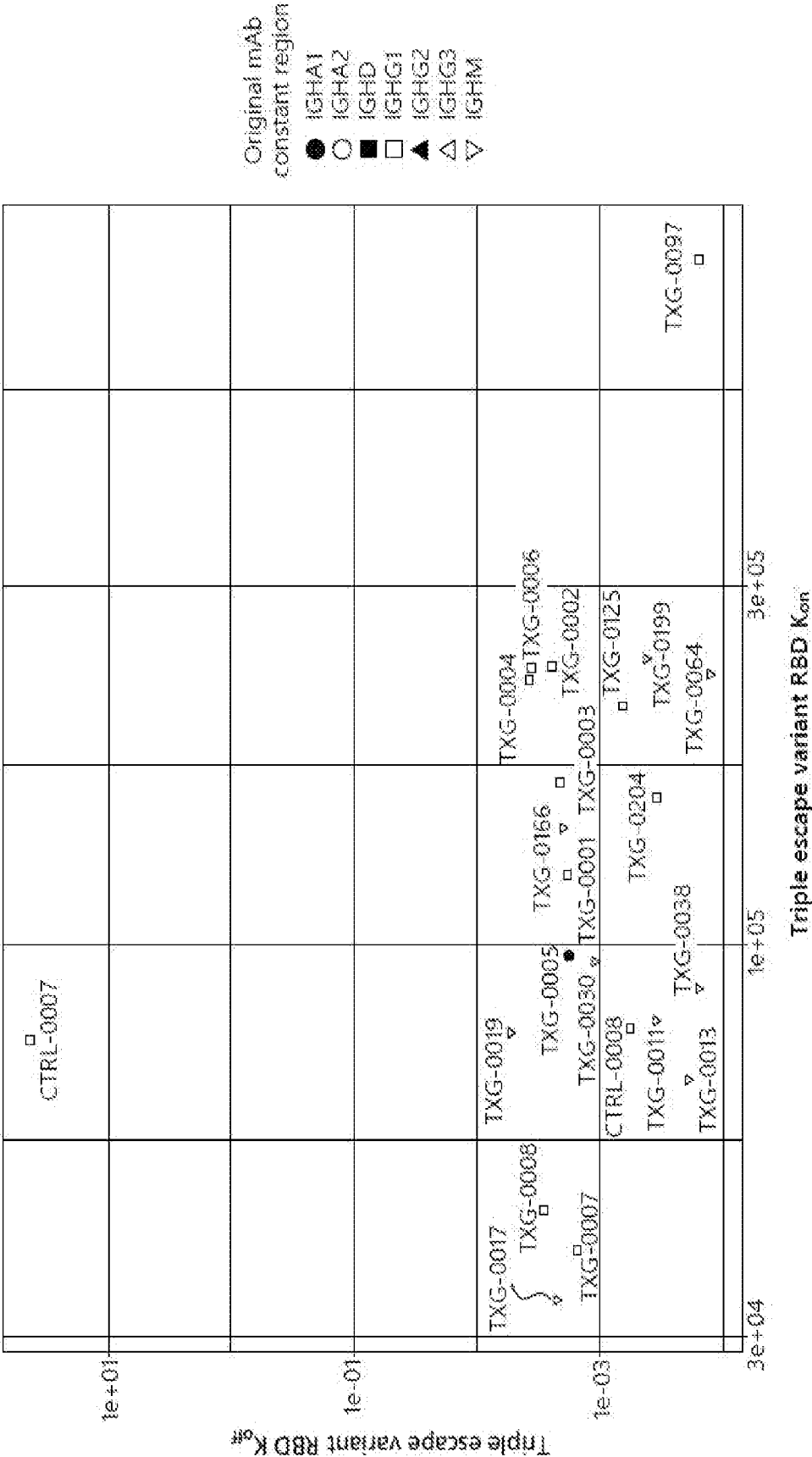


FIG. 17A

RBD kinetics: In comparison to FDA-approved therapeutic antibodies

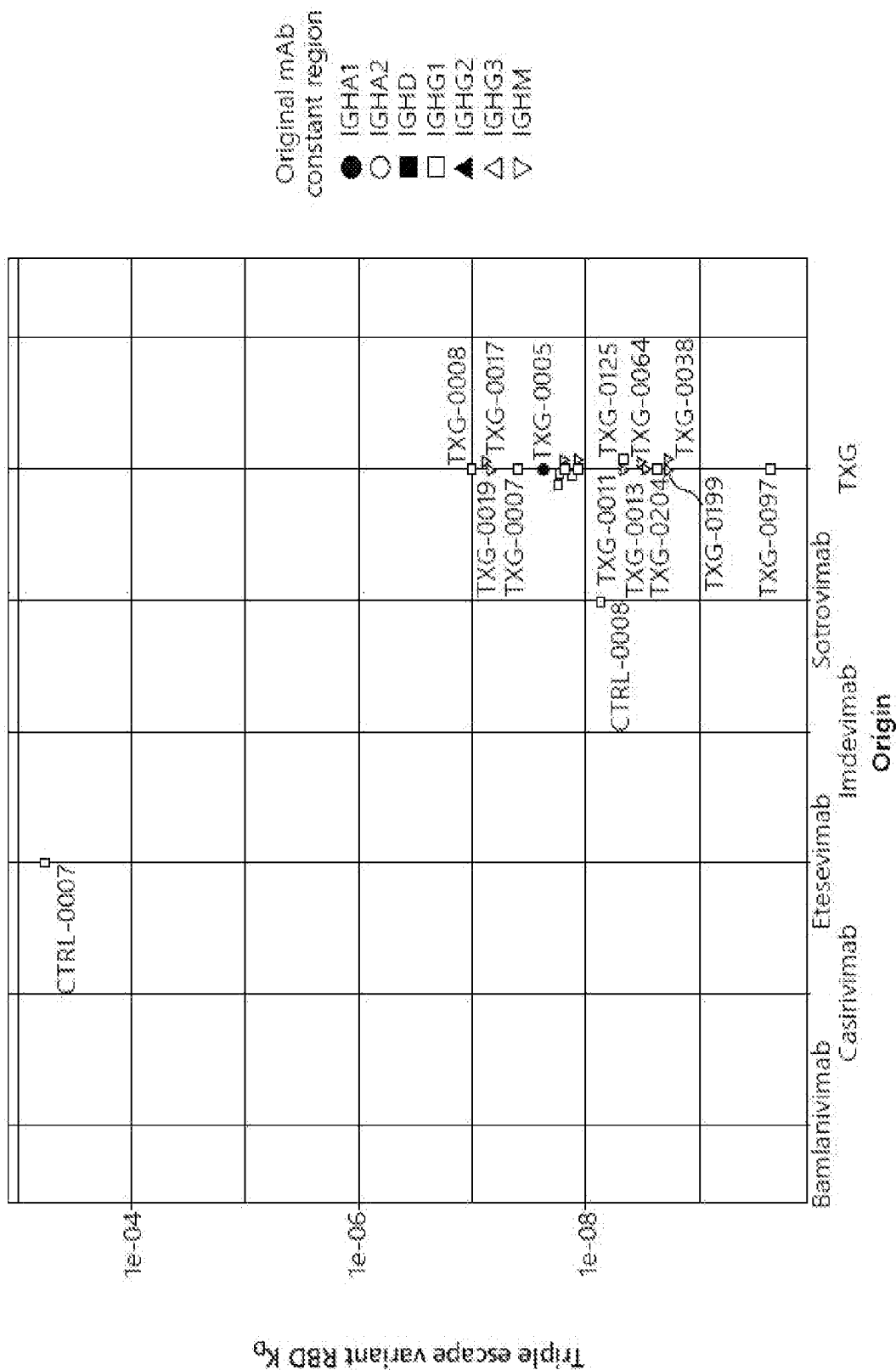


FIG. 17B

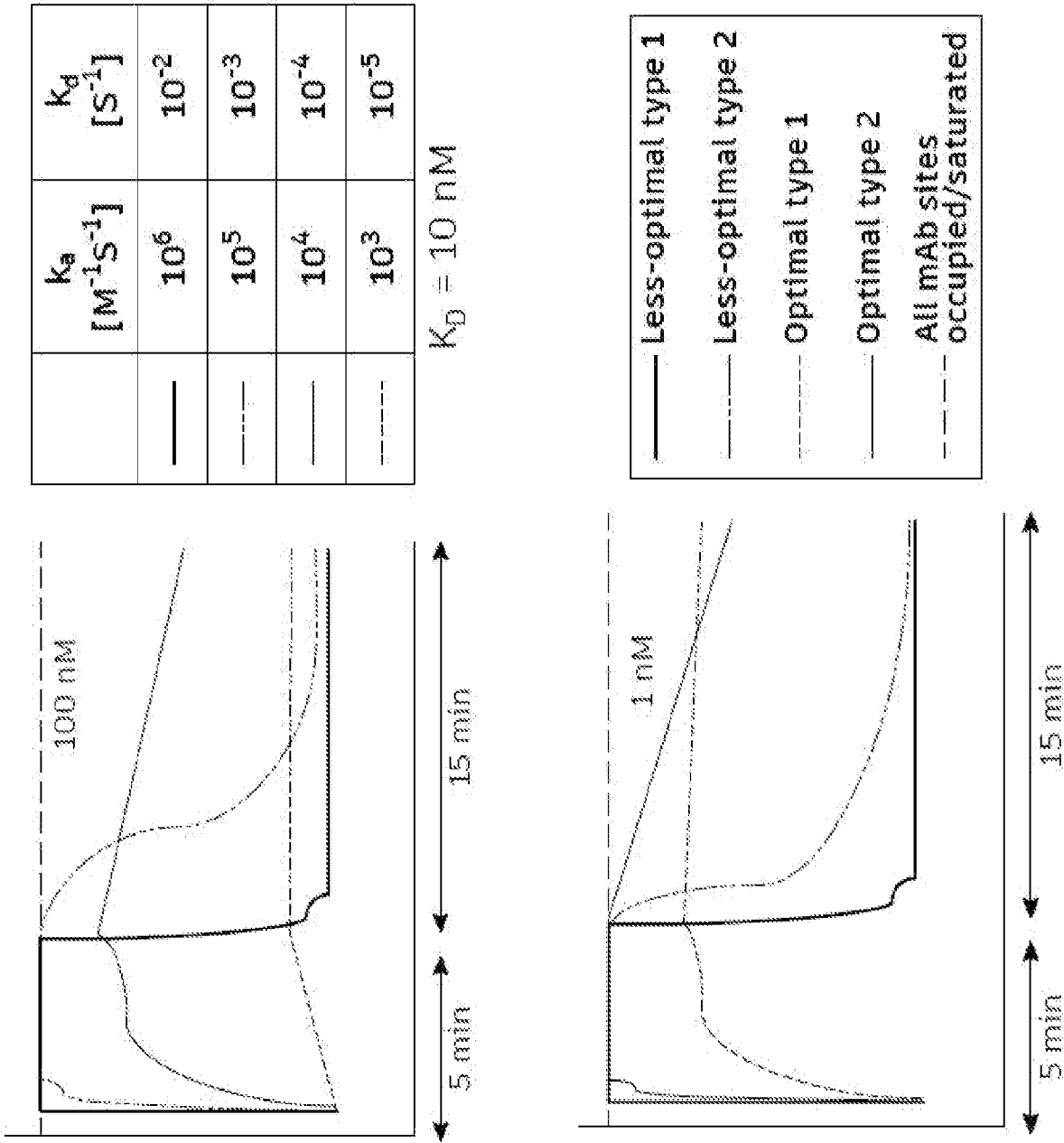


FIG. 18A

FIG. 18B	FIG. 18B (Cont. 7)	FIG. 18B (Cont. 14)	FIG. 18B (Cont. 21)
FIG. 18B (Cont. 1)	FIG. 18B (Cont. 8)	FIG. 18B (Cont. 15)	FIG. 18B (Cont. 22)
FIG. 18B (Cont. 2)	FIG. 18B (Cont. 9)	FIG. 18B (Cont. 16)	FIG. 18B (Cont. 23)
FIG. 18B (Cont. 3)	FIG. 18B (Cont. 10)	FIG. 18B (Cont. 17)	FIG. 18B (Cont. 24)
FIG. 18B (Cont. 4)	FIG. 18B (Cont. 11)	FIG. 18B (Cont. 18)	FIG. 18B (Cont. 25)
FIG. 18B (Cont. 5)	FIG. 18B (Cont. 12)	FIG. 18B (Cont. 19)	FIG. 18B (Cont. 26)
FIG. 18B (Cont. 6)	FIG. 18B (Cont. 13)	FIG. 18B (Cont. 20)	FIG. 18B (Cont. 27)

KEY to FIG. 18B

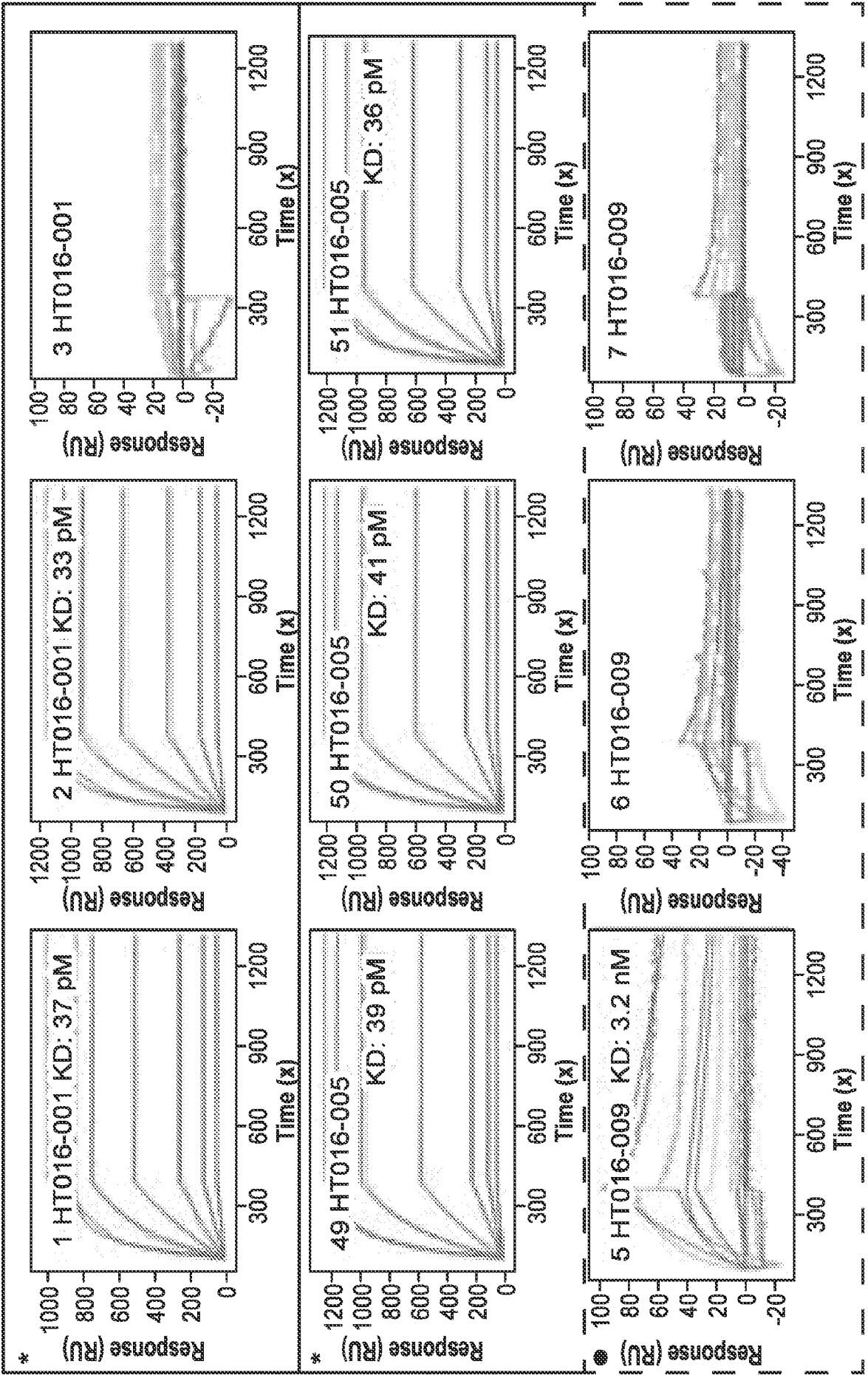


FIG. 18B

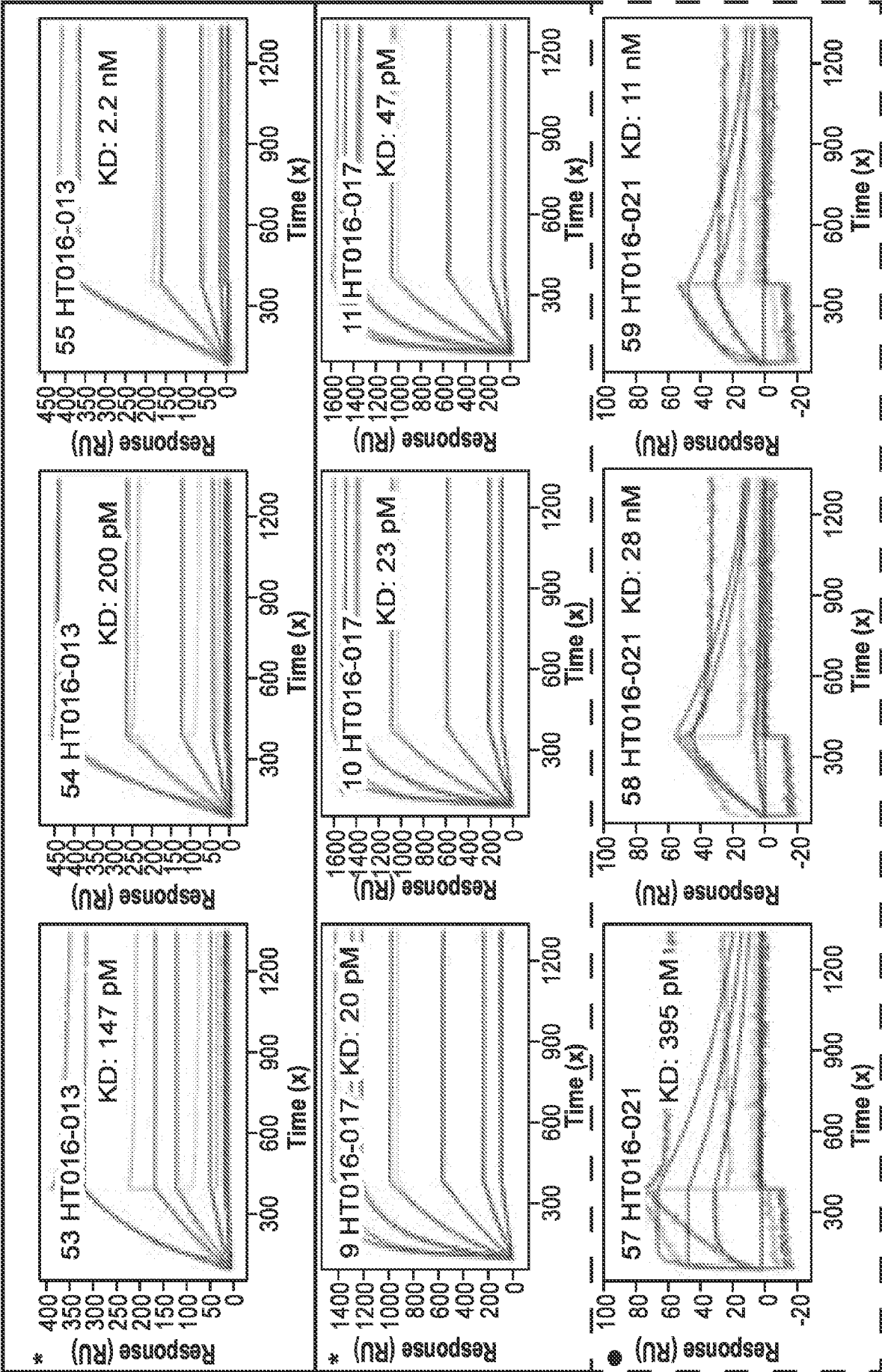


FIG. 18B (Cont. 1)

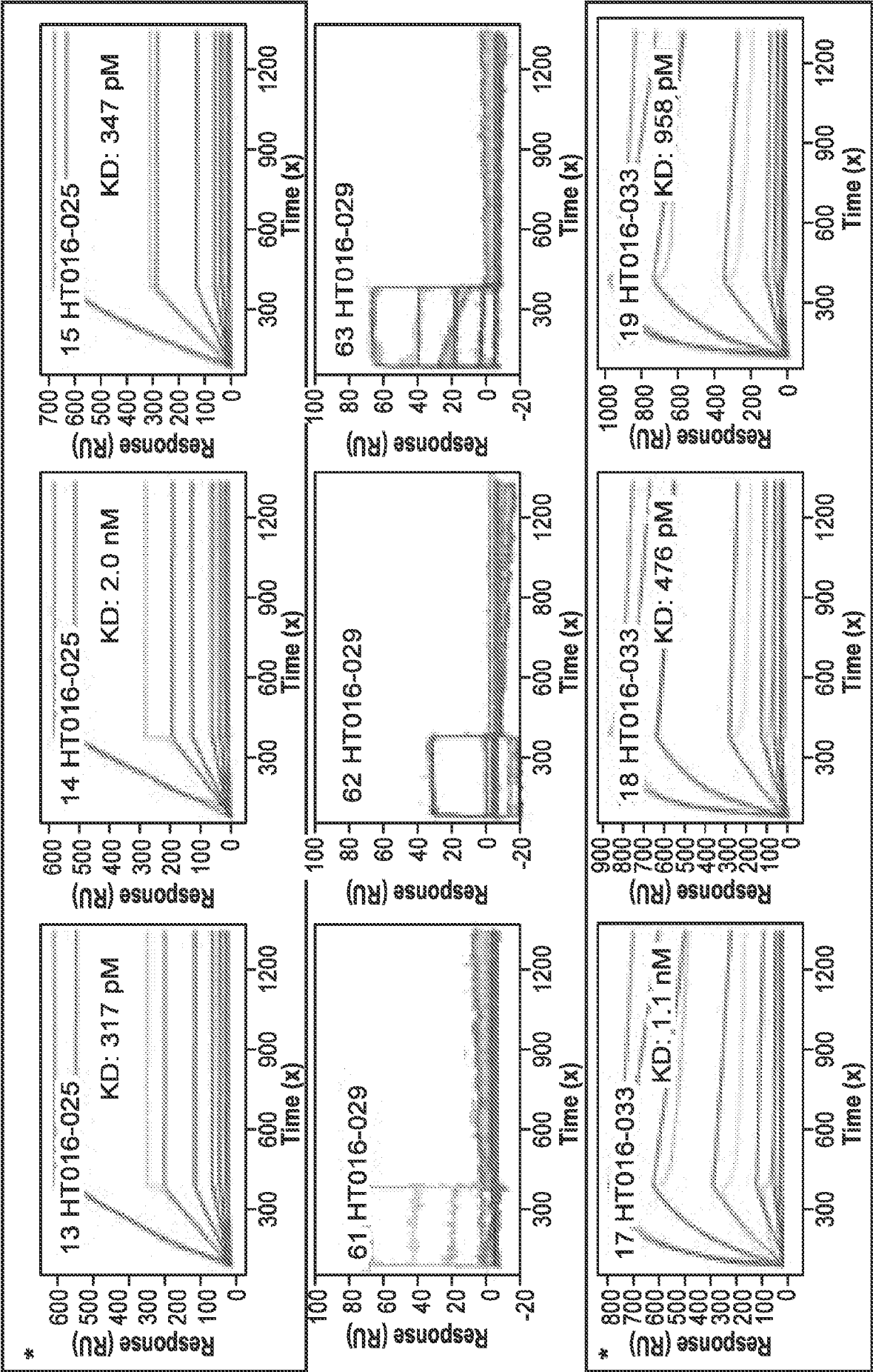


FIG. 18B (Cont. 2)

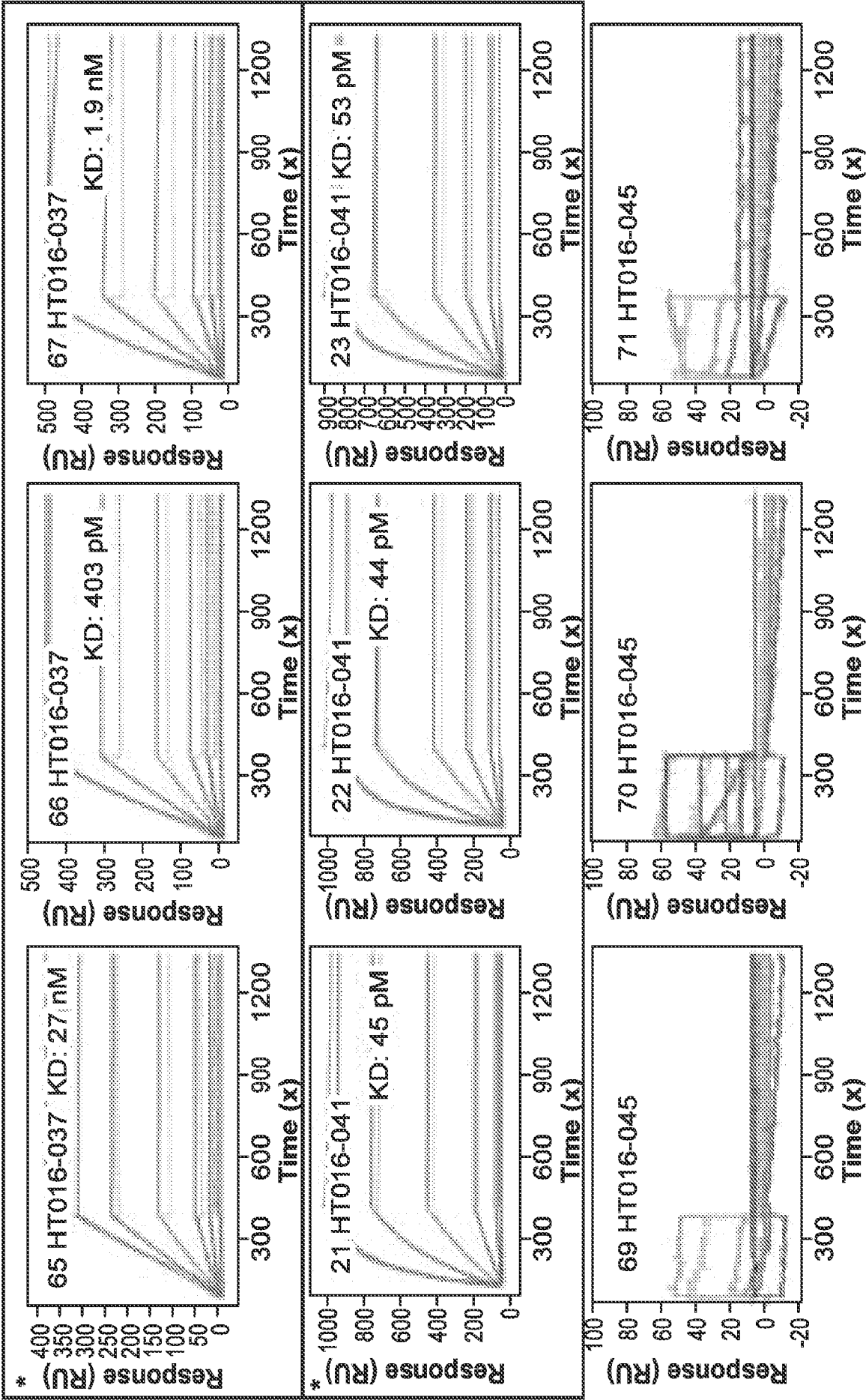


FIG. 18B (Cont. 3)

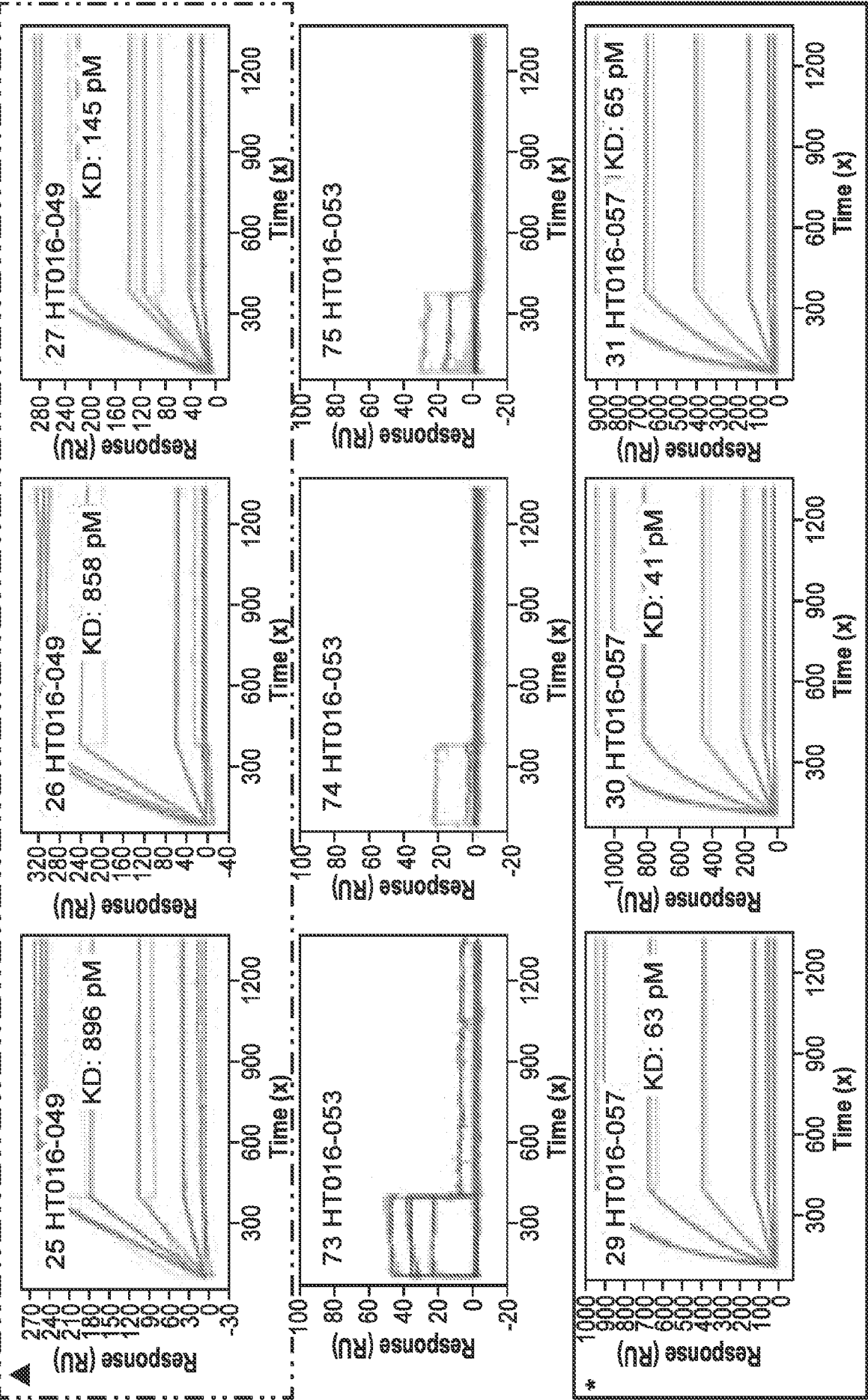


FIG. 18B (Cont. 4)

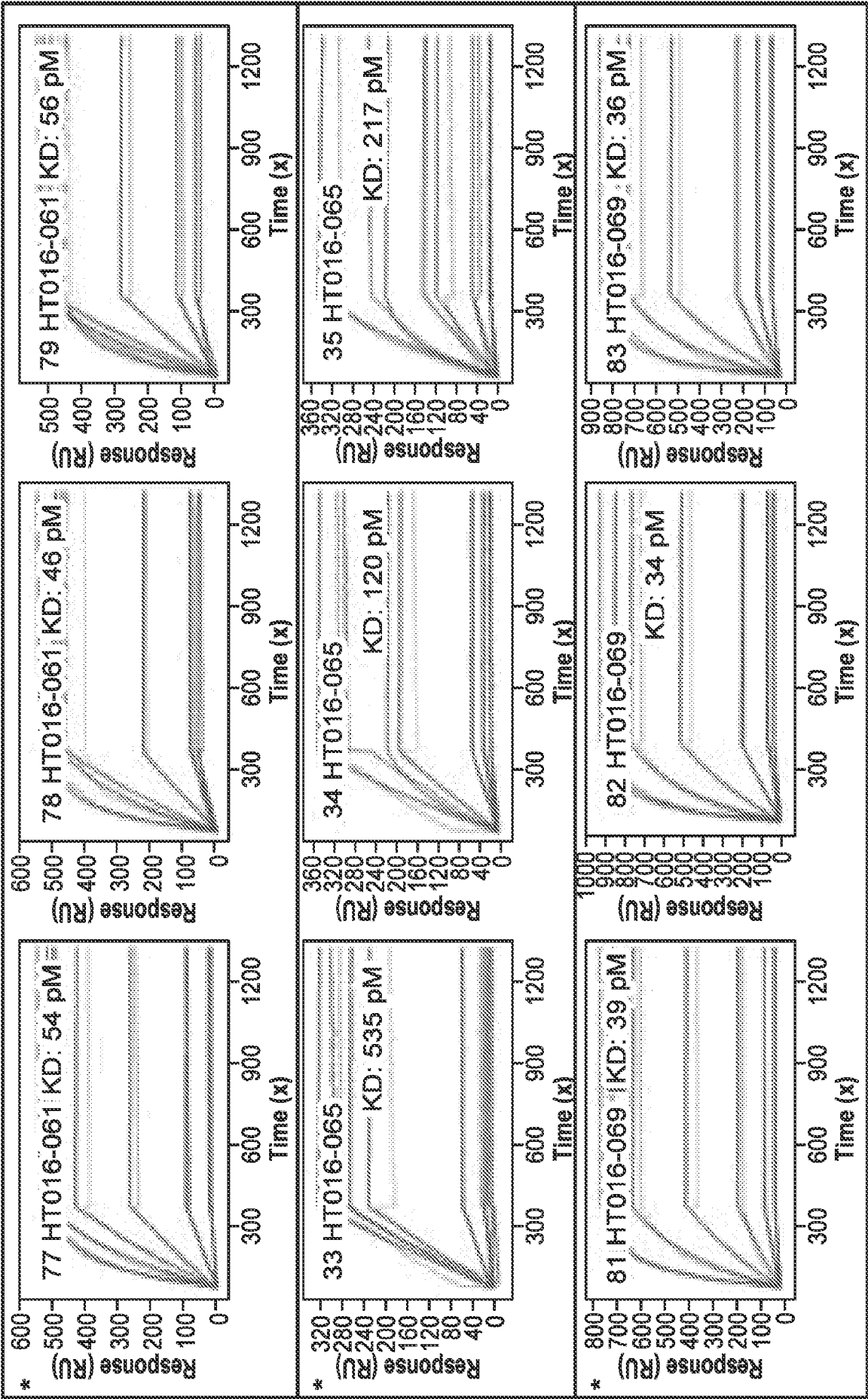


FIG. 18B (Cont. 5)

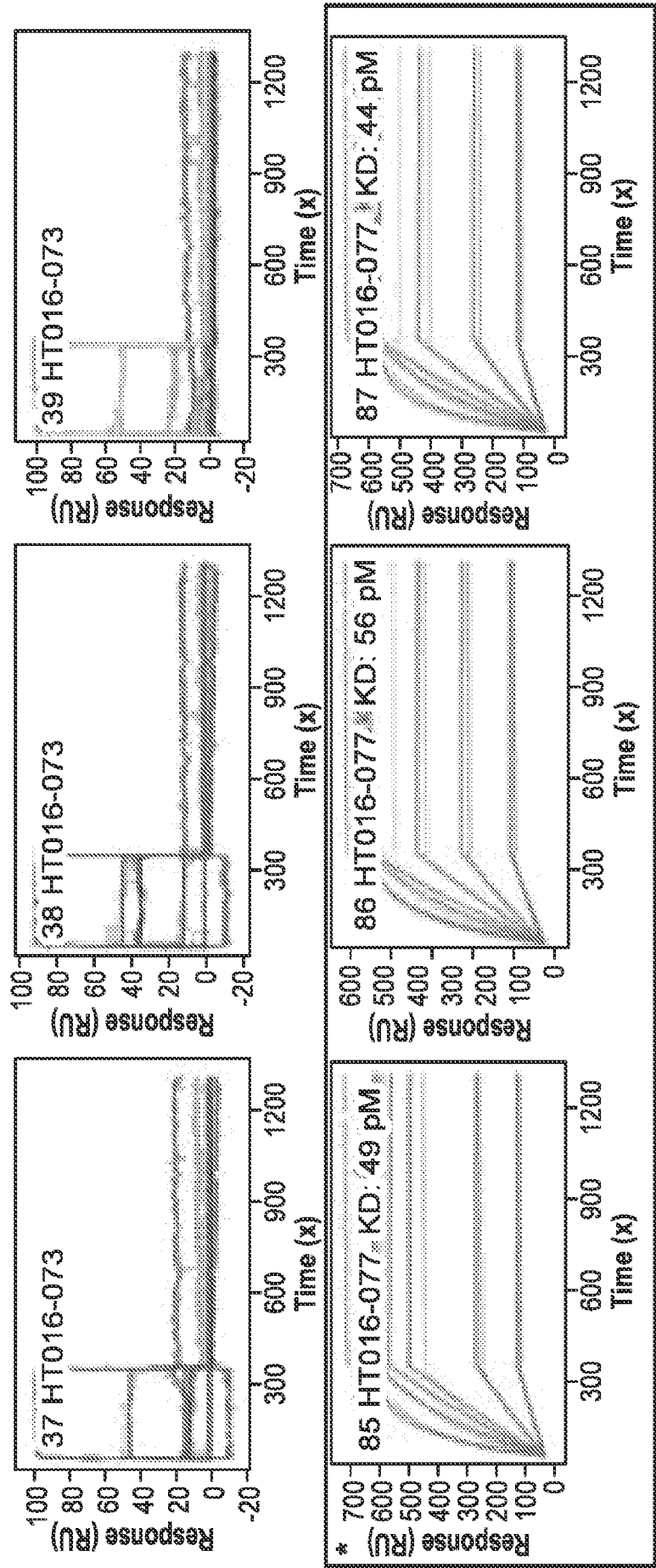


FIG. 18B (Cont. 6)

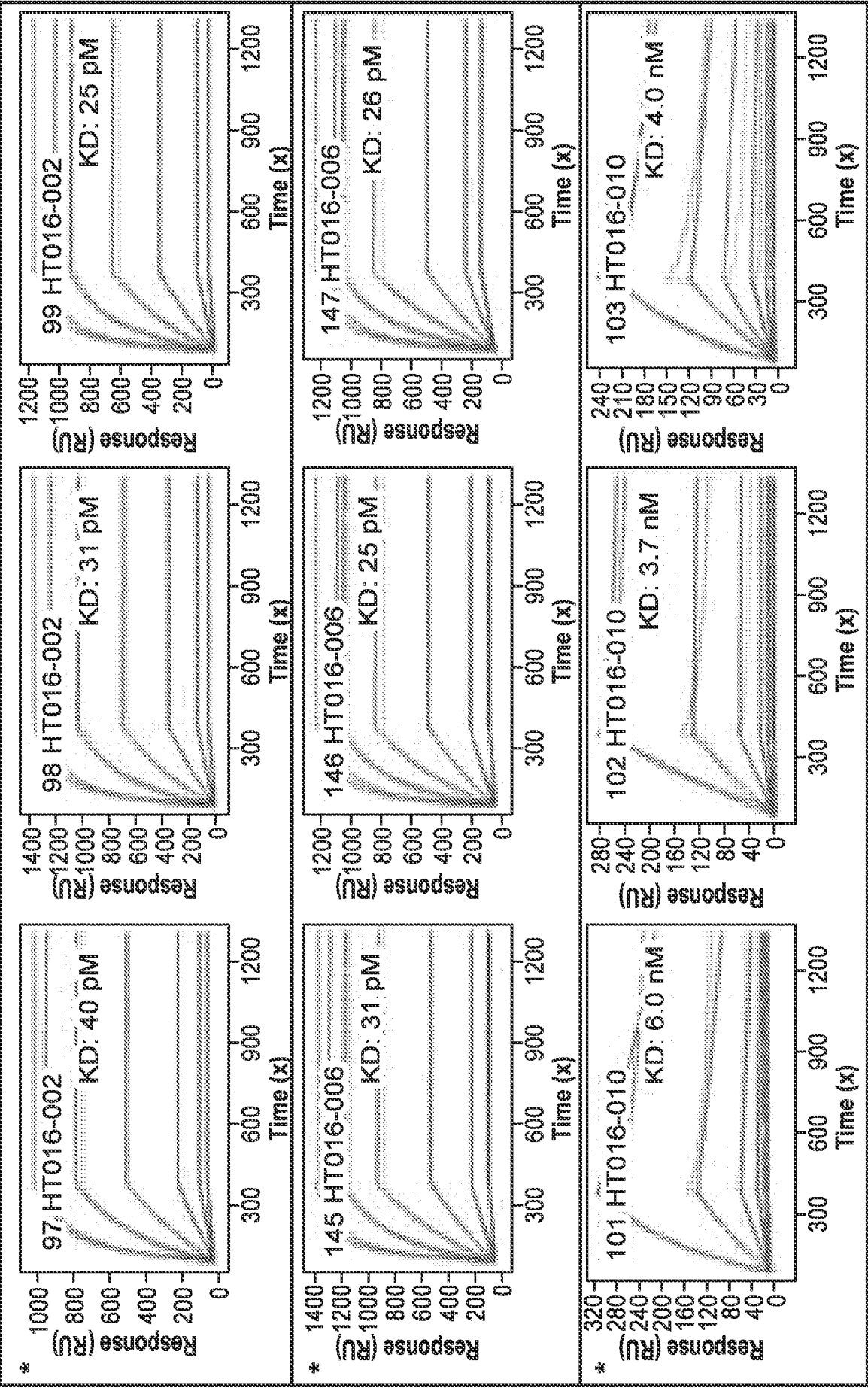


FIG. 18B (Cont. 7)

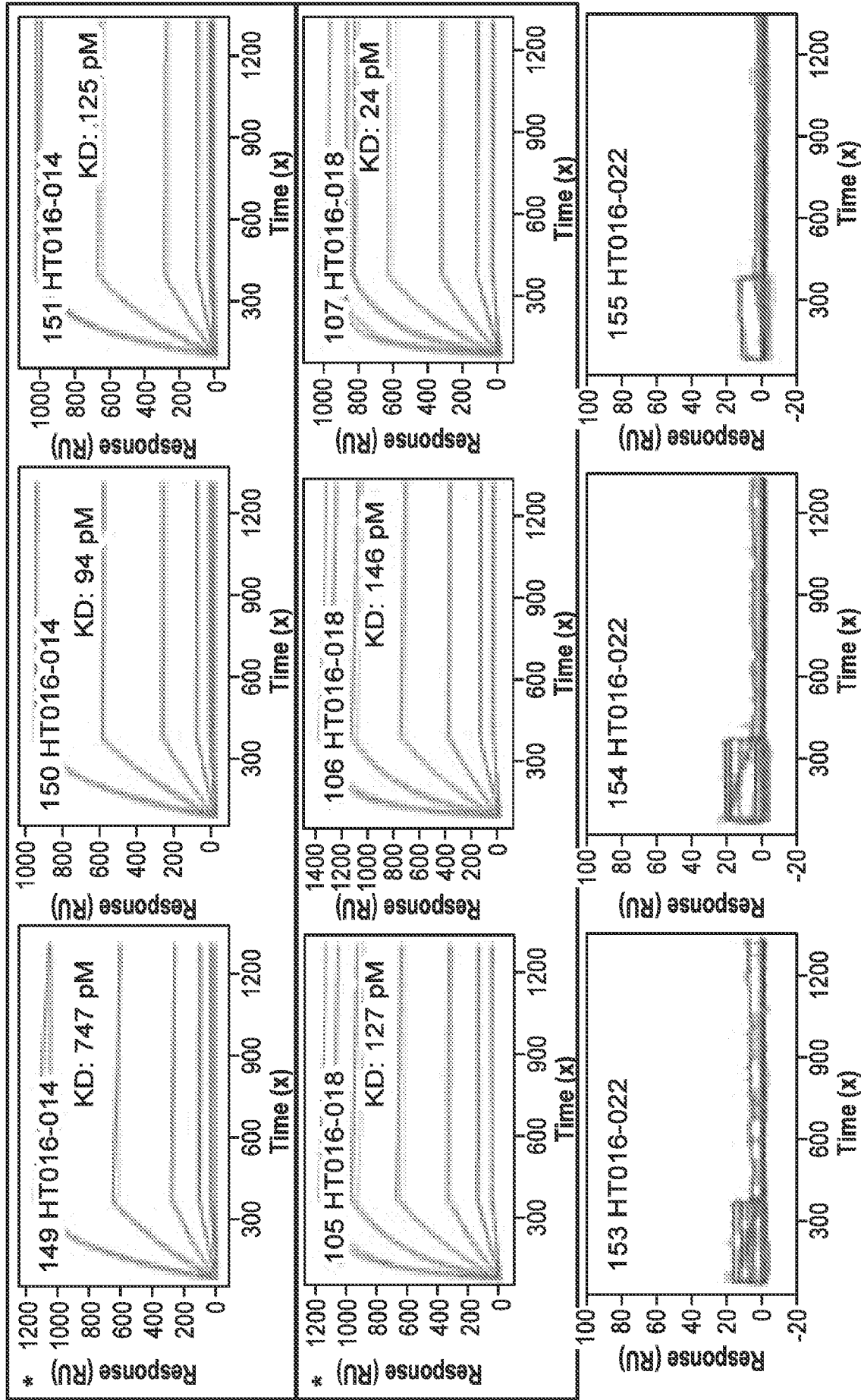


FIG. 18B (Cont. 8)

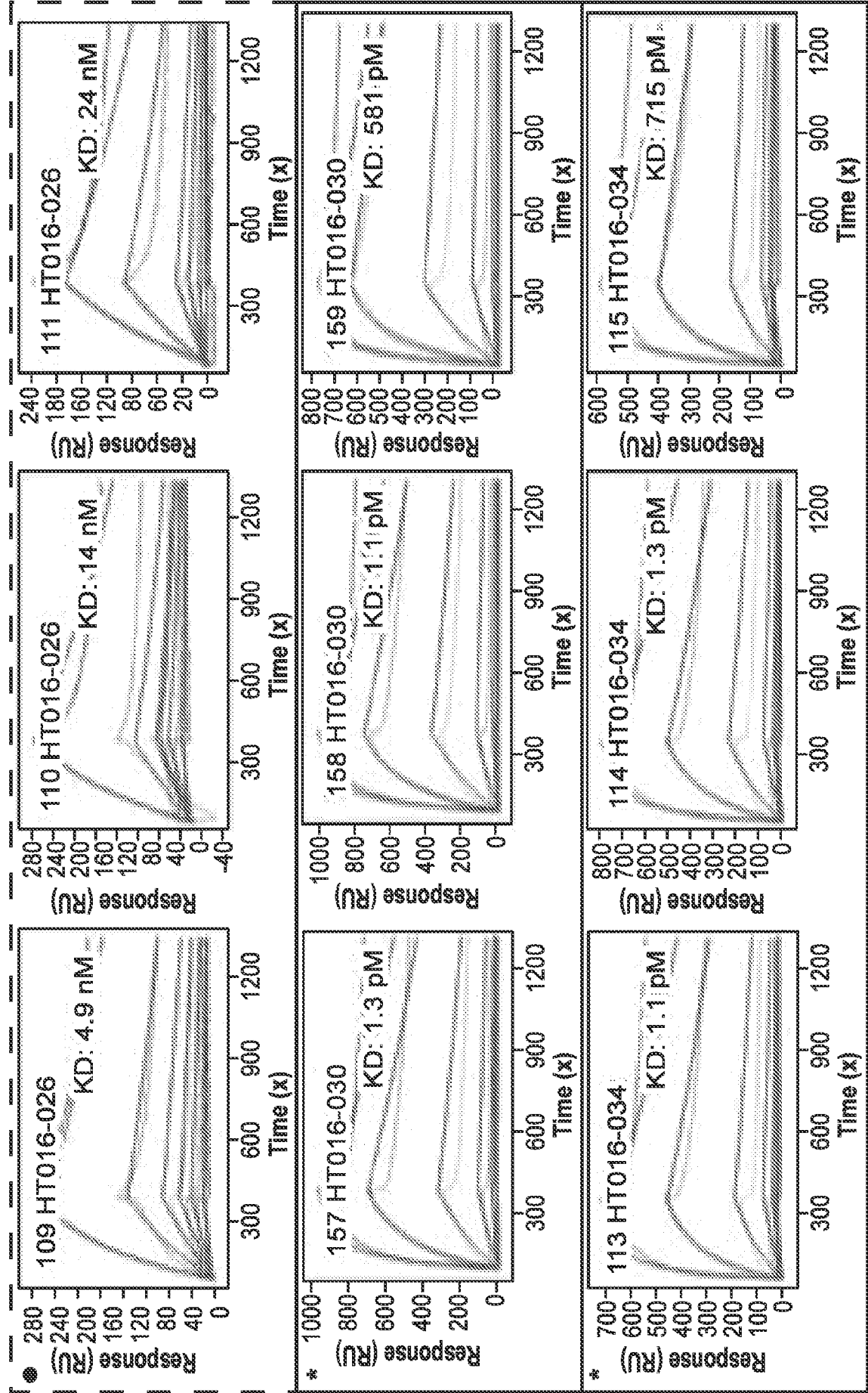


FIG. 18B (Cont. 9)

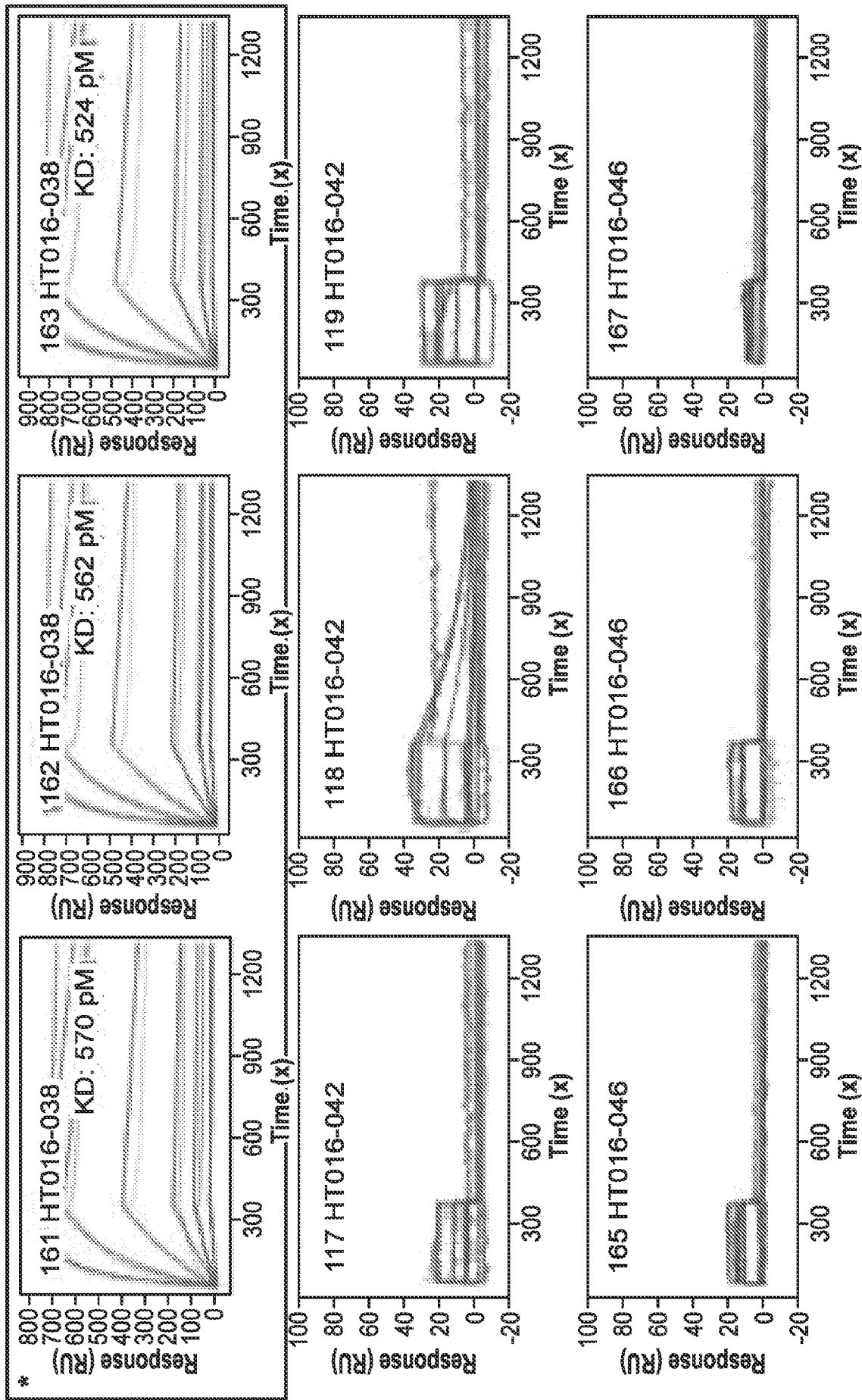


FIG. 18B (Cont. 10)

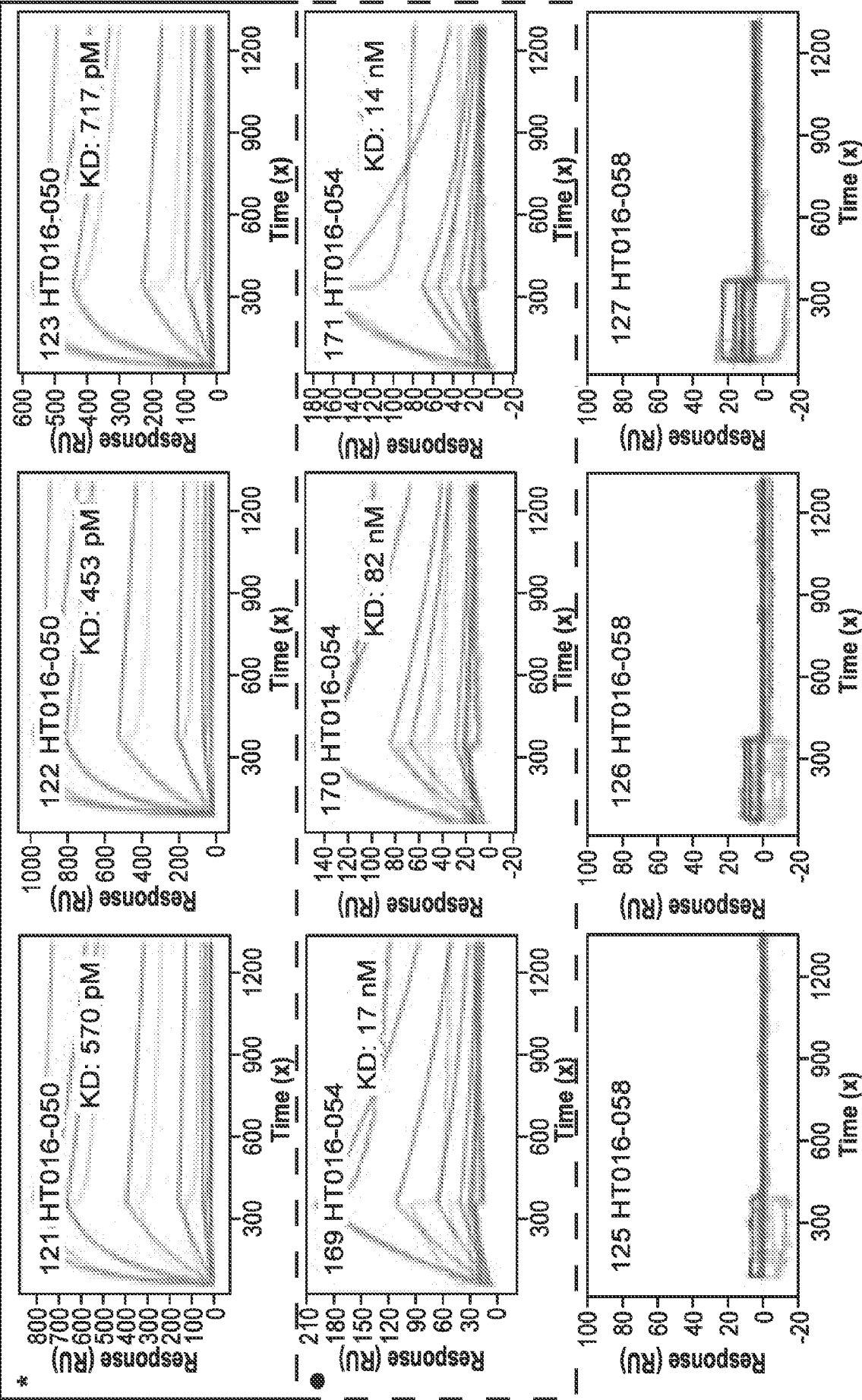


FIG. 18B (Cont. 11)

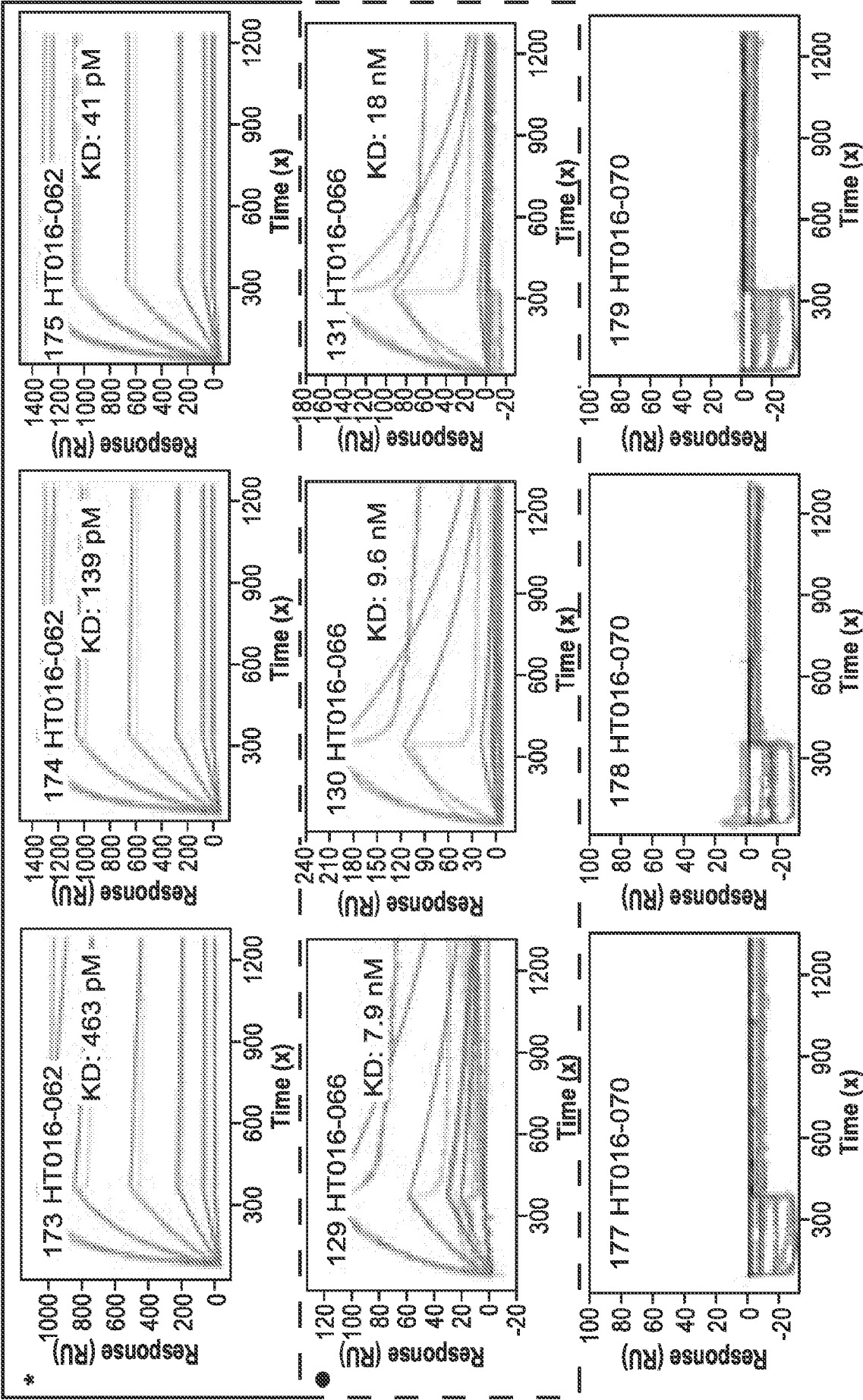


FIG. 18B (Cont. 12)

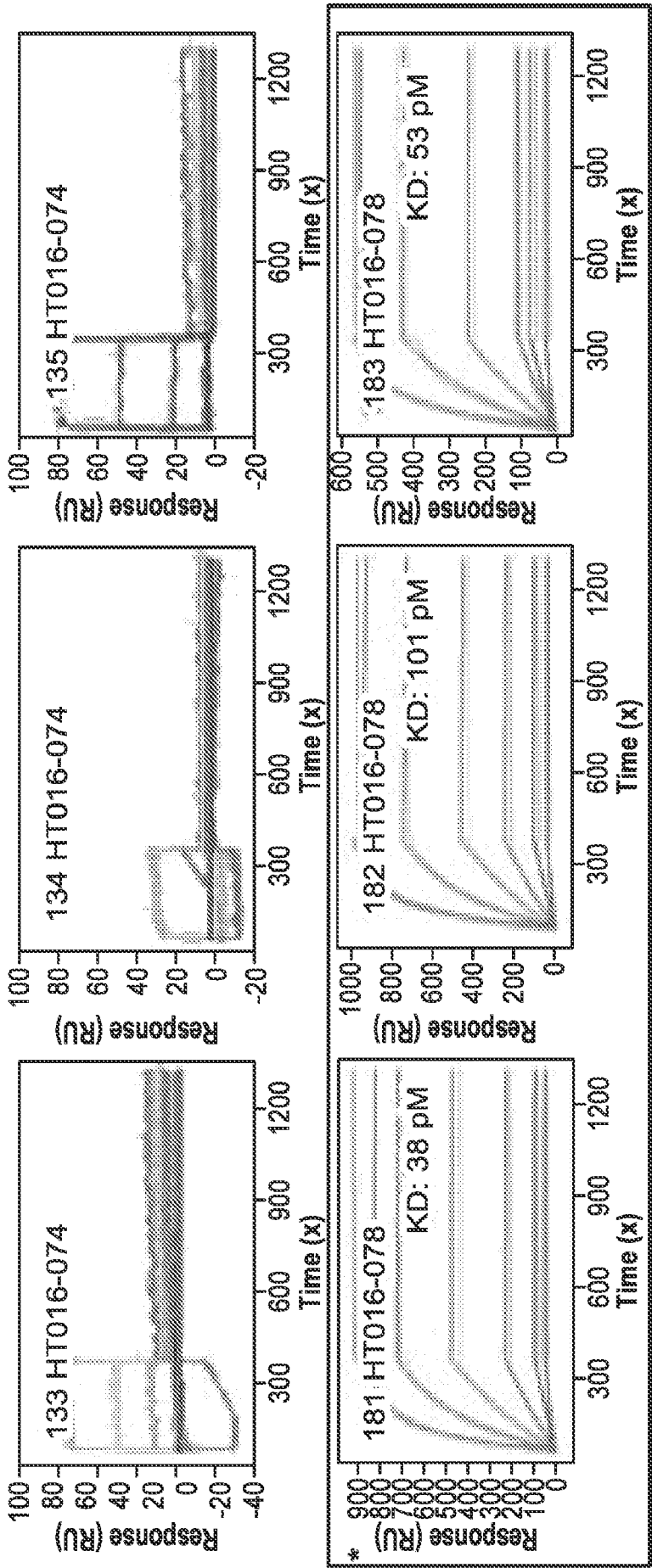


FIG. 18B (Cont. 13)

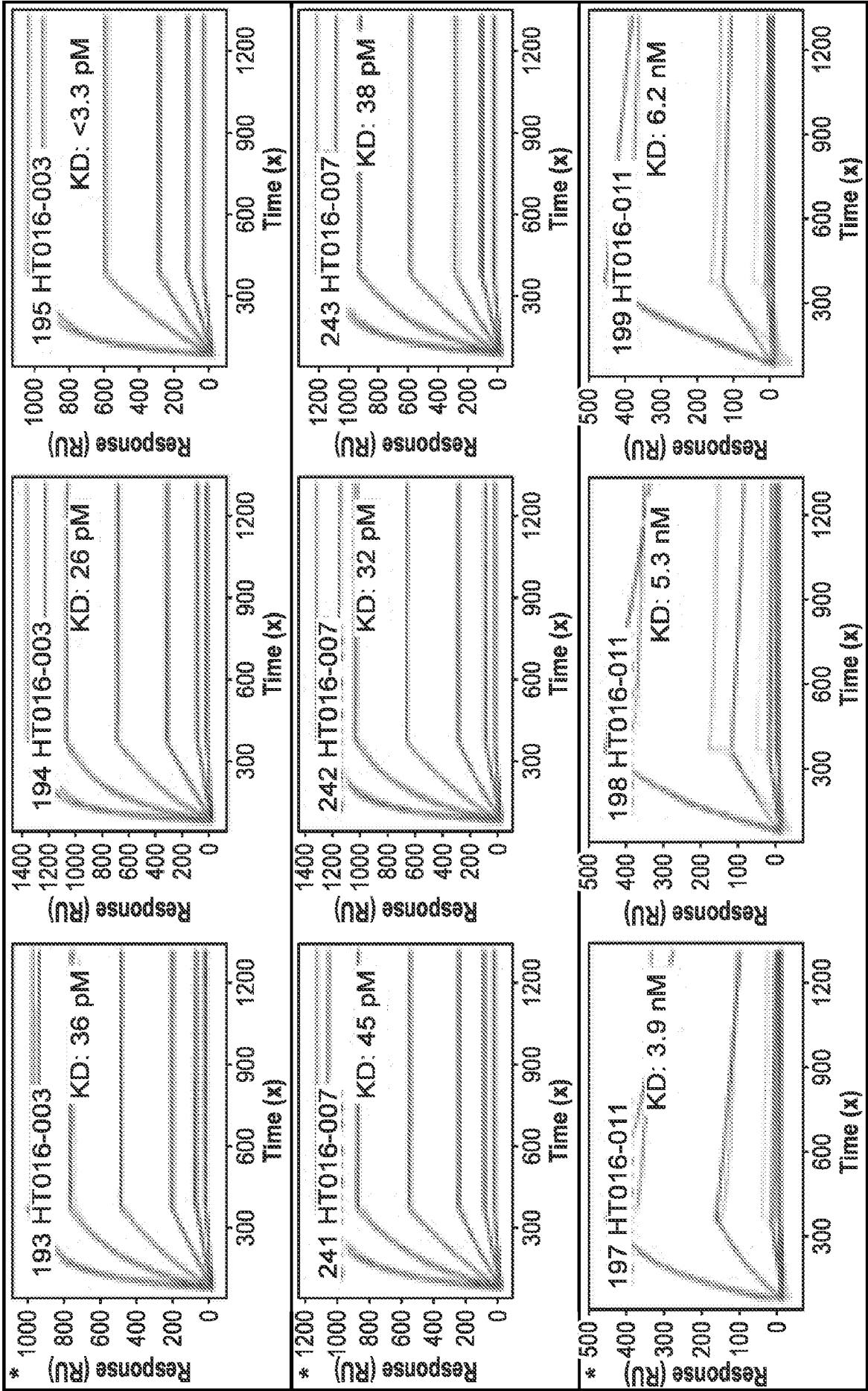


FIG. 18B (Cont. 14)

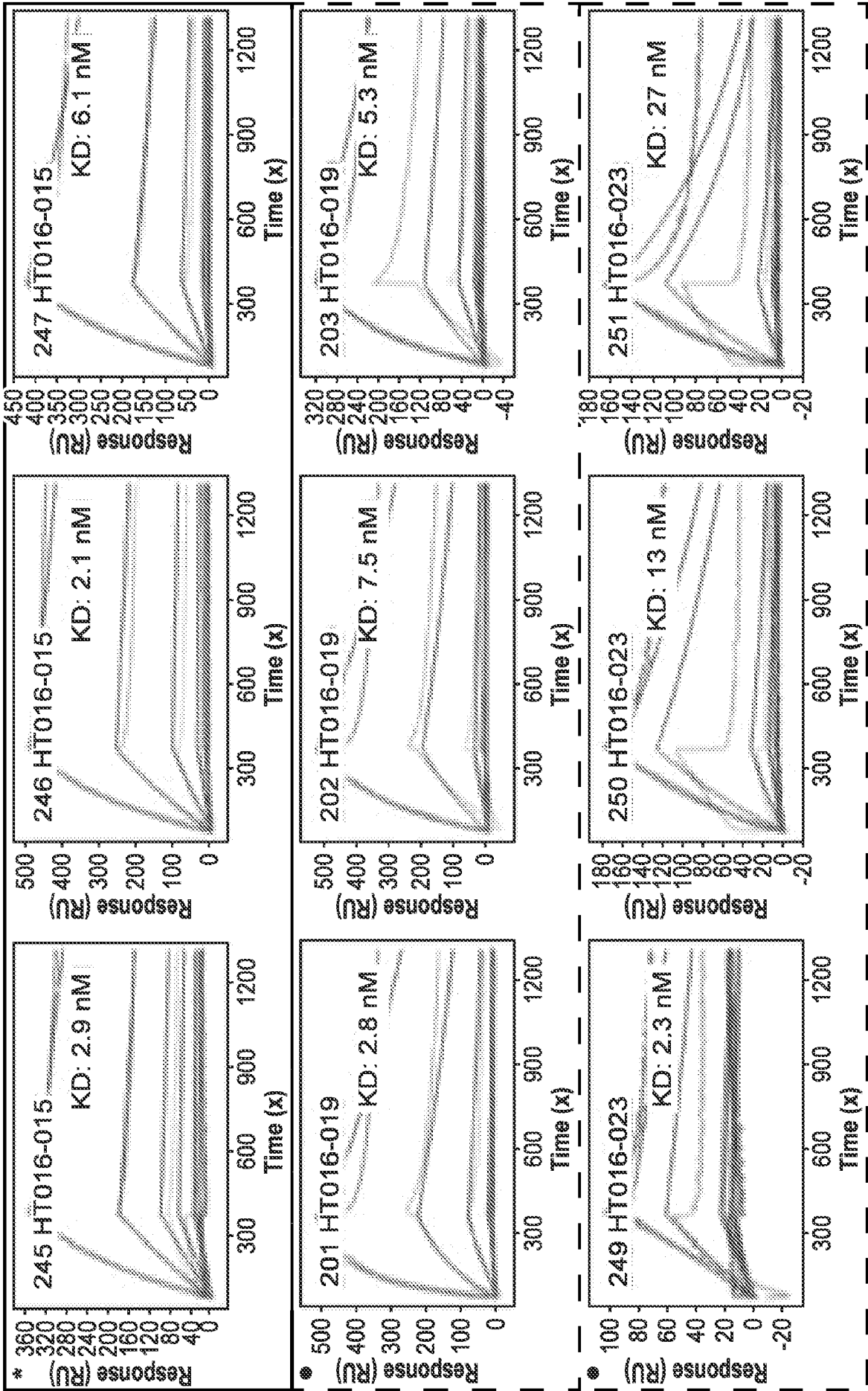


FIG. 18B (Cont. 15)

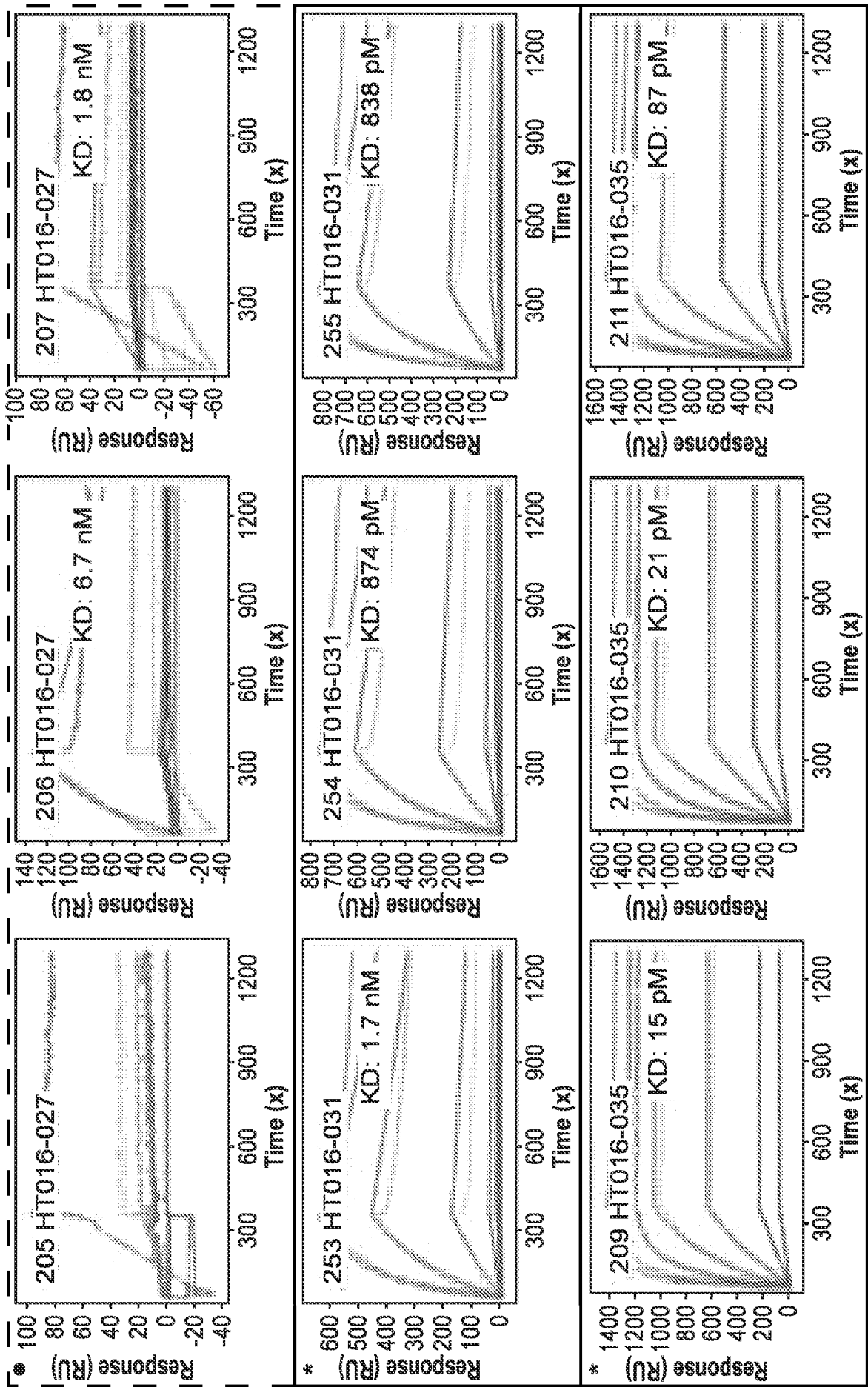


FIG. 18B (Cont. 16)

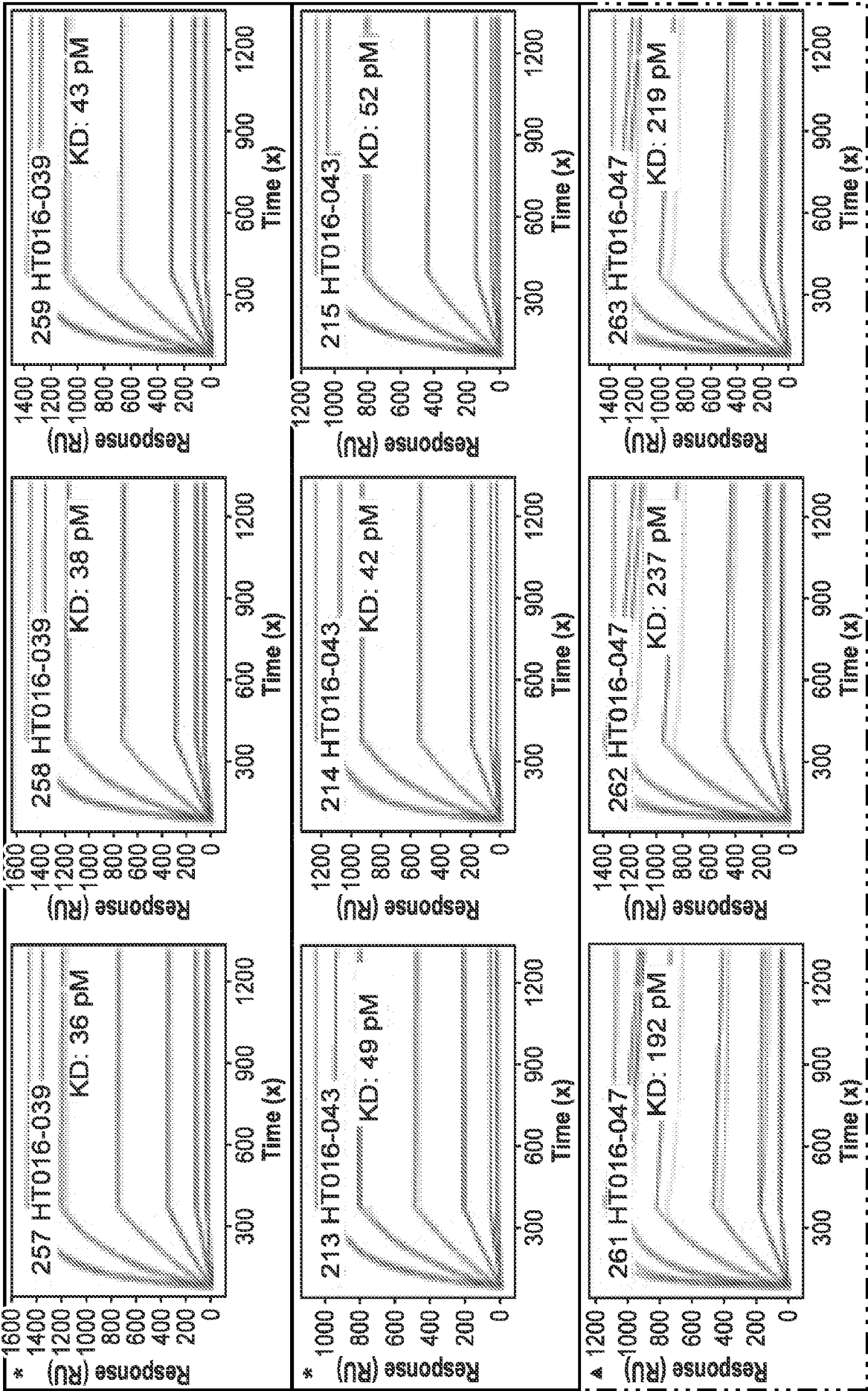


FIG. 18B (Cont. 17)

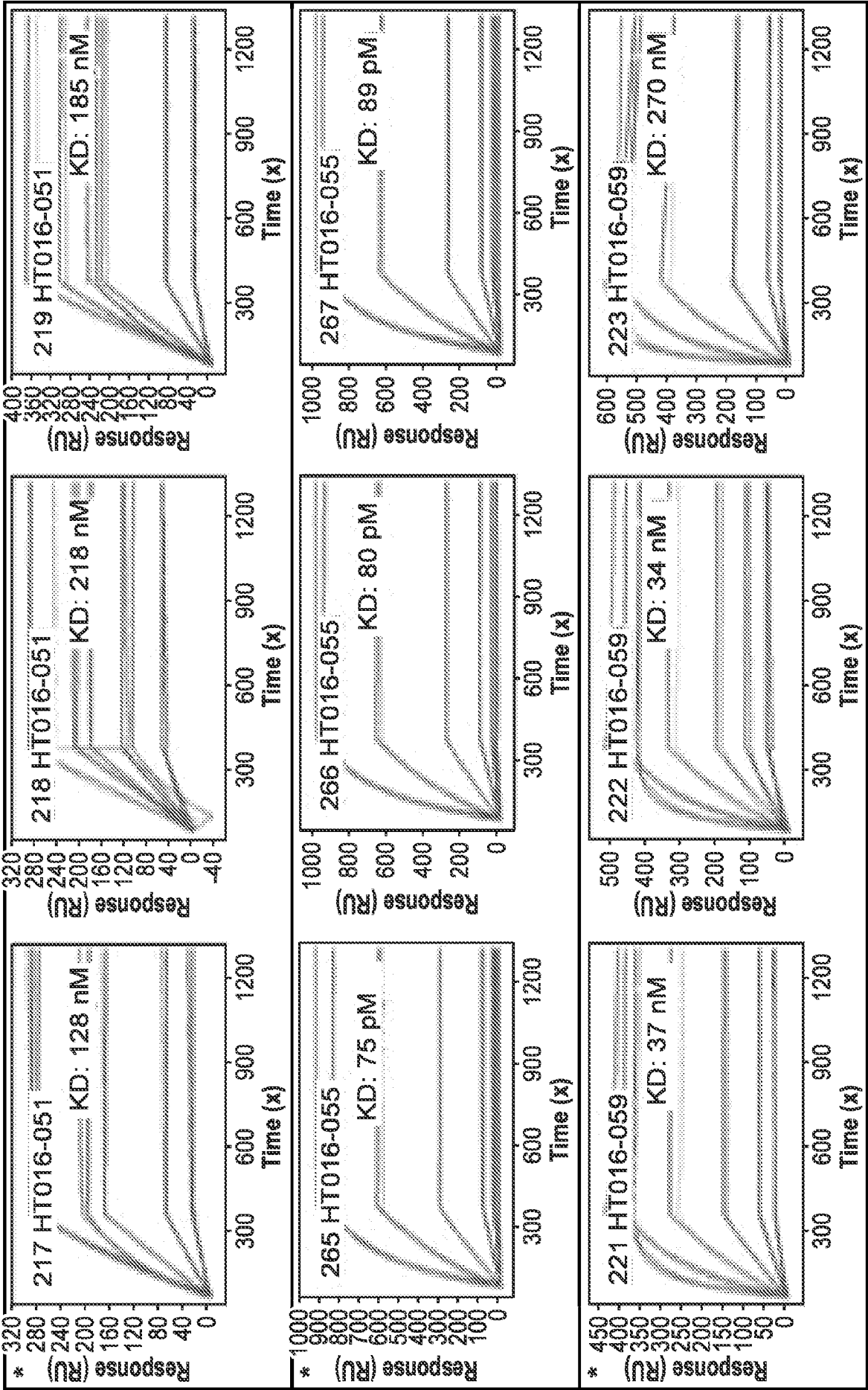


FIG. 18B (Cont. 18)

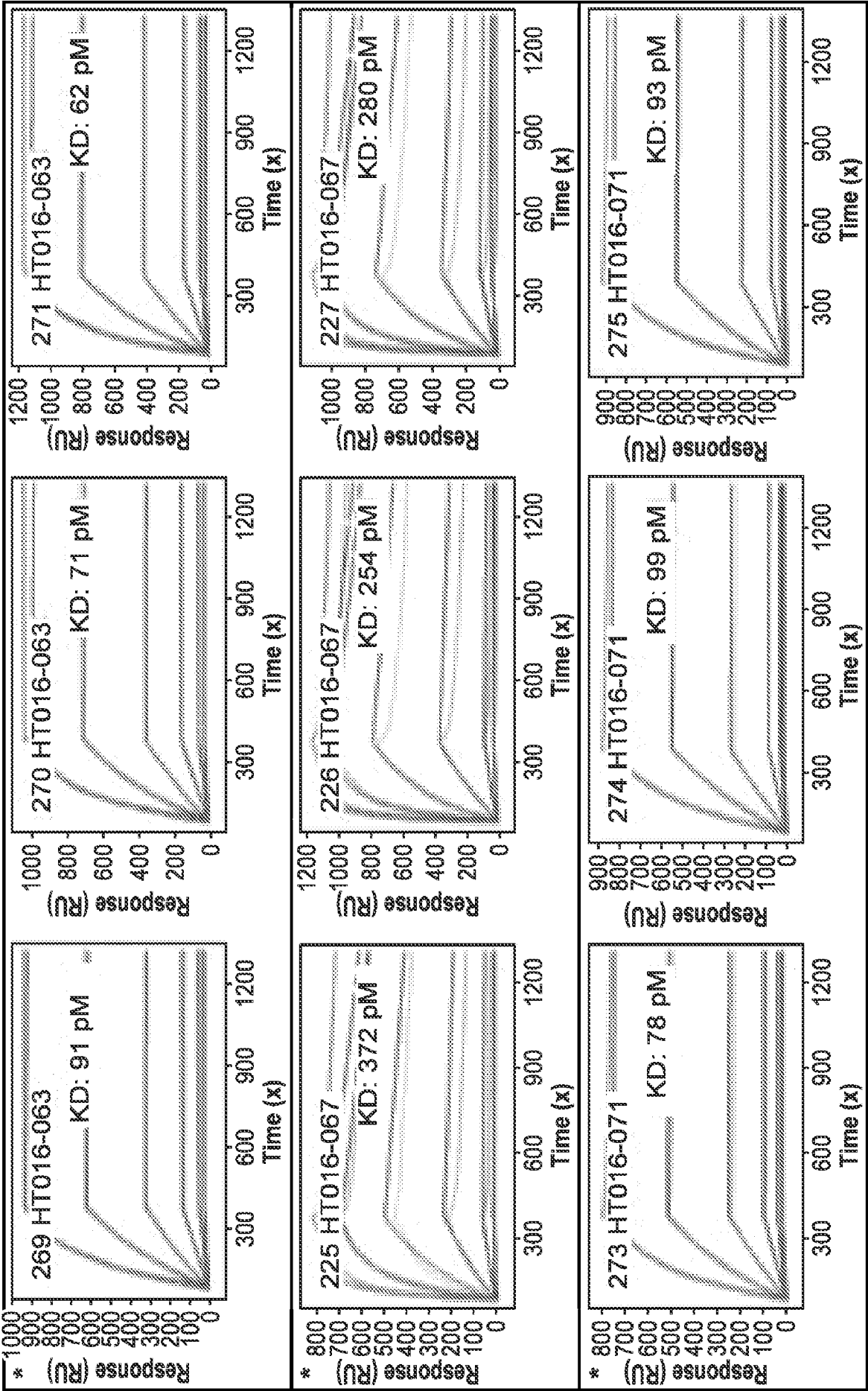


FIG. 18B (Cont. 19)

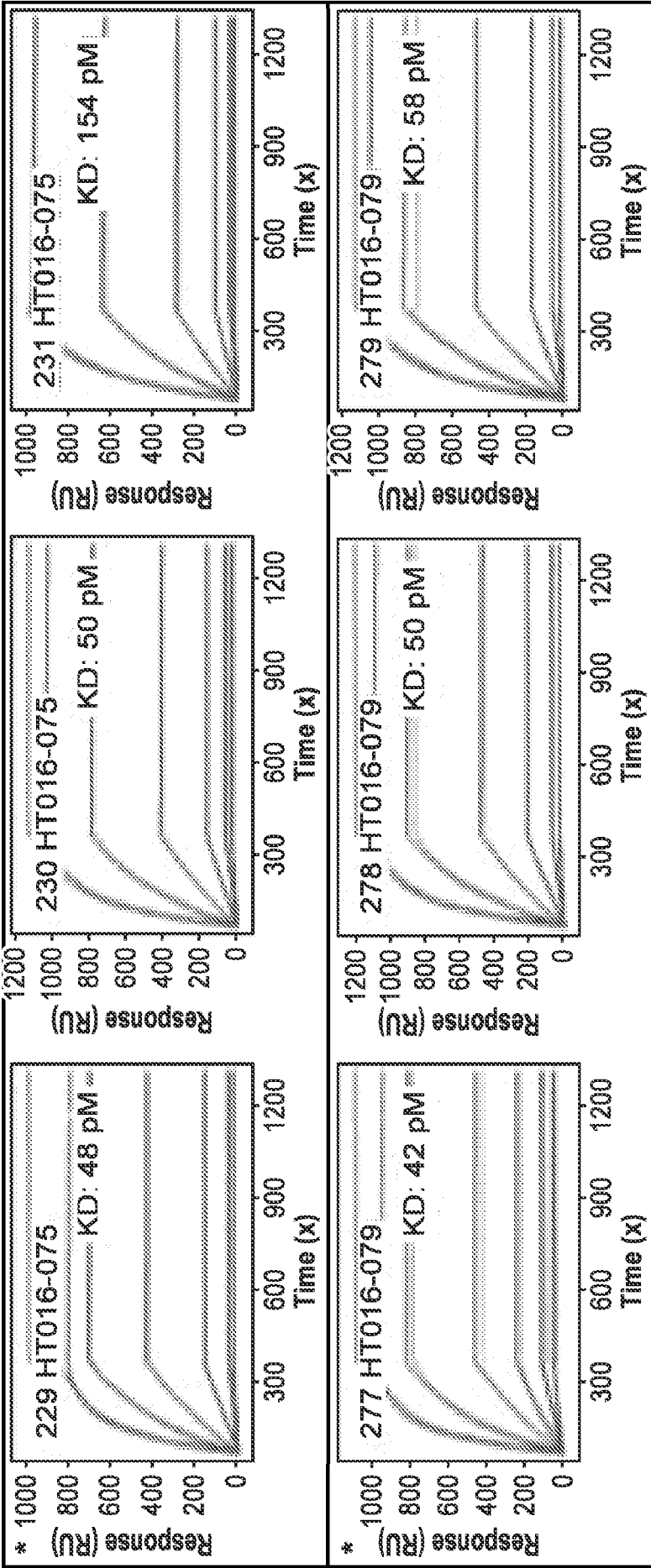


FIG. 18B (Cont. 20)

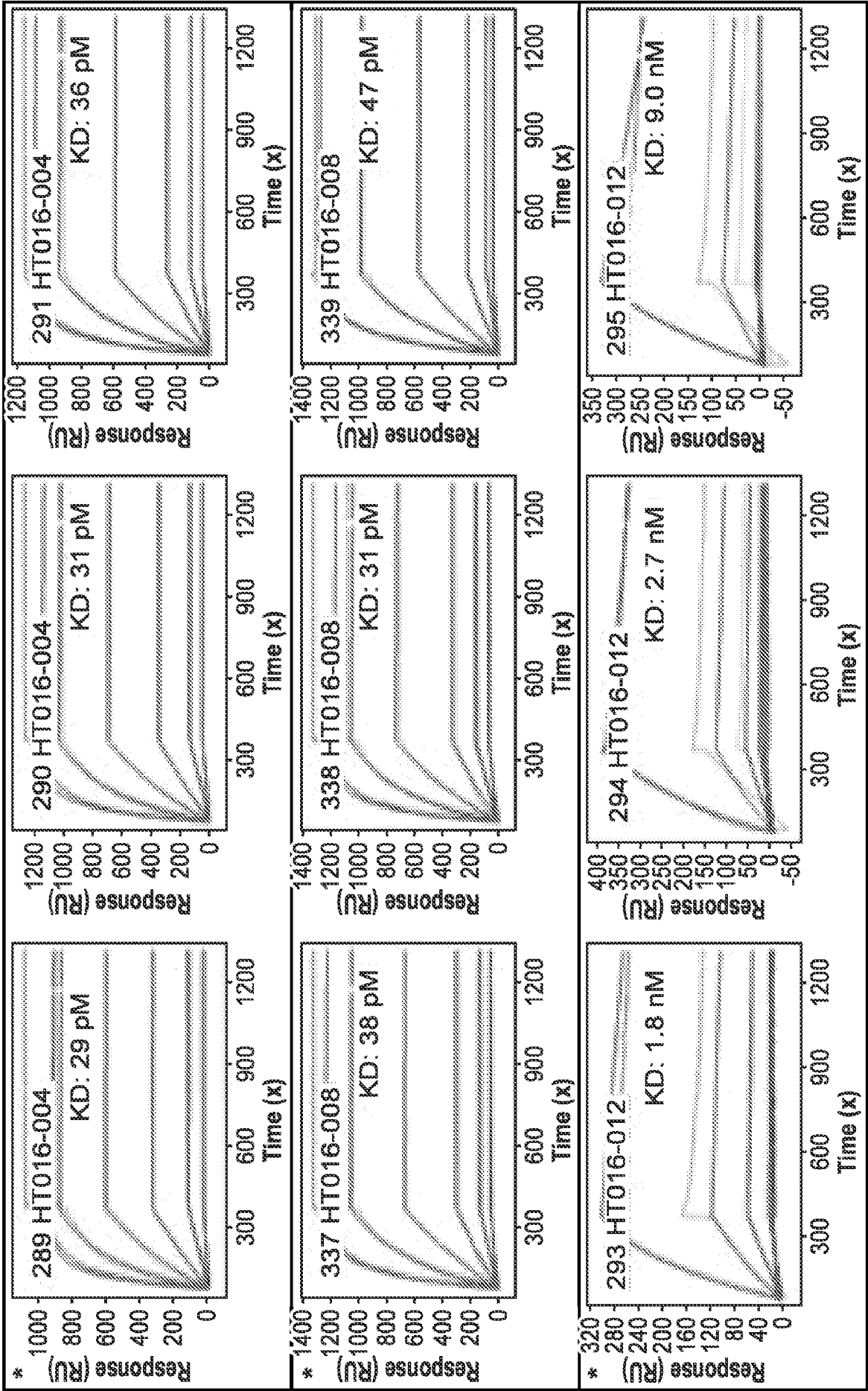


FIG. 18B (Cont. 21)

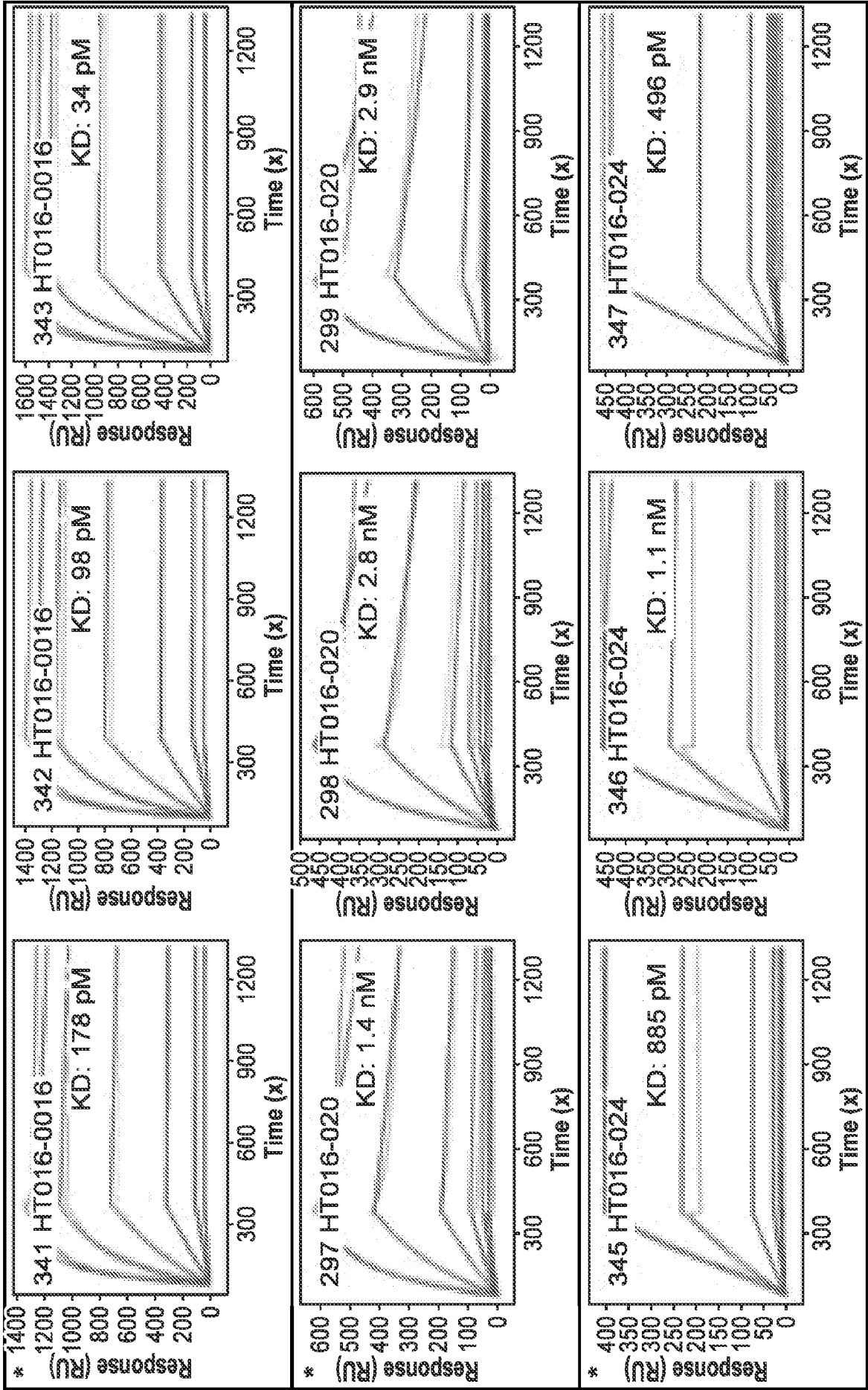


FIG. 18B (Cont. 22)

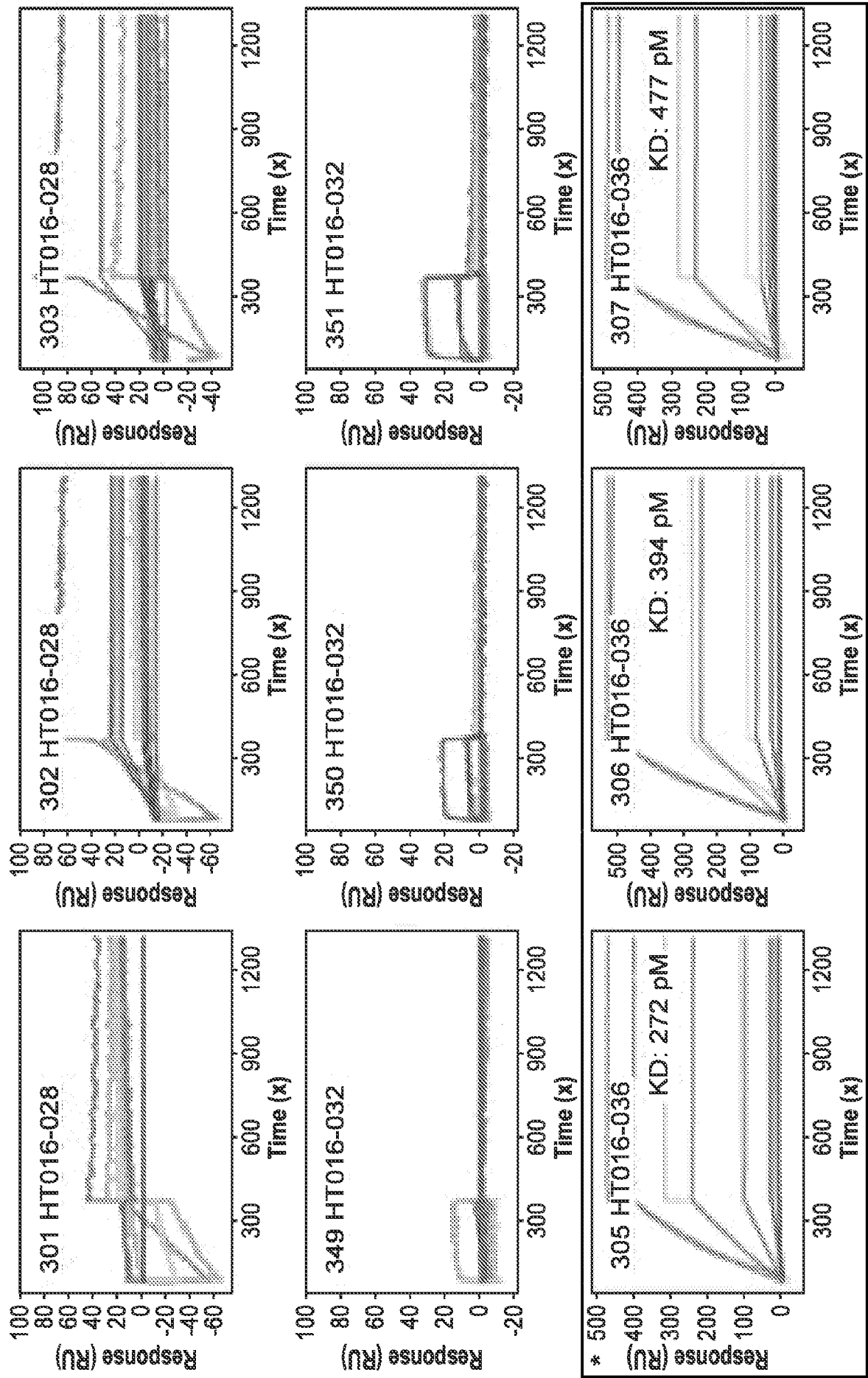


FIG. 18B (Cont. 23)

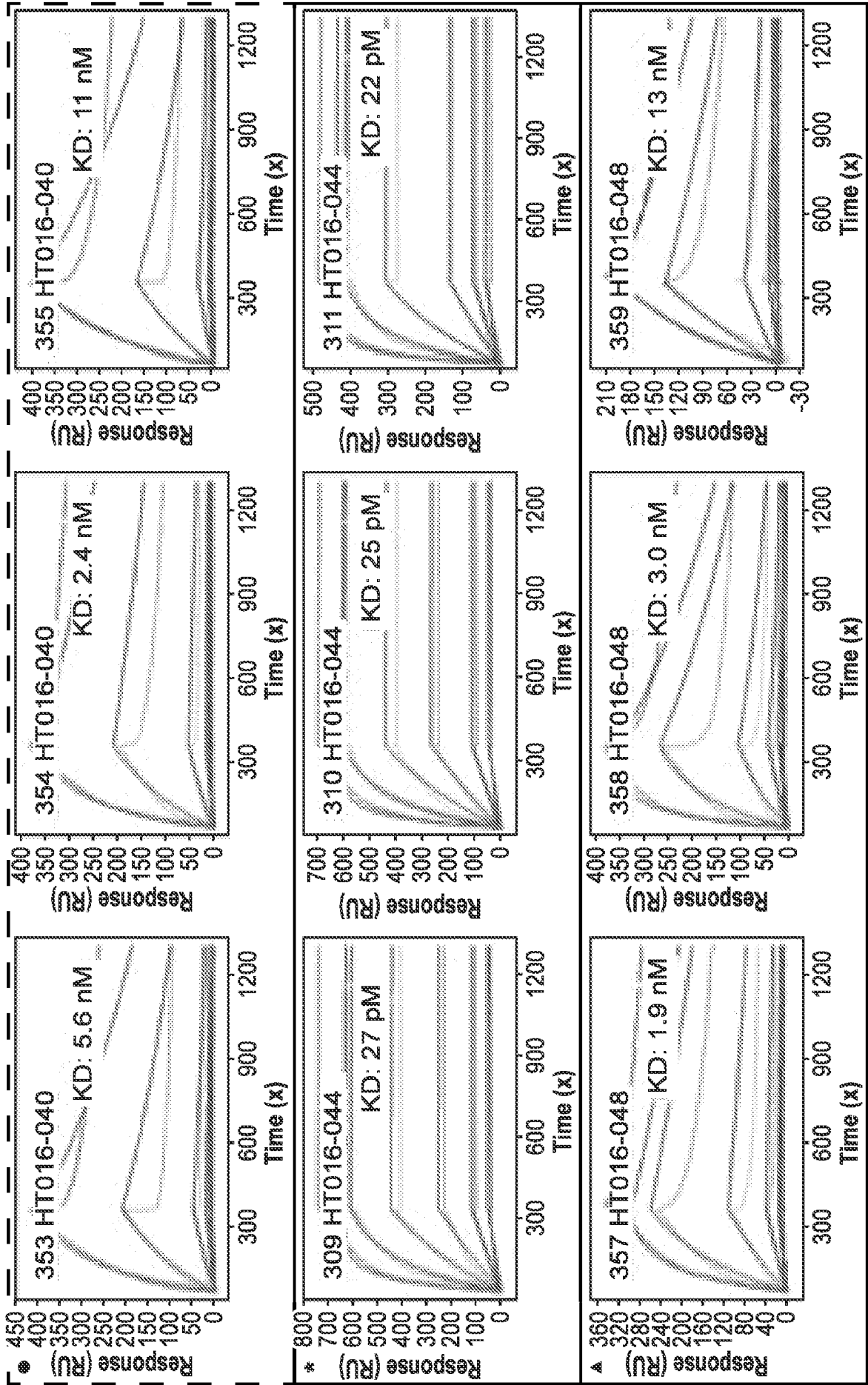


FIG. 18B (Cont. 24)

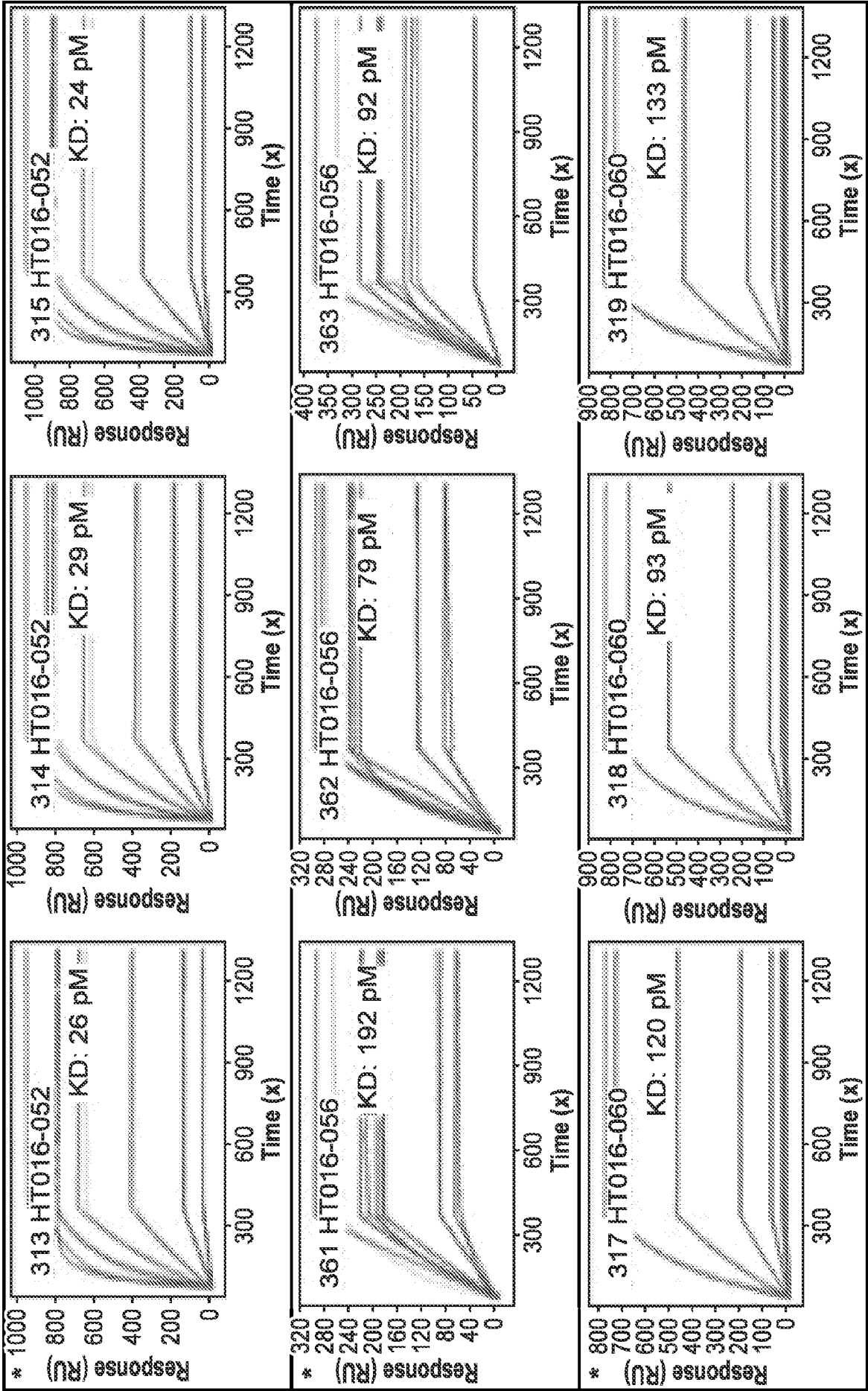


FIG. 18B (Cont. 25)

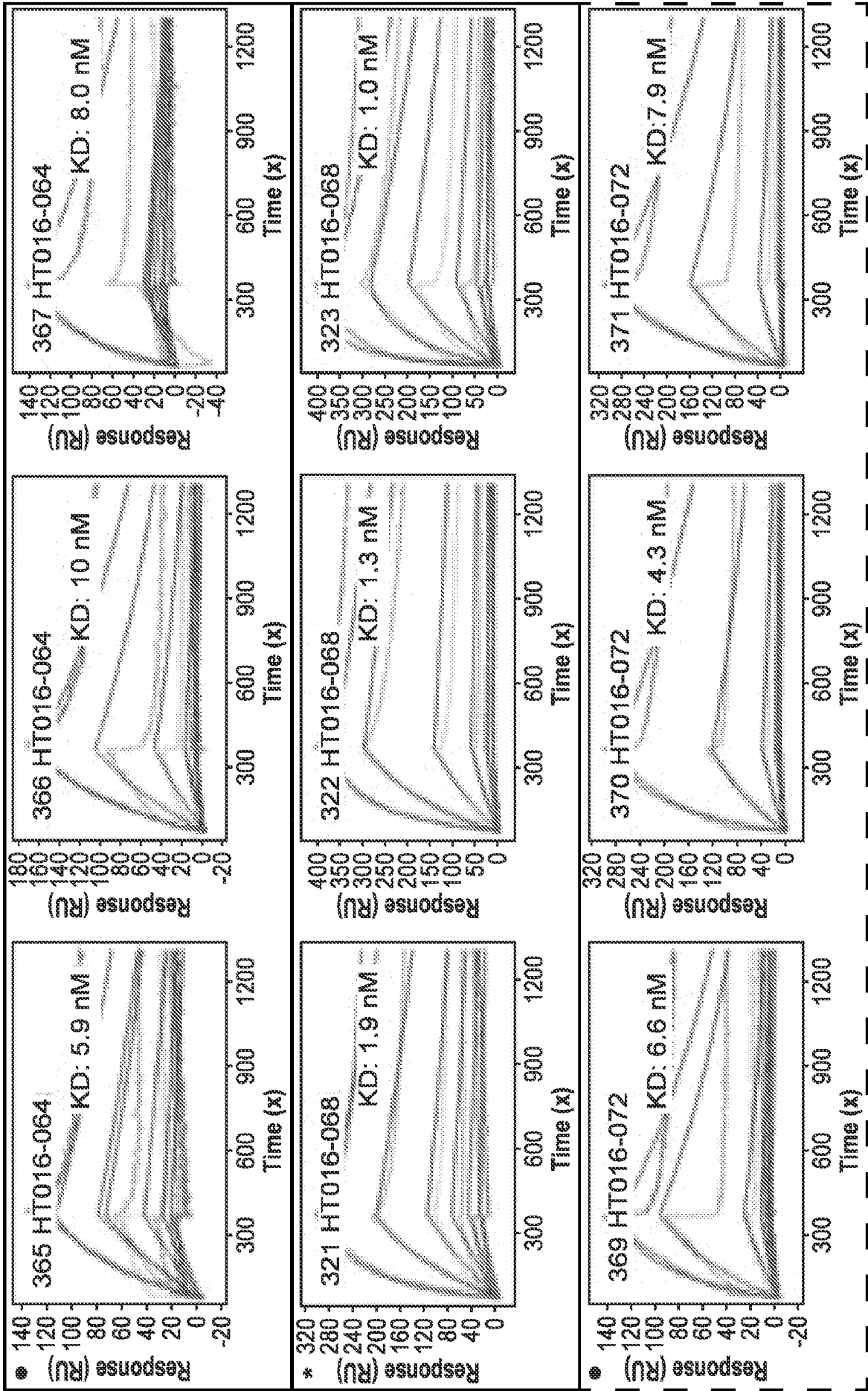


FIG. 18B (Cont. 26)

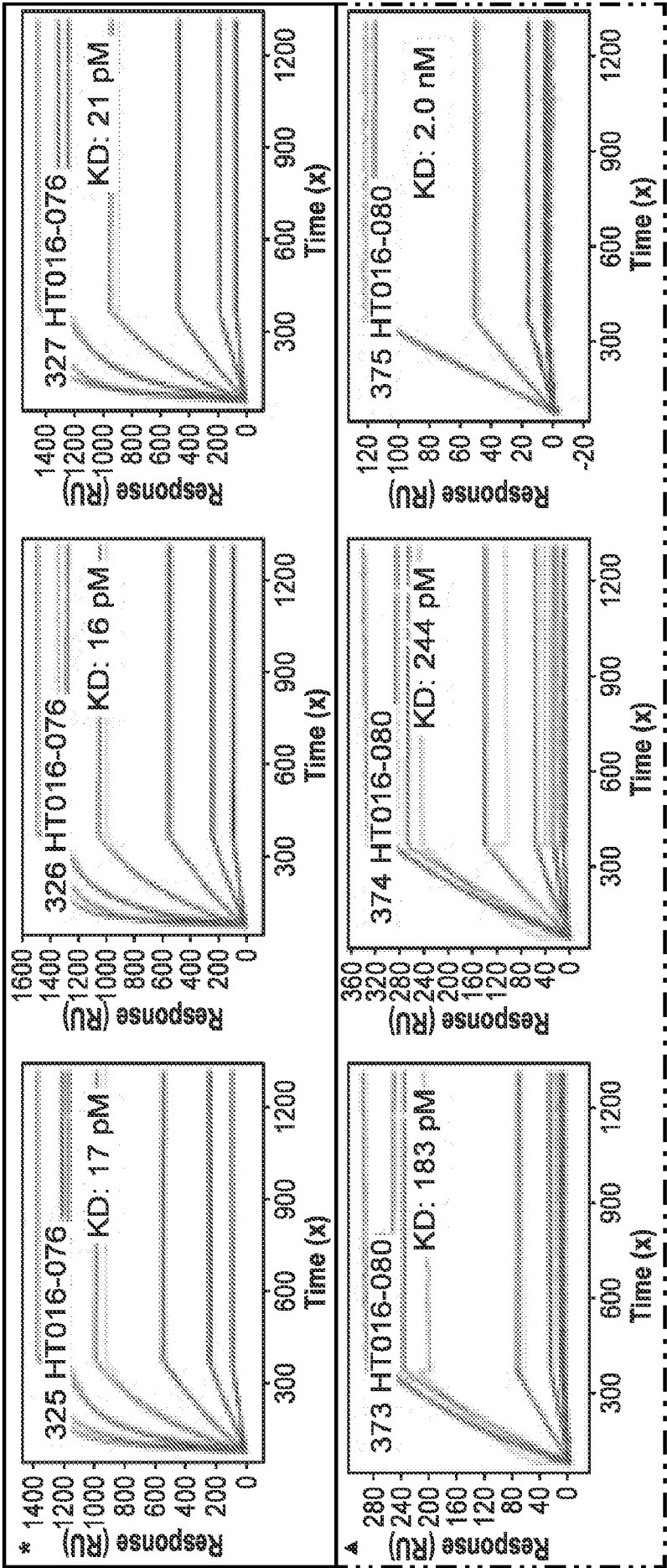


FIG. 18B (Cont. 27)

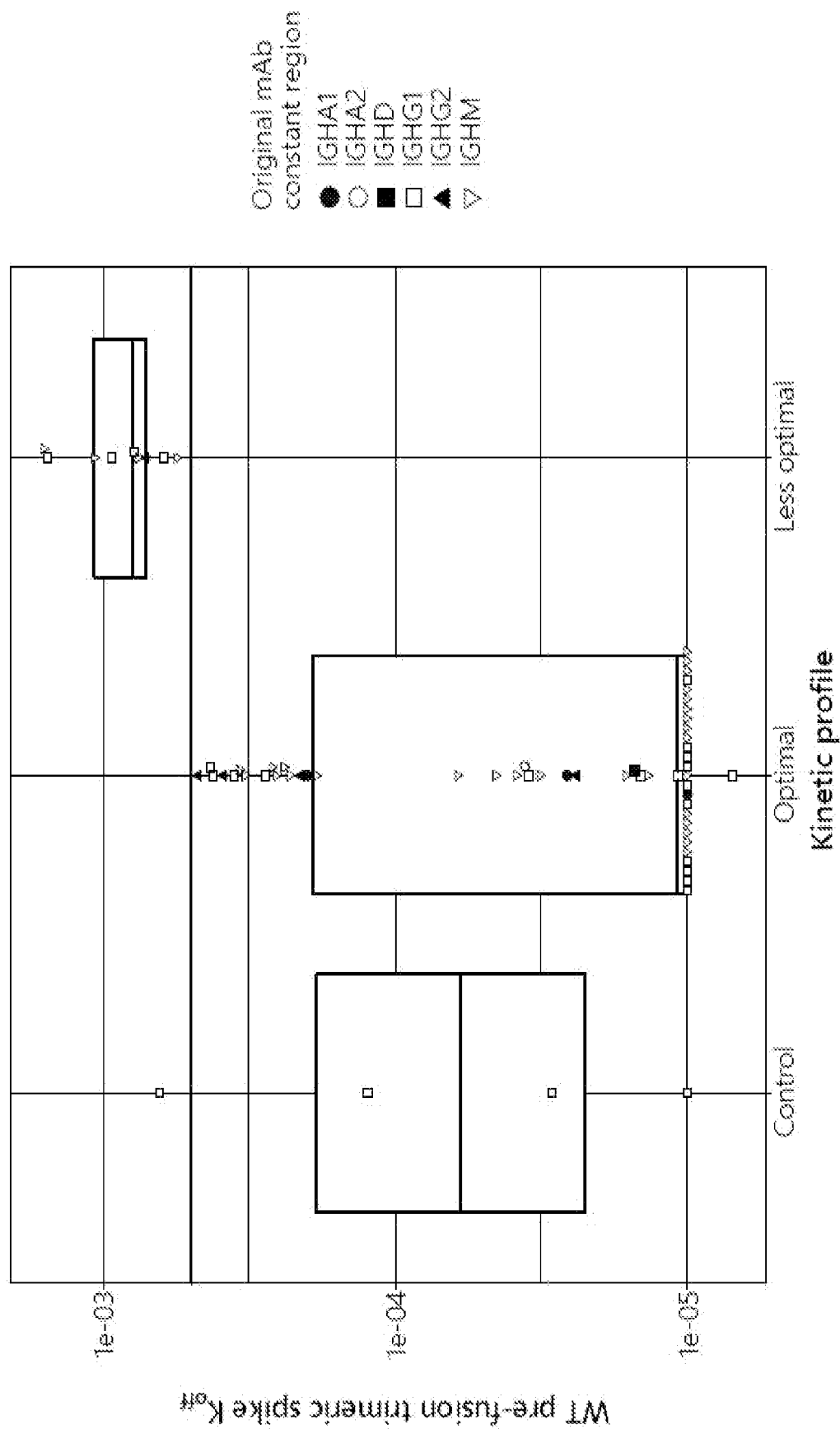


FIG. 18C

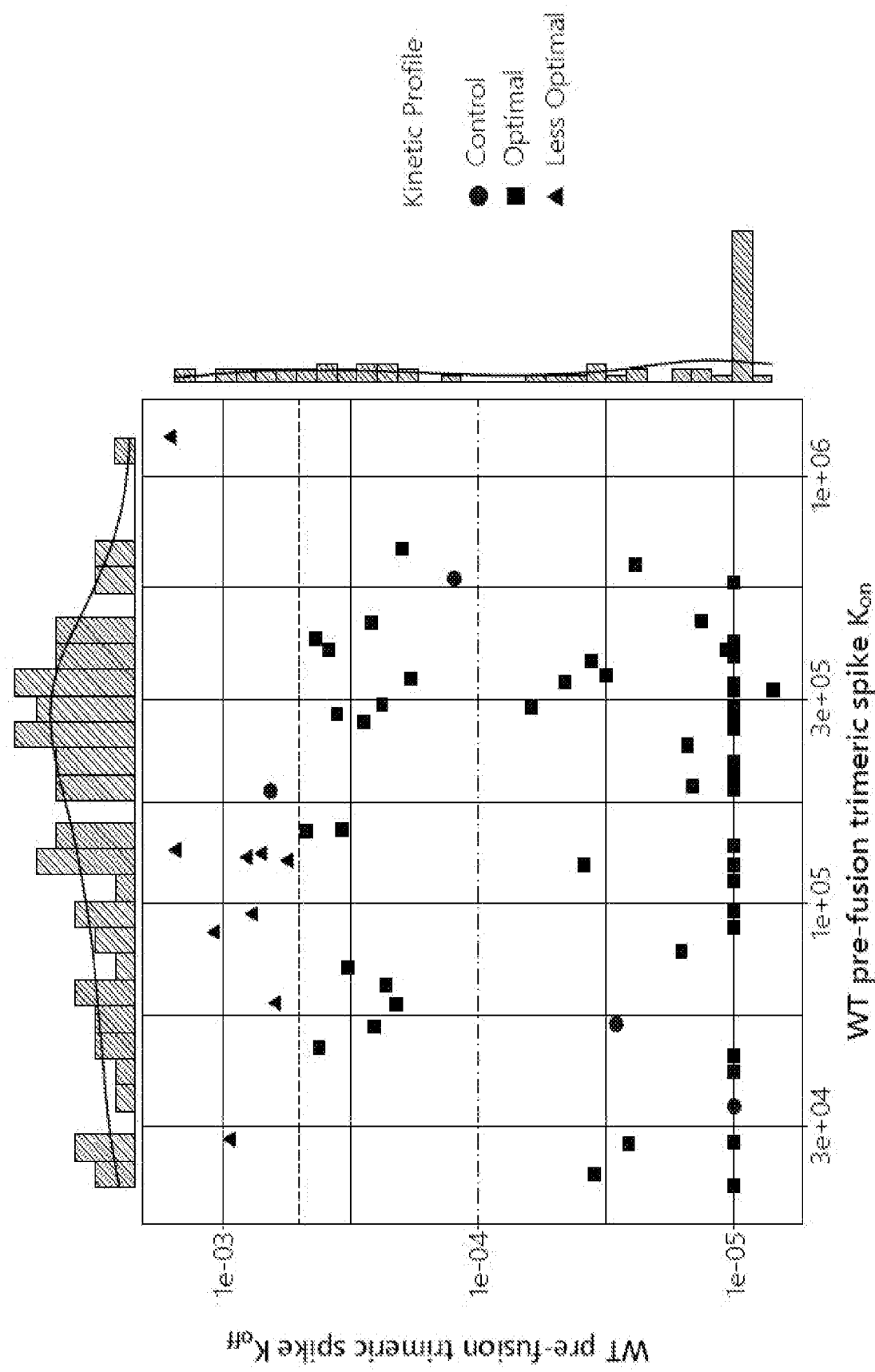


FIG. 18D

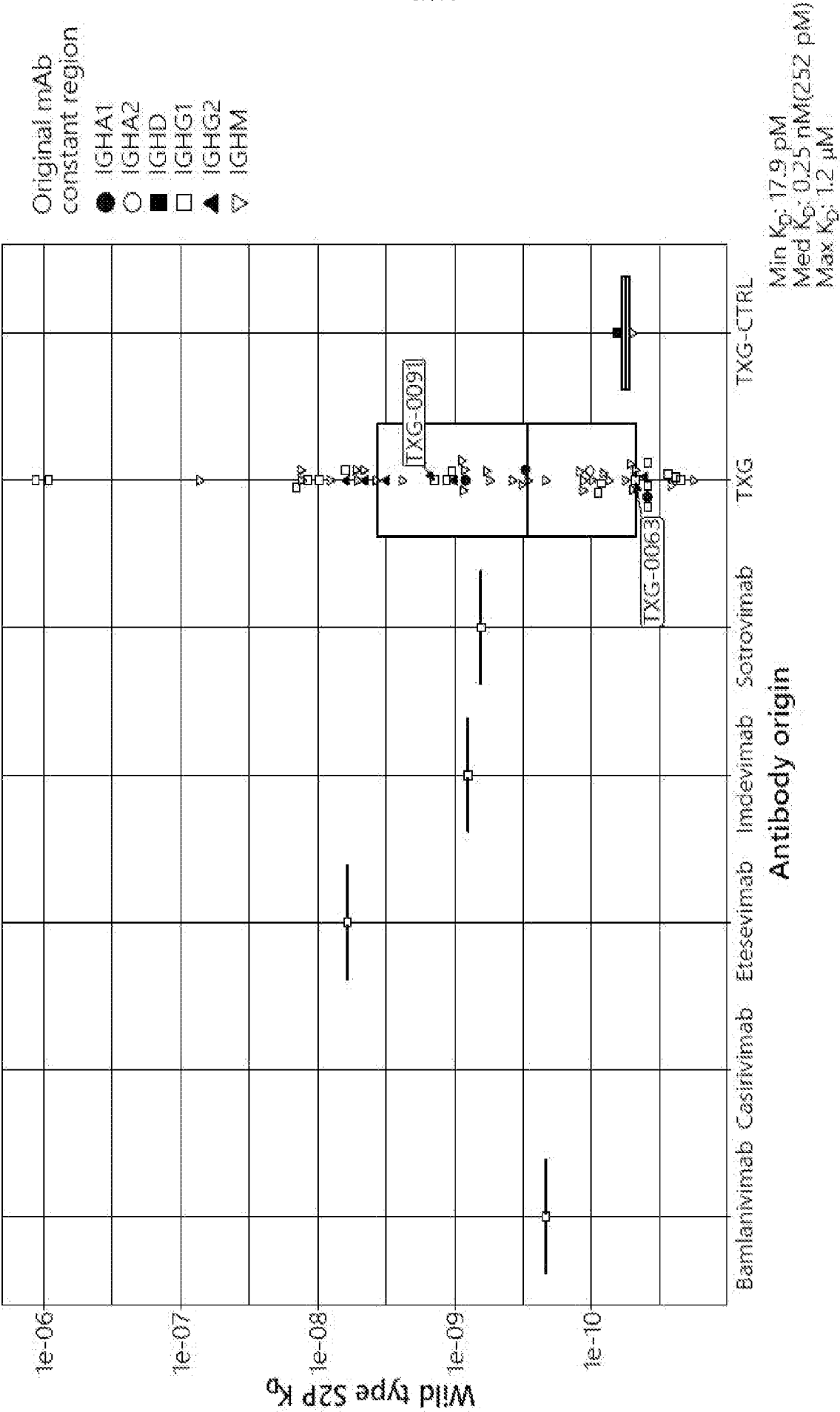


FIG. 19

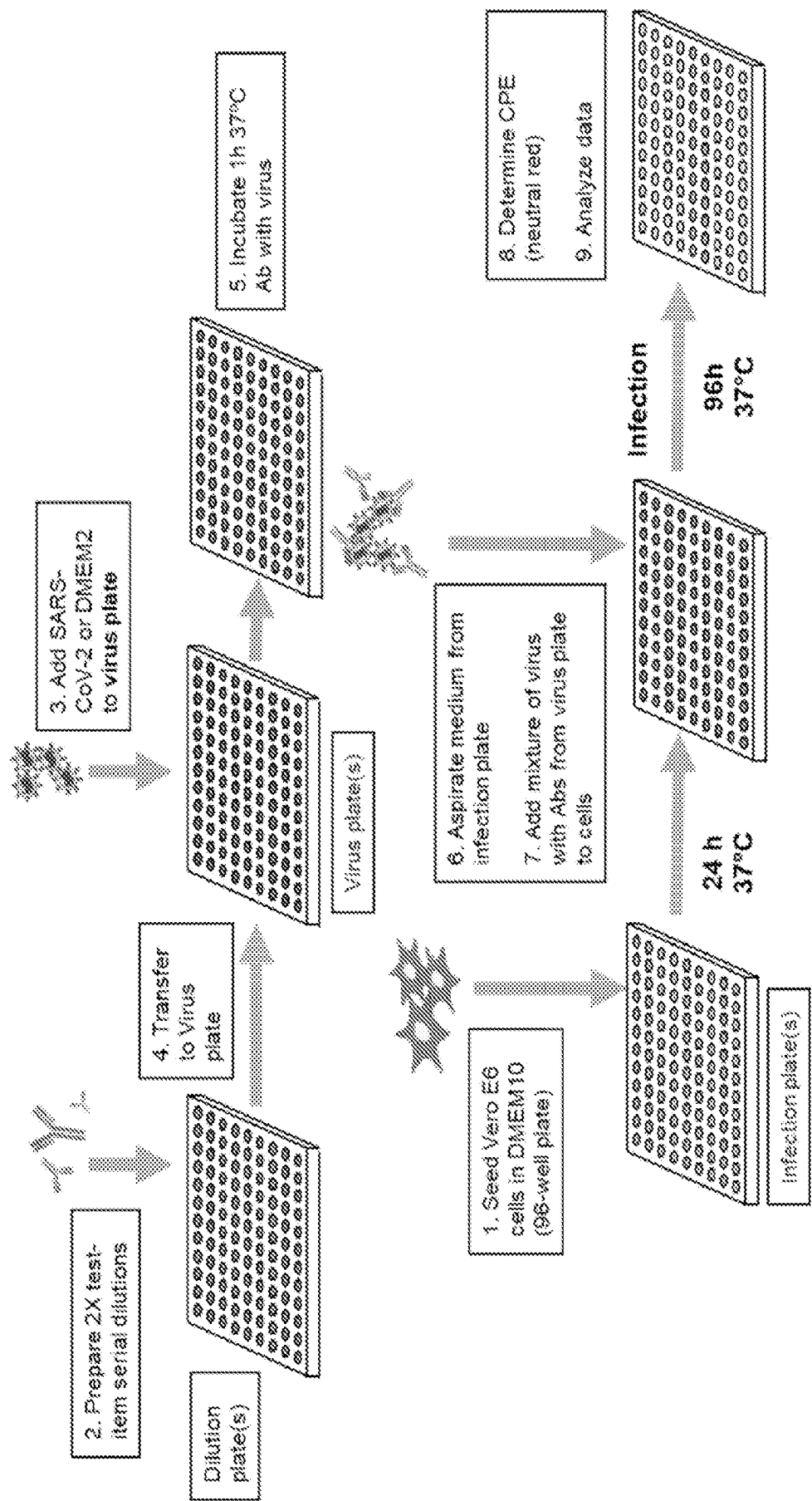


FIG. 20

SARS CoV-2 Antiviral Assay (A540)

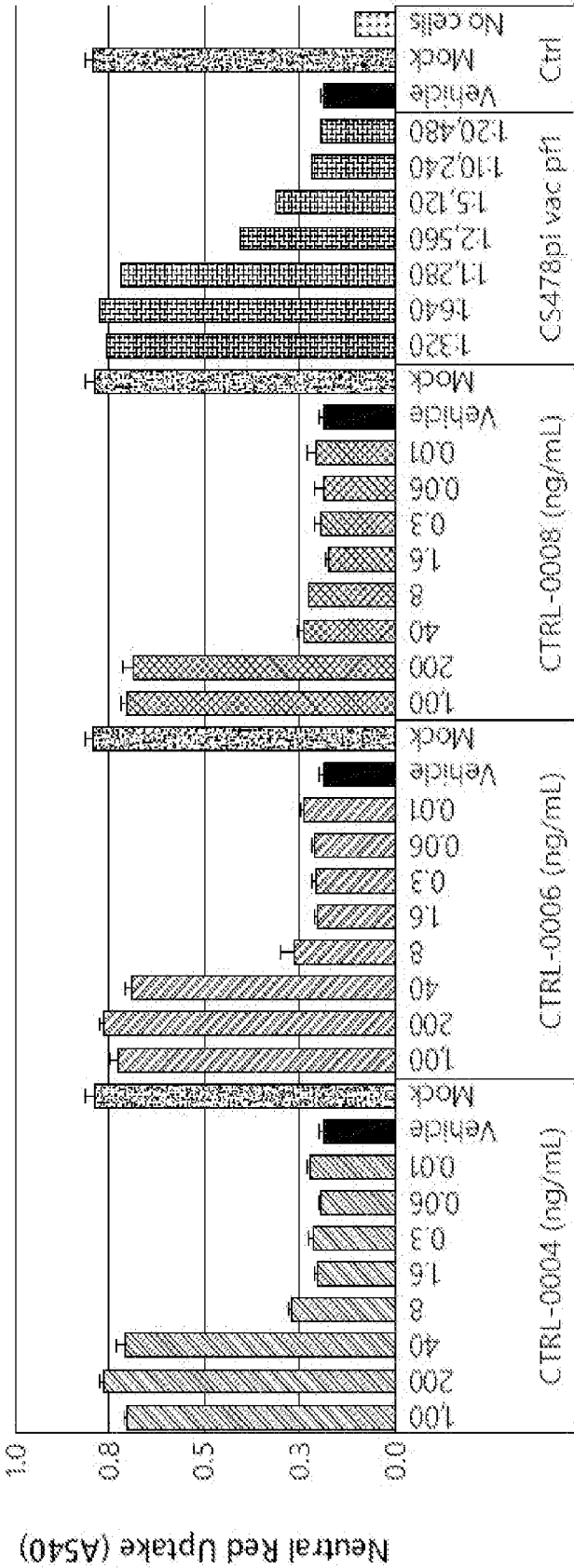


FIG. 21

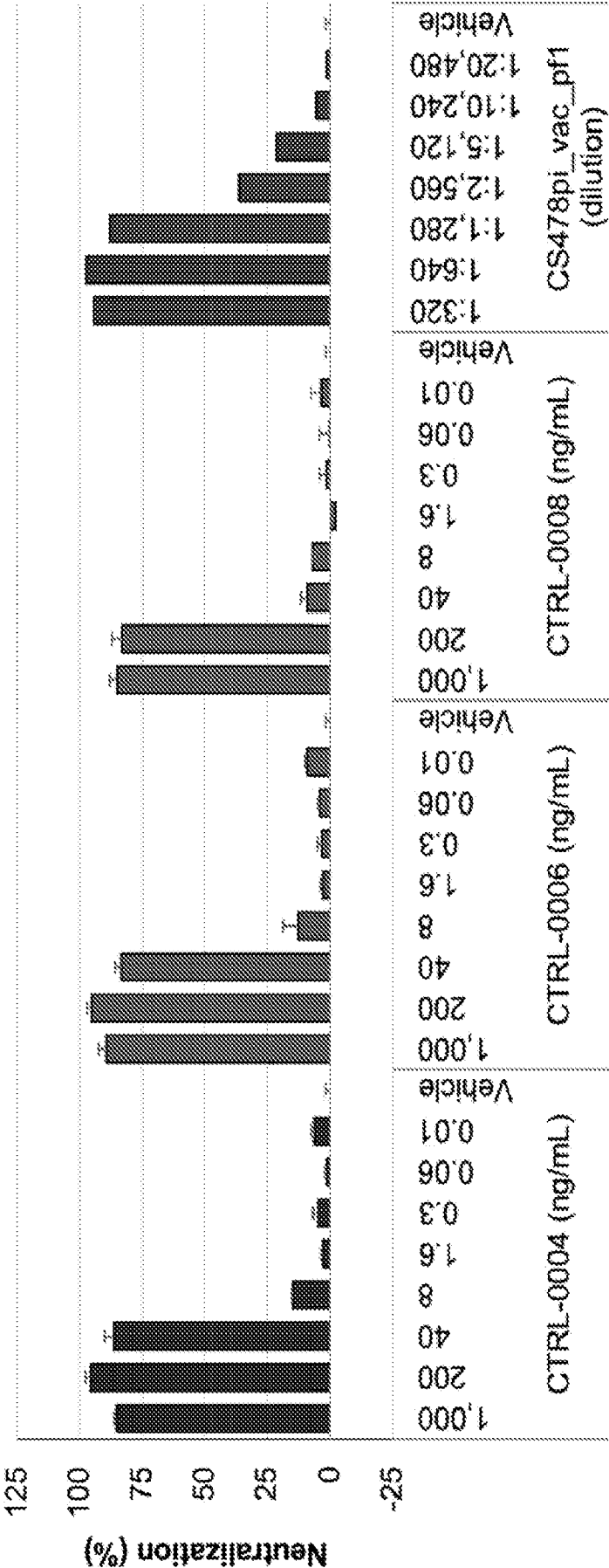


FIG. 22

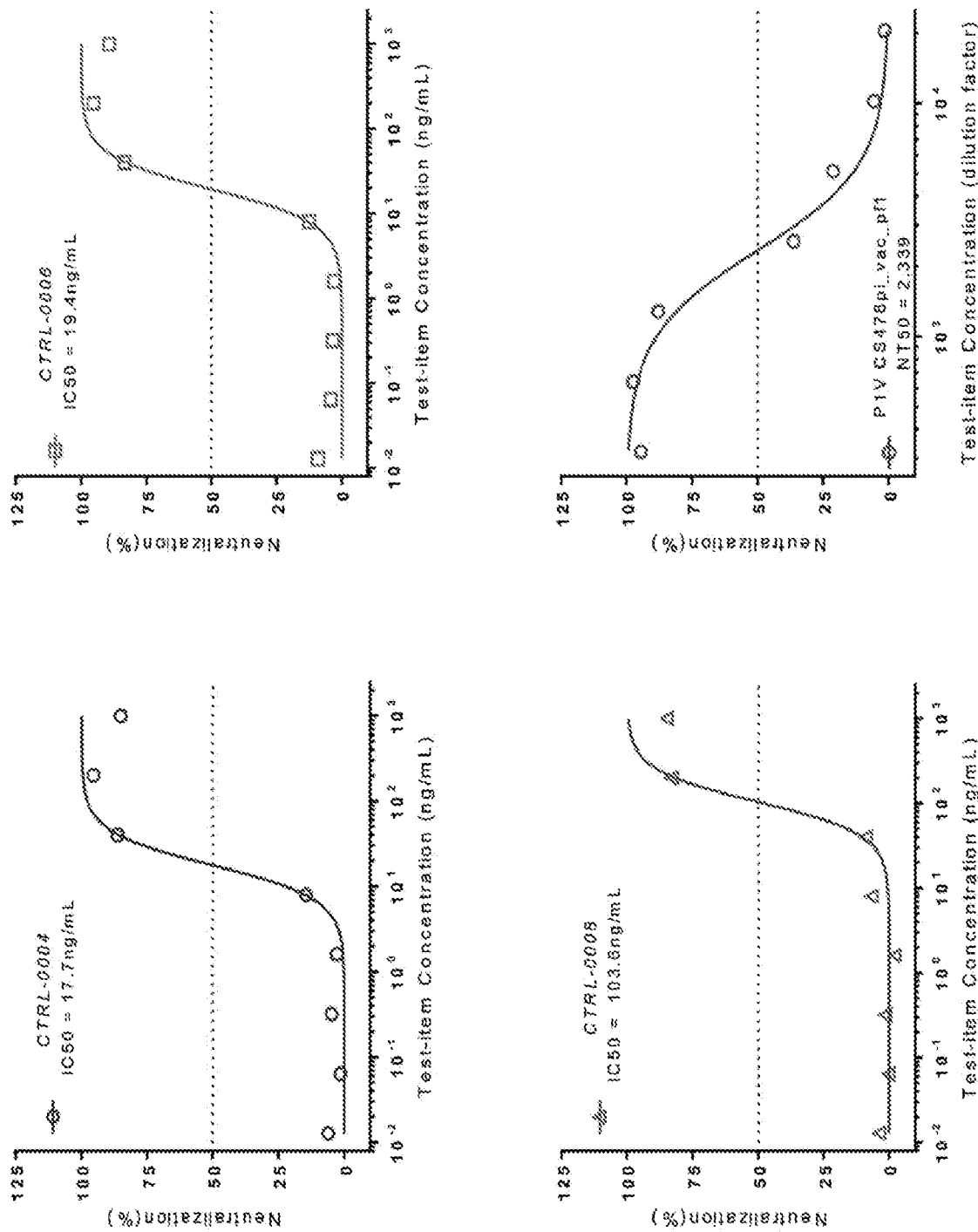


FIG. 23

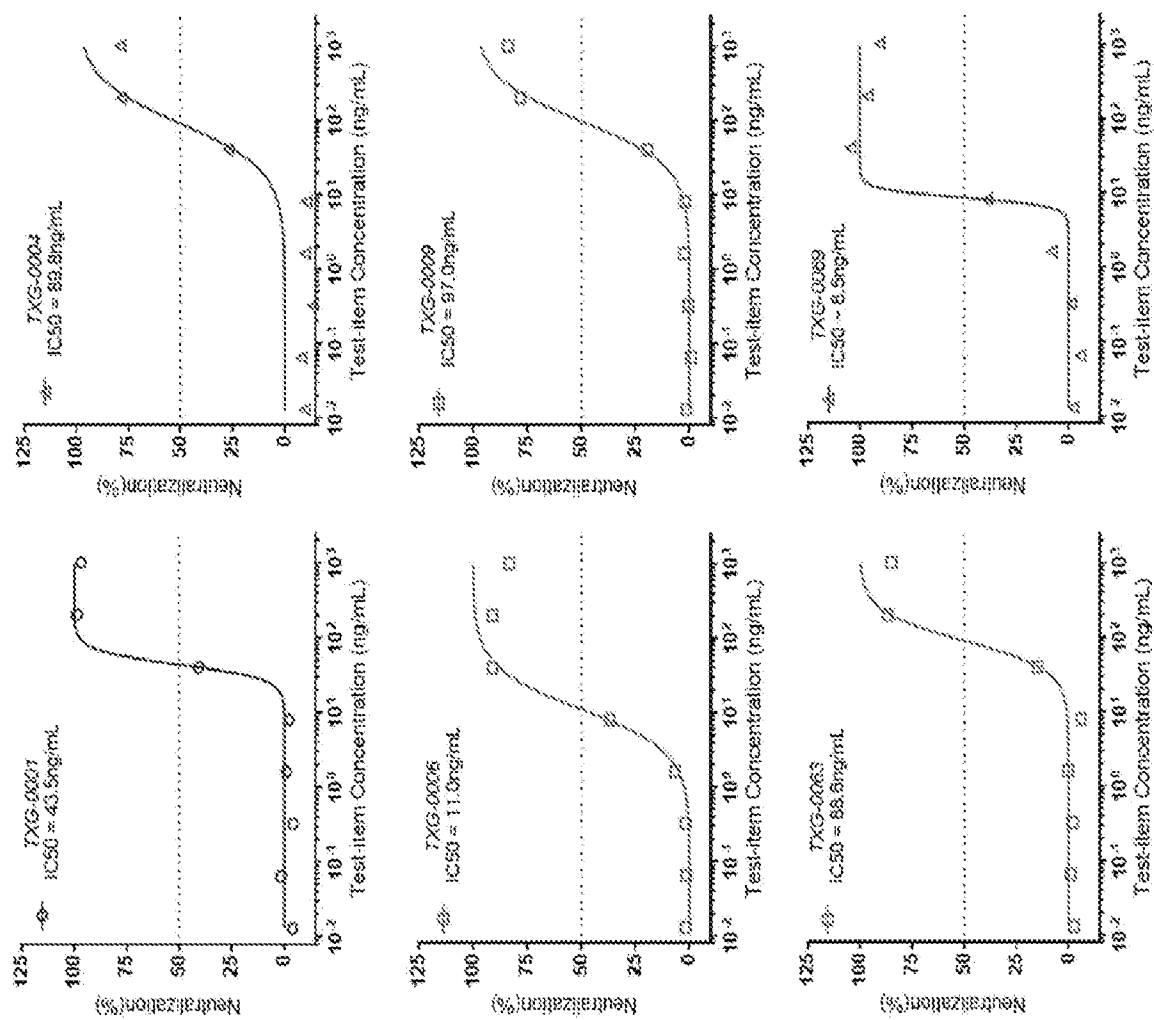


FIG. 24

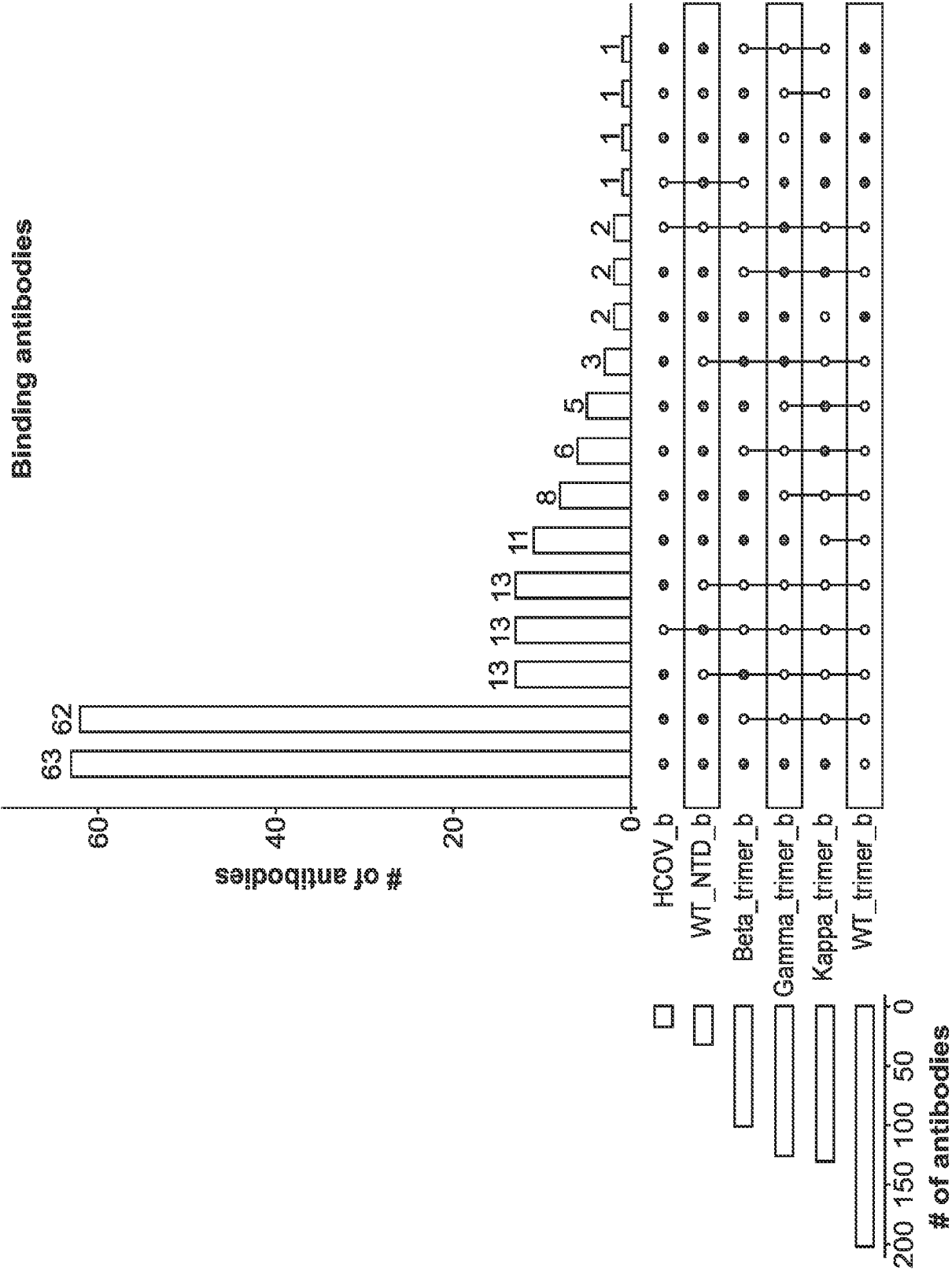


FIG. 25

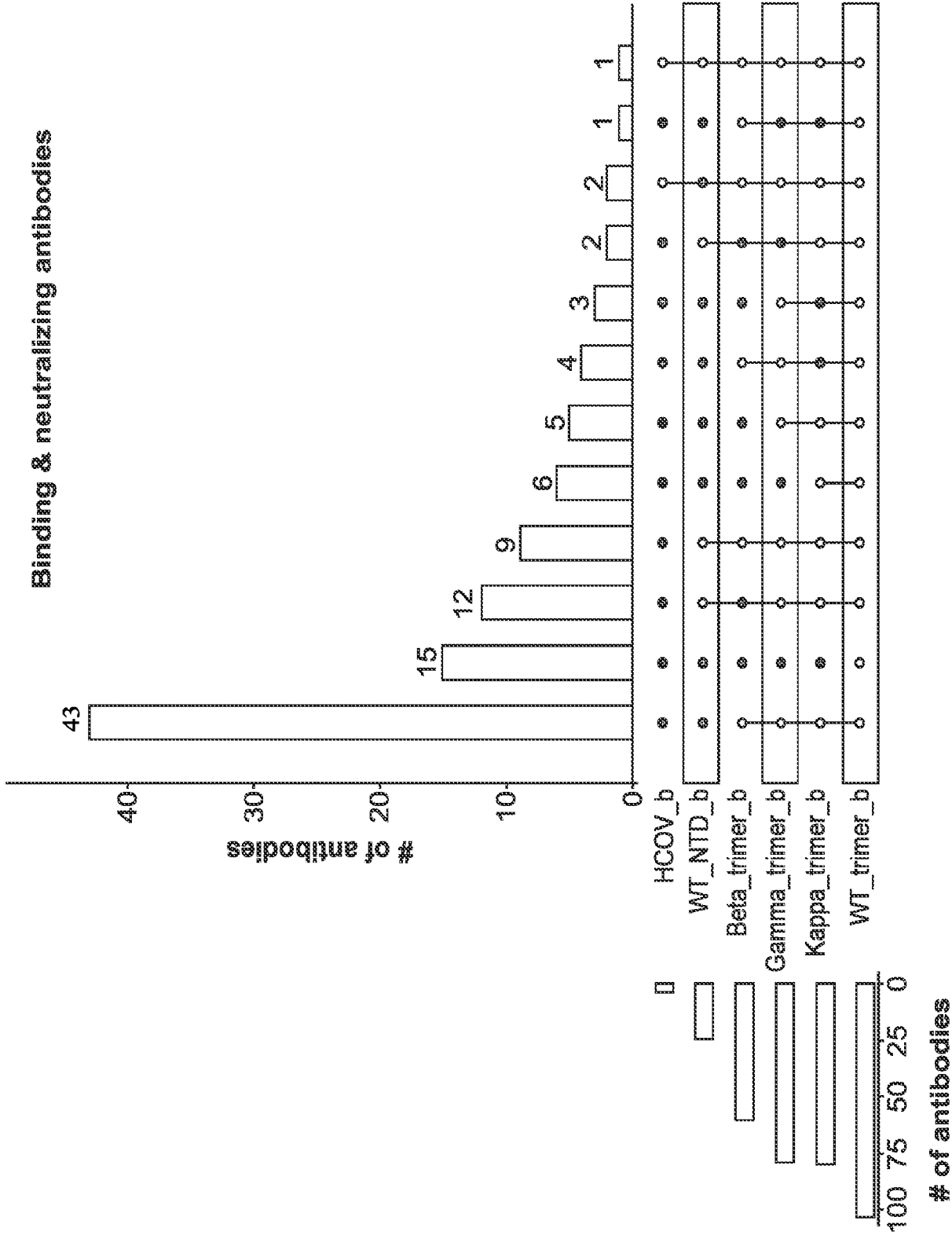


FIG. 26

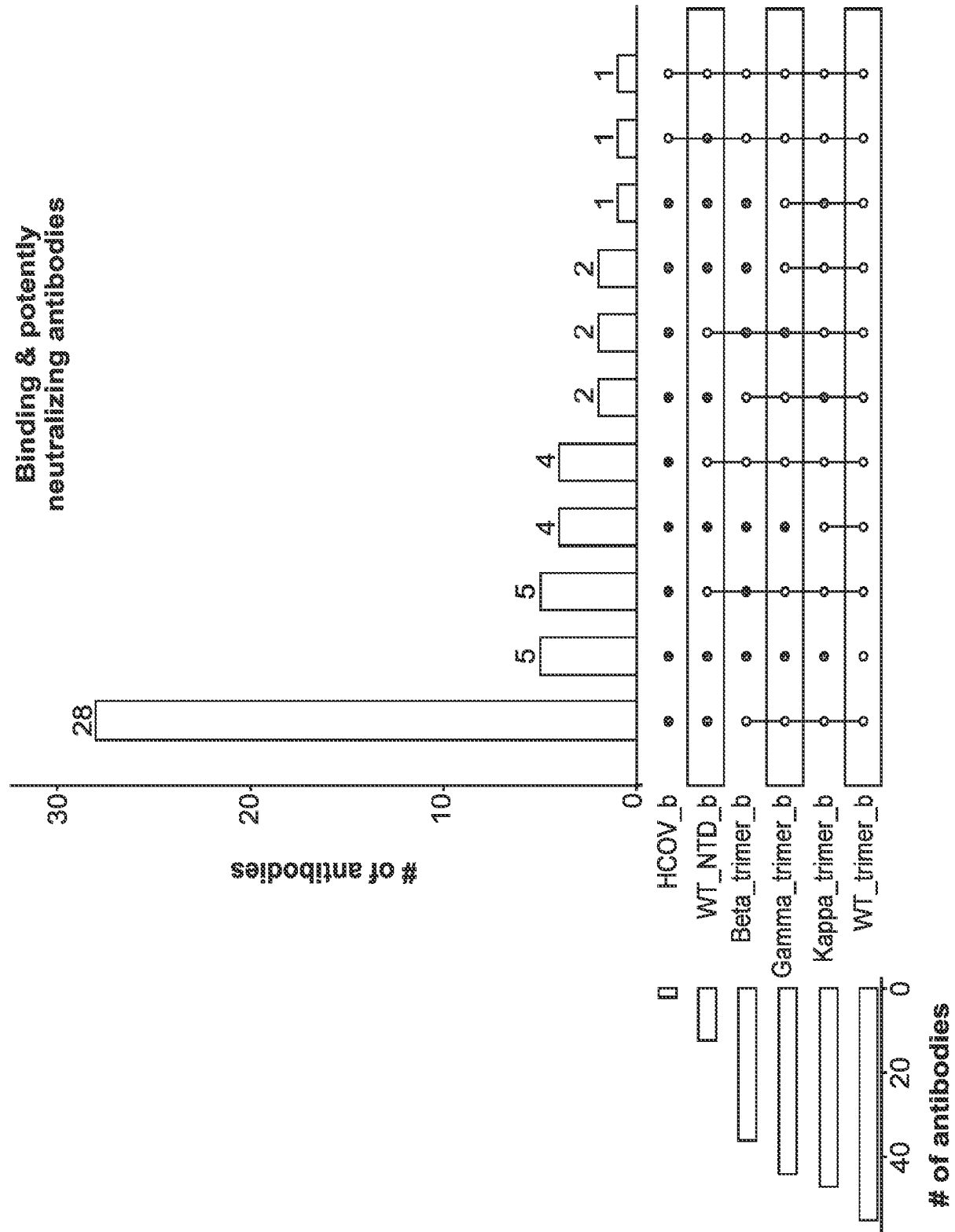


FIG. 27A

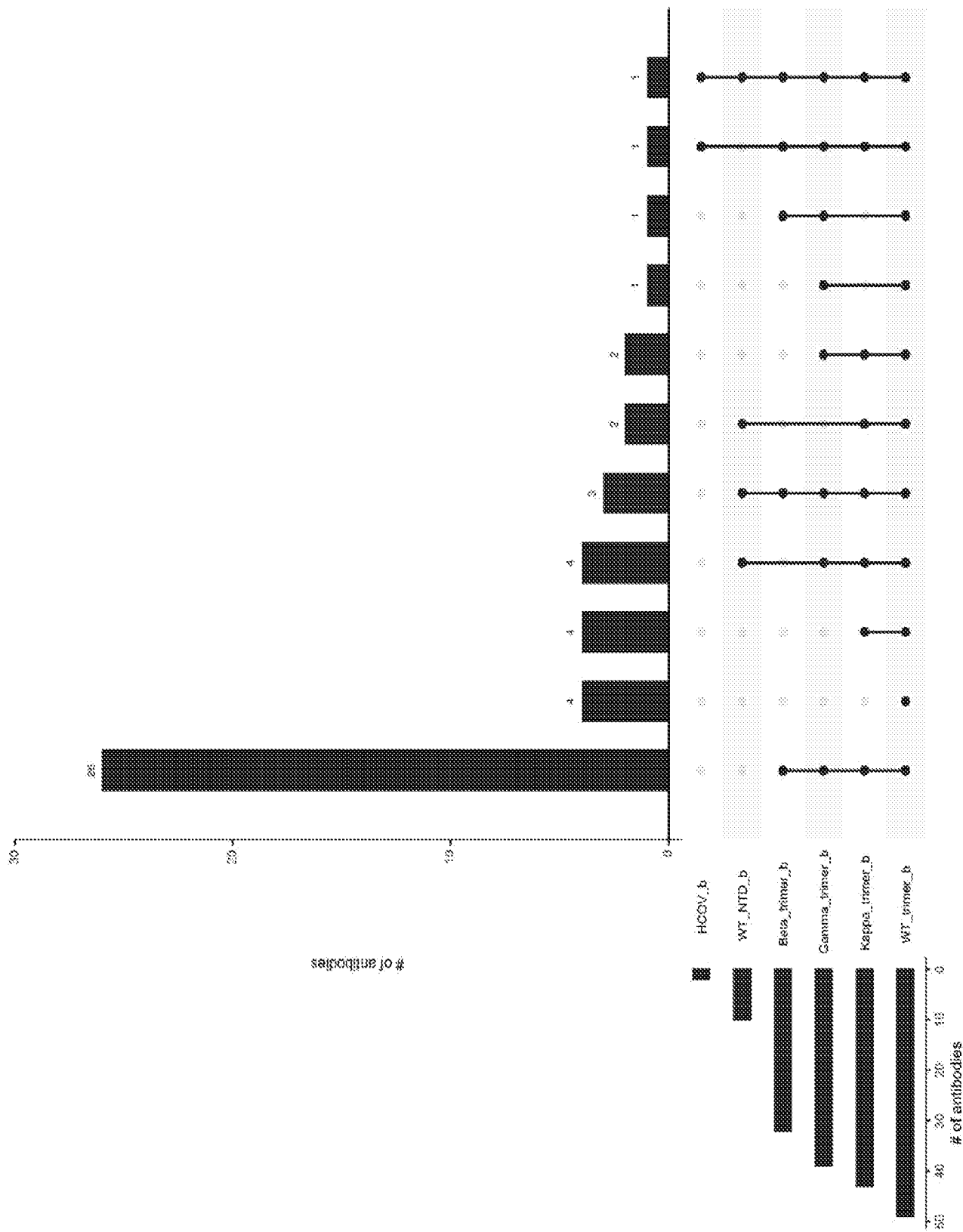


FIG. 27B

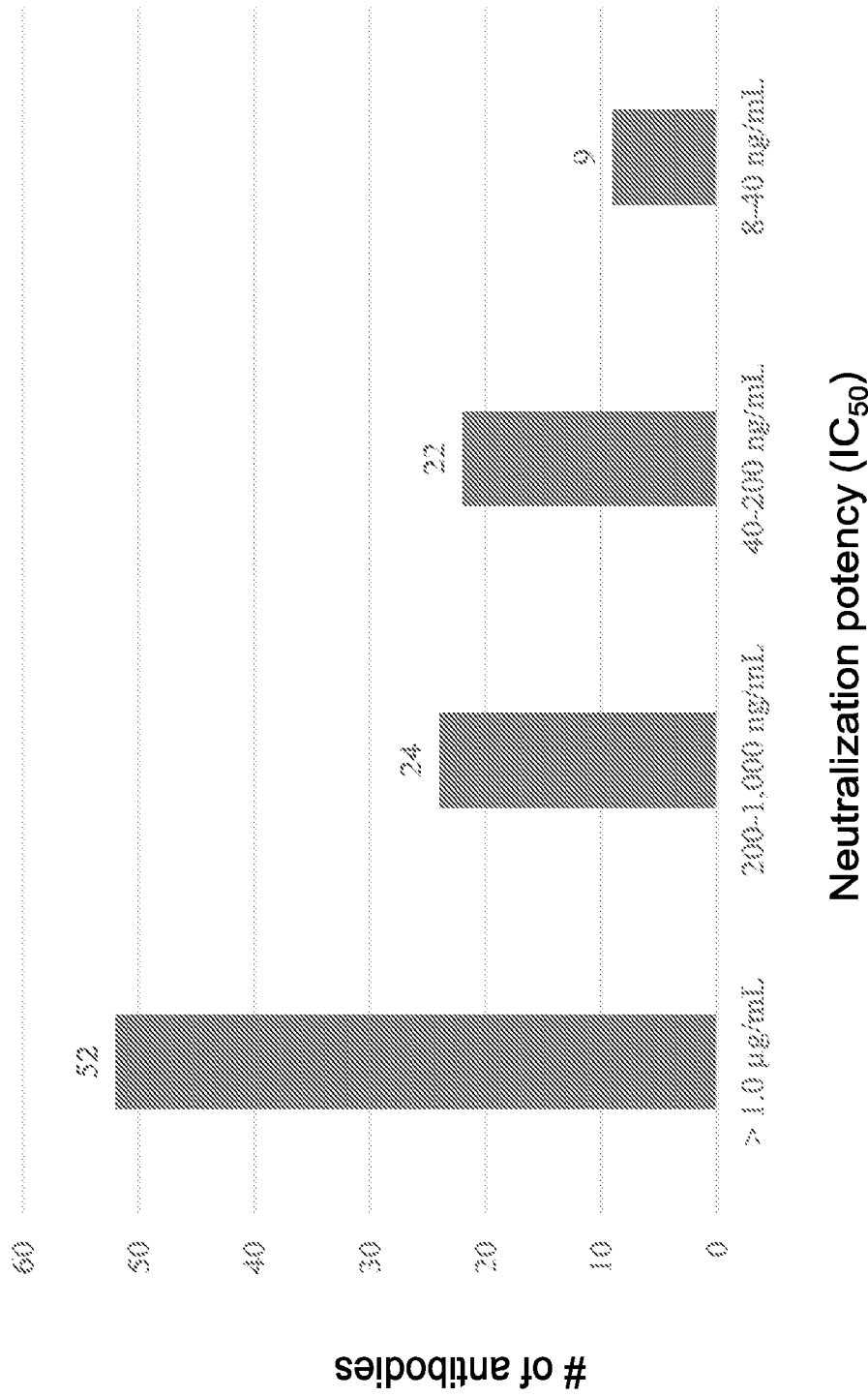


FIG. 28

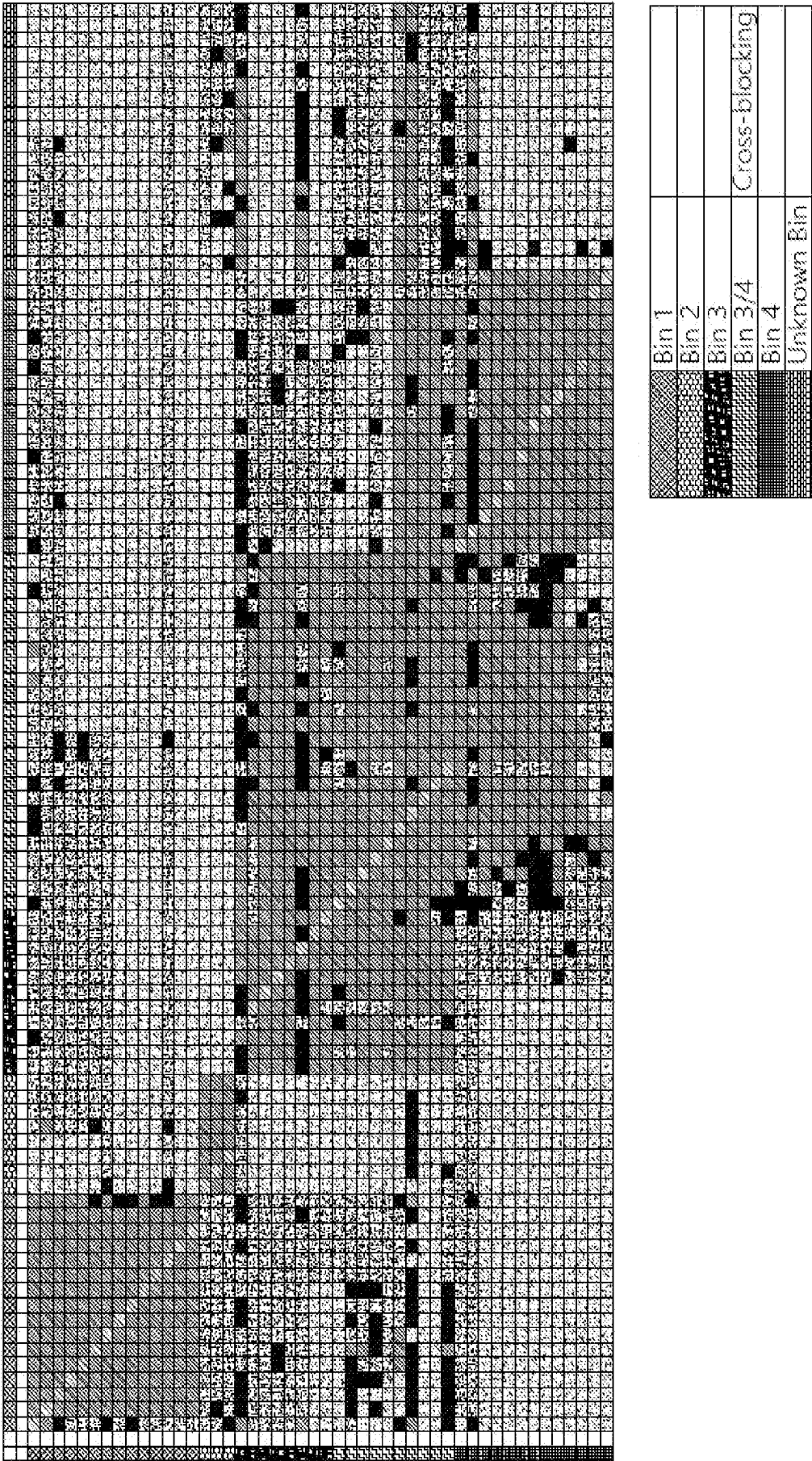


FIG. 29

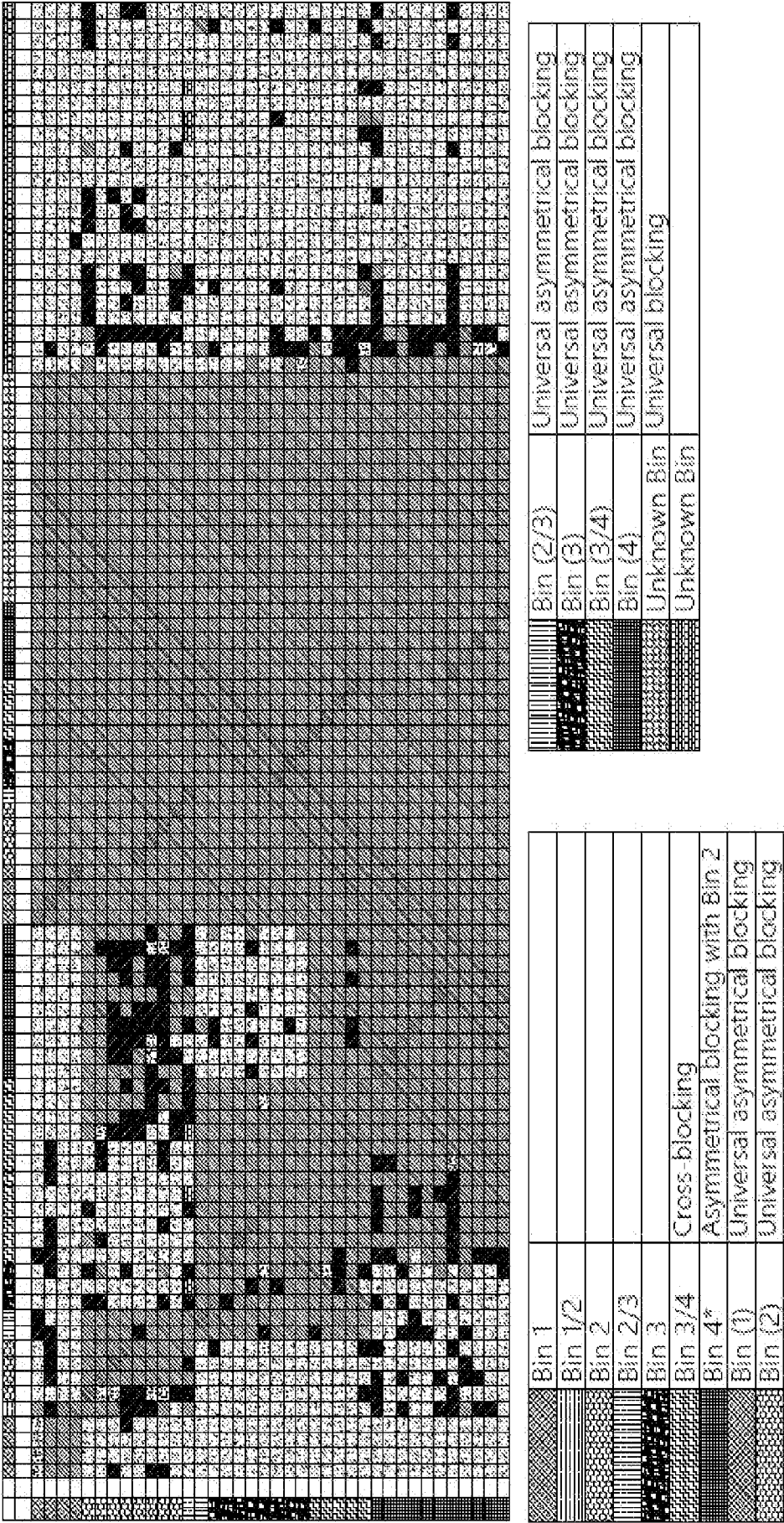


FIG. 30

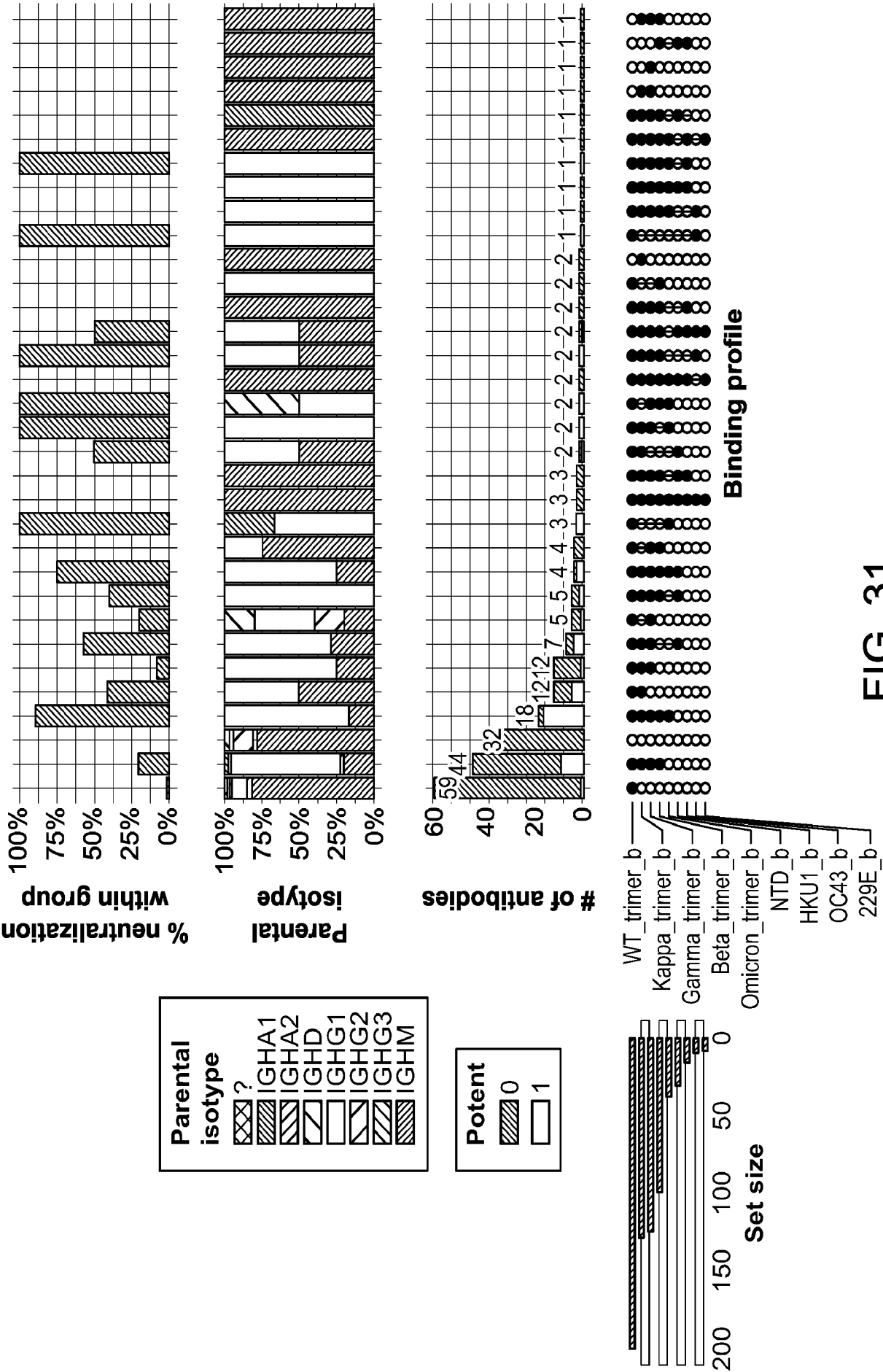


FIG. 31

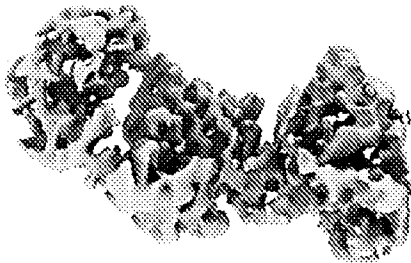


FIG. 32A

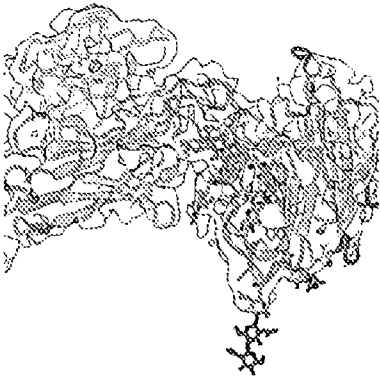


FIG. 32B

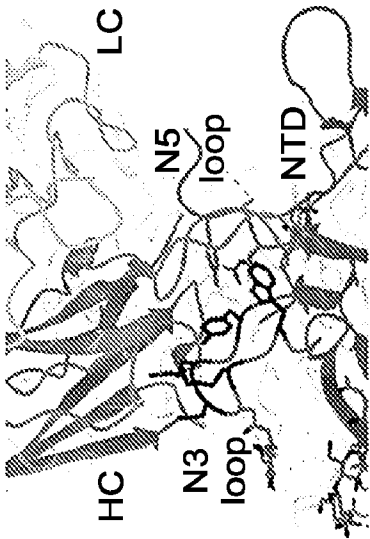
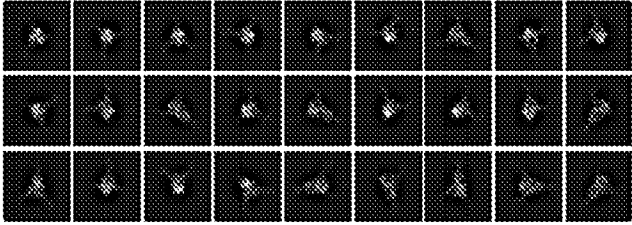
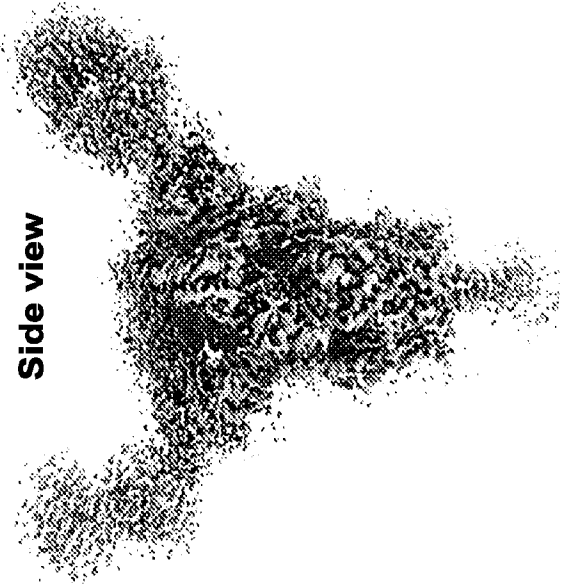


FIG. 32C

2D classes



Side view



Top view

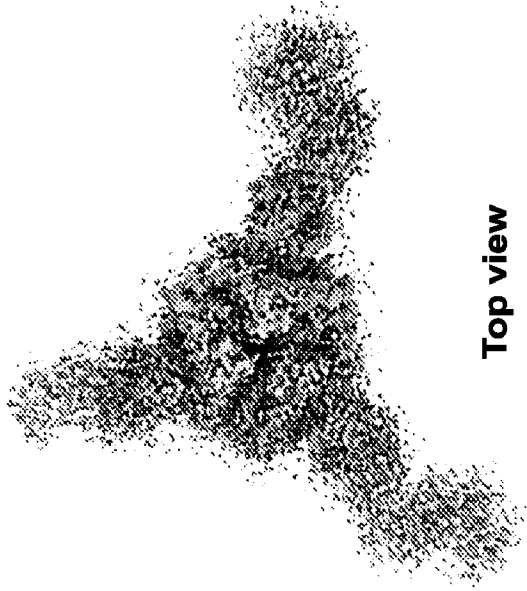


FIG. 32D

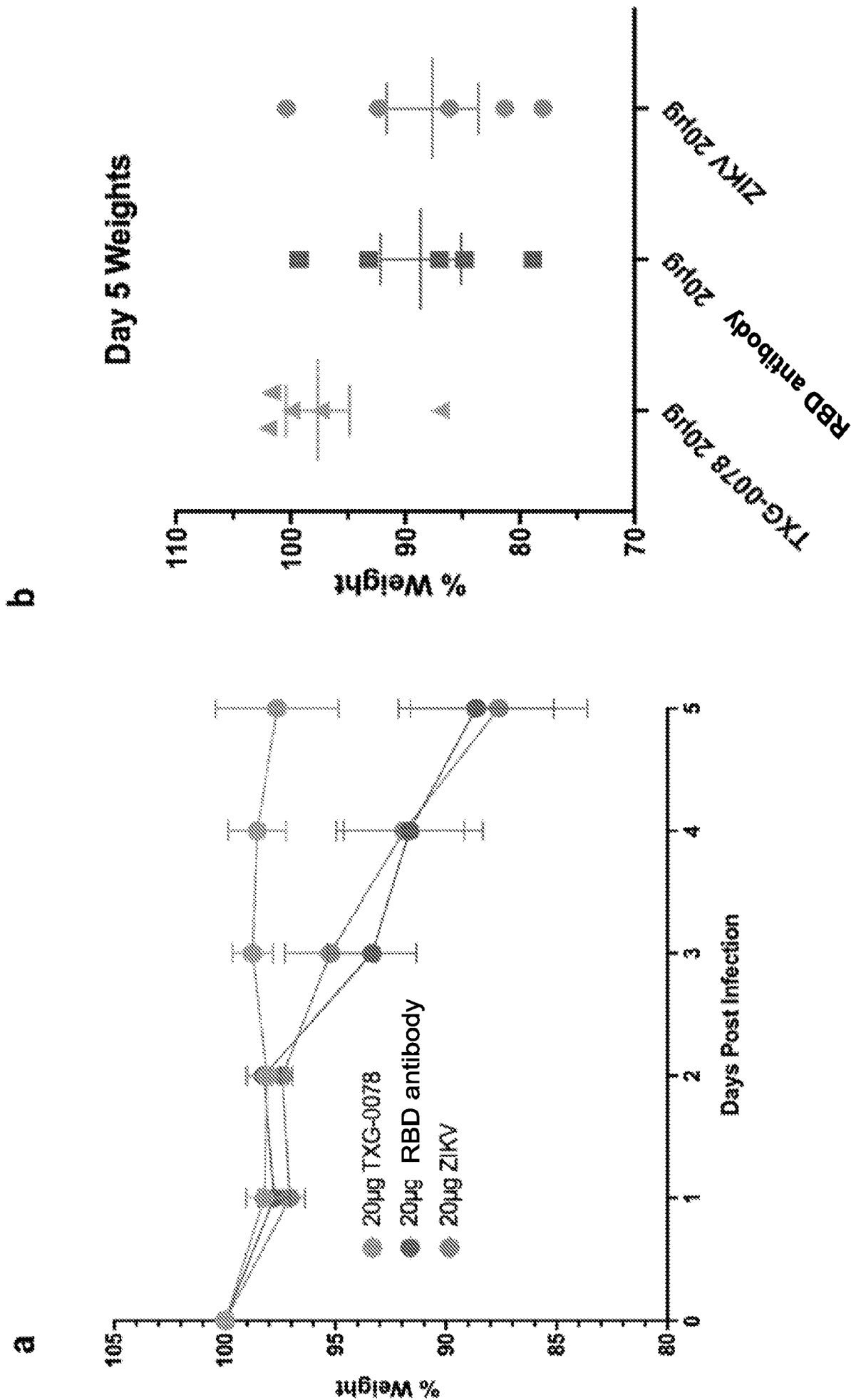


FIG. 33

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2023/064439

A. CLASSIFICATION OF SUBJECT MATTER INV. A61P31/14 C07K16/10 ADD.		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) A61P C07K		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) EPO-Internal, BIOSIS, EMBASE, SCISEARCH, WPI Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2021/045836 A1 (REGENERON PHARMA [US]) 11 March 2021 (2021-03-11) examples 10-20 -----	1-71
Y	WO 2021/183195 A1 (1 ABCELLERA BIOLOGICS INC [CA] ET AL.) 16 September 2021 (2021-09-16) examples 9-13 table 10.2 ----- -/--	1-71
☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.		
* Special categories of cited documents : "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance;; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance;; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search		Date of mailing of the international search report
24 May 2023		26/07/2023
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Authorized officer Domingues, Helena

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2023/064439

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

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:
 - a. ☒ forming part of the international application as filed.
 - b. ☐ furnished subsequent to the international filing date for the purposes of international search (Rule 13*ter*.1(a)).

☐ accompanied by a statement to the effect that the sequence listing does not go beyond the disclosure in the international application as filed.
2. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, this report has been established to the extent that a meaningful search could be carried out without a WIPO Standard ST.26 compliant sequence listing.
3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2023/064439

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

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

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

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

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

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

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

see additional sheet

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

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

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

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims;; it is covered by claims Nos.:
1-71 (partially)

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2023/064439

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	TORTORICI M. ALEJANDRA ET AL: "Ultrapotent human antibodies protect against SARS-CoV-2 challenge via multiple mechanisms - Supplement", SCIENCE, vol. 370, no. 6519, 20 November 2020 (2020-11-20), pages 950-957, XP055880643, US ISSN: 0036-8075, DOI: 10.1126/science.abe3354 Retrieved from the Internet: URL:https://www.science.org/doi/suppl/10.1126/science.abe3354/suppl_file/abe3354-tortorici-sm.pdf> figures 1,5, page 6 -----	1-71
Y	Cathcart Andrea L. ET AL: "The dual function monoclonal antibodies VIR-7831 and VIR-7832 demonstrate potent in vitro and in vivo activity against SARS-CoV-2", bioRxiv, 10 March 2021 (2021-03-10), pages 1-44, XP055841313, DOI: 10.1101/2021.03.09.434607 Retrieved from the Internet: URL:https://www.biorxiv.org/content/10.1101/2021.03.09.434607v1.full.pdf [retrieved on 2021-09-15] the whole document -----	1-71
Y	DONG JINHUI ET AL: "Genetic and structural basis for SARS-CoV-2 variant neutralization by a two-antibody cocktail", NATURE MICROBIOLOGY, NATURE PUBLISHING GROUP UK, LONDON, vol. 6, no. 10, 21 September 2021 (2021-09-21), pages 1233-1244, XP037575408, DOI: 10.1038/S41564-021-00972-2 the whole document ----- -/--	1-71

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2023/064439

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	CERUTTI GABRIELE ET AL: "Potent SARS-CoV-2 neutralizing antibodies directed against spike N-terminal domain target a single supersite", CELL HOST & MICROBE, vol. 29, no. 5, 1 May 2021 (2021-05-01), pages 819-833.e7, XP055971778, NL ISSN: 1931-3128, DOI: 10.1016/j.chom.2021.03.005 page 826 figure 4	1-71
X,P	WO 2022/150654 A2 (10X GENOMICS INC [US]) 14 July 2022 (2022-07-14) tables 3A, 4, 5, ,7-10 examples 6-14	1-71

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2023/064439

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2023/064439

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
		US 2021388066 A1	16-12-2021
		US 2022356229 A1	10-11-2022
		WO 2021183195 A1	16-09-2021
		WO 2021183359 A1	16-09-2021

WO 2022150654 A2	14-07-2022	TW 202237642 A	01-10-2022
		WO 2022150654 A2	14-07-2022

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

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

1. claims: 1-71 (partially)

Concerns aspects related to a composition comprising a nucleic acid encoding an anti-SARS-CoV-2-Spike antibody or antigen-binding fragment thereof and to a composition comprising such an antibody or antigen-binding fragment thereof, wherein the antibody comprises the six CDRs of Ab TXG-0001 identified in table 1A.

2-59. claims: 1-71 (partially)

Concerns a group of inventions each related to aspects of a composition comprising a nucleic acid encoding an anti-SARS-CoV-2-Spike antibody or antigen-binding fragment thereof and to aspects of a composition comprising such an antibody or antigen-binding fragment thereof, wherein each composition encompassed by inventions 2-59 comprises one of the antibodies defined in dependent claims 3, 27, 31, 35 and independent claims 36, 38, 40, 64, 69, 70 and 71, with the exception of Ab TXG-0001, in the order defined in these claims. Concretely invention 2 relates to aspects of Ab TXG-0002 and invention 59 relates to aspects of Ab TXG-0230. It is noted that dependent claims 4, 42 and 65 mention a subset of 20 Abs and are only part of the inventions relating to these particular antibodies (inventions 1-8, 13, 17, 19, 20, 30, 31, 38, 41, 42, 43, 48 and 54).

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.2

Claims Nos.: 1, 2 (partially)

Incomplete Search for independent claims 1 and 2

The set of claims on file comprises eight independent claims, namely claims 1, 2, 36, 38, 40, 64, 69, 70 and 71.

Independent claims 1 and 2

are directed to a composition comprising: i) a nucleic acid encoding an anti-SARS-CoV-2 antibody or an antigen-binding fragment thereof (claim 1) or; ii) a comprising such an anti-SARS-CoV-2 antibody or an antigen-binding fragment thereof (claim 2), wherein the antibody or antigen-binding fragment thereof comprises all six complementary determining regions (CDRs) from an antibody identified in Tables 1A and 1B. Table 1A extends from pg. 26-30 and table 1B extends from pg. 30 to pg. 32. These tables contain a plethora of antibodies for which no SARS-CoV-2 neutralizing activity has been shown. In fact, according to example 13, [0427], only 40% of these antibodies display measurable neutralization activity against SARS-CoV-2, including some of the Abs defined in dependent claim 3. The most potent antibodies were TXG-0006, TXG-0129, and TXG-0154 (cf. [0430]). All or part of the antibodies mentioned in dependent claim 3 are also referred to in dependent claims 4, 27, 31 and 35.

Due to the very high number of antibodies encompassed by claims 1 and 2 for which not technical effect, in particular no neutralization activity has been shown in the application, it was not possible to carry out a comprehensive search over the entire scope of independent claims 1 and 2. Therefore, the subject-matter of claims 1 and 2 was only searched in as far as it relates to antibodies for which a technical effect, namely the ability to neutralize SARS-CoV-2, is supported by the data disclosed in the application. These are the Abs defined in dependent claims 3, 4, 27, 31, 35 and also in independent claims 36, 38, 40, 64, 69, 70 and 71.

The present search report thus covers these antibodies and aspects related thereto.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guidelines C-IV, 7.2), should the problems which led to the Article 17(2) PCT declaration be overcome.