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Dynamic human heavy chain antibody libraries

Abstract

Provided herein are libraries containing polynucleotides, where one of the polynucleotides encodes an antibody heavy chain with specific hypervariable regions HVR-H1 and HVR-H2. Further provided herein are libraries containing polynucleotides encoding a plurality of unique antibodies, wherein each antibody comprises a heavy chain variable region and a light chain variable region. Also provided are antibodies, polypeptide libraries, vector libraries, cells, non-human animals, antibody heavy chains, methods of making an antibody library, kits, and methods of generating a bispecific antibody related thereto.

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Background/Summary

CROSS REFERENCE TO RELATED APPLICATIONS (1) This application is a divisional application of U.S. application Ser. No. 16/640,679, issued as a U.S. Pat. No. 11,578,426 and having an international filing date of Aug. 21, 2017, which is a national stage application under 35 U.S.C. § 371 of International Application No. PCT/CN2017/098299, filed internationally on Aug. 21, 2017, the contents of which are hereby incorporated by reference in their entireties.

REFERENCE TO AN ELECTRONIC SEQUENCE LISTING
(1) The content of the electronic sequence listing (6954020002012SeqList.xml; Size: 367,770 bytes; and Date of Creation: Jan. 10, 2023) is herein incorporated by reference in its entirety.
FIELD OF THE INVENTION
(2) The present disclosure relates to libraries containing synthetic polynucleotides that encode antibody heavy chains (e.g., heavy chains of a dynamic human antibody), as well as antibody heavy chains, antibodies, cells, animals, methods, and kits related thereto.
BACKGROUND
(3) Monoclonal antibodies have become extremely useful in a wide variety of fields, including biological research, medical diagnosis, and pharmaceutical products. The variability of potential binding specificities allows for antibodies with valuable specificity and potency. However, this variability makes it difficult and laborious to screen through a huge number of antibodies to identify one or more with the desired properties.
(4) One method of identifying an antibody of interest is to screen through an antibody library, such as a library of cloned B cell sequences, a phage display library, a yeast display library, and so forth. These libraries allow one to screen through a large number of antibodies, representing a multitude of unique antibody sequences, to identify antibodies with specific properties of interest, e.g., binding to particular target, binding affinity, selectivity, and the like. However, current libraries have particular limitations. Libraries derived from a biological source, such as a human B cell repertoire, are limited to those antibody sequences that can be cloned from the source. Synthetic libraries may include non-naturally occurring sequences as compared to biologically derived libraries, but they too are limited by the amount of antibodies that can be synthesized in a particular timeframe. Further, extremely large libraries require more time-consuming and exhaustive screening approaches; otherwise, only a fraction of the library can practically be screened for an antibody of interest.
(5) Therefore, a need exists for the development of dynamic antibody libraries containing a robust set of dynamic units with well-defined developable sequence profiles for designing and constructing dynamic antibodies that are potentially more relevant functionally. Such libraries would greatly improve not only the diversity of the antibody binding sites on antibodies within the library, but also the efficiency of screening for antibodies harboring novel and/or conformational epitopes on a given antigen. Moreover, such libraries would increase the likelihood with which a particular antibody of interest might be identified with a high affinity and developability profile.
(6) All references cited herein, including patent applications, patent publications, and UniProtKB/Swiss-Prot Accession numbers are herein incorporated by reference in their entirety, as if each individual reference were specifically and individually indicated to be incorporated by reference.
BRIEF SUMMARY
(7) To meet the above and other needs, disclosed herein are antibody sequences, such as heavy chain hypervariable regions (HVRs) and heavy chain variable regions (e.g., V.sub.Hregions), that allow for dynamic human antibodies. These sequences were designed to allow for antibodies with highly flexible HVR sequence loops that are able to bind their targets with high potency and/or recognize multiple useful epitopes,

and/or cross-react with epitopes shared among different species at low sequence identity (around 60% sequence identity or less). Advantageously, these antibody sequences allow the creation of much smaller libraries that nonetheless contain a multitude of useful antibodies, and/or a much larger diversity at a given library size. Such libraries can be used to identify new antibodies of interest that are specific for a wide range of targets or, in some cases, cross-reactive against multiple targets of interest. Furthermore, a novel concept and methodology is introduced and implemented herein for designing and constructing dynamic antibody libraries using newly identified dynamic units to capture a broad range of conformational flexibility of antibody binding sites in compact physical libraries. Moreover, the results using such antibodies (as described below) highlight the ability to identify antibodies from these libraries which target conformational epitopes and/or evolutionally conserved sites on a given antigen from different species with low sequence identity (e.g., below 60% to 70%).

(8) Accordingly, in one aspect, provided herein are one or more HVR-H1 amino acid sequences, and/or one or more polynucleotides (e.g., synthetic polynucleotides) encoding the same, wherein the HVR-H1 comprises an amino acid sequence according to a formula selected from the group consisting of: Formula (I): X1TFX2X3YX4IHWV (SEQ ID NO:198), wherein X1 is F or Y, X2 is S or T, X3 is D, G, N, or S, and X4 is A, G, or W; Formula (II): YSIX1SGX2X3WX4WI (SEQ ID NO:199), wherein X1 is S or T, X2 is H or Y, X3 is H or Y, and X4 is A, D, G, N, S, or T; and Formula (III): FSLSTX1GVX2VX3WI (SEQ ID NO:200), wherein X1 is G or S, X2 is A or G, and X3 is A, G, S, or T. In some embodiments, the HVR-H1 comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:1-52 and 137-158. In some embodiments, the HVR-H1 comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:1-52.

(9) In another aspect, provided herein are one or more HVR-H2 amino acid sequences, and/or one or more polynucleotides (e.g., synthetic polynucleotides) encoding the same, wherein the HVR-H2 comprises an amino acid sequence according to a formula selected from the group consisting of: Formula (IV): LAX1IX2WX3X4DKX5YSX6SLKSRL (SEQ ID NO:201), wherein X1 is L or R, X2 is D or Y, X3 is A, D, S, or Y, X4 is D or G, X5 is R, S, or Y, and X6 is P or T; Formula (V): IGX1IX2X3SGSTYYSPSLKSRV (SEQ ID NO:202), wherein X1 is A, D, E, S, or Y, X2 is S or Y, and X3 is H or Y; Formula (VI): IGXIIYX2SGX3TX4YNPSLKSRV (SEQ ID NO:203), wherein X1 is D, E, R, S, or Y, X2 is H or Y, X3 is N or S, and X4 is N or Y; Formula (VII): VSXIISGX2GX3X4TYYADSVKGRF (SEQ ID NO: 204), wherein X1 is A, G, S, V, or Y, X2 is A, D, S, or Y, X3 is D, G, or S, and X4 is S or T; Formula (VIII): IGXIINPNX2GX3TX4YAQKFQGRV (SEQ ID NO:205), wherein X1 is I, R, or W, X2 is F or R, X3 is D, G, or S, and X4 is K or N; Formula (IX): IGX1IX2PSX3GX4TX5YAQKFQGRV (SEQ ID NO:206), wherein X1 is I, R, or W, X2 is S or Y, X3 is G or S, X4 is D, G, or S, and X5 is K or N; and Formula (X): VGRIXISKX2X3GX4TTX5YAAX6VKGRF (SEQ ID NO: 207), wherein X1 is K or R, X2 is A or T, X3 is D or Y, X4 is G or Y, X5 is D or E, and X6 is P or S. In some embodiments, the HVR-H2 comprises an amino acid sequence according to a formula selected from the group consisting of: Formula (IV); Formula (VII); Formula (VIII); Formula (IX); Formula (XI): IGX1IX2X3SGSTYYSPSLKSRV (SEQ ID NO:208), wherein X1 is A, D, or E, X2 is S or Y, and X3 is H or Y; Formula (XII): IGXIIYX2SGX3TX4YNPSLKSRV (SEQ ID NO:209), wherein X1 is D, E, or S, X2 is H or Y, X3 is N or S, and X4 is N or Y; and Formula (XIII): VGRIXISKX2X3GX4TTEYAAX5VKGRF (SEQ ID NO:210), wherein X1 is K or R, X2 is A or T, X3 is D or Y, X4 is G or Y, X5 is P or S. In some embodiments, the HVR-H2 comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 53-136 and 159-164. In some embodiments, the HVR-H2 comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 53-136.

(10) In another aspect, provided herein are one or more HVR-H3 amino acid sequences, and/or one or more polynucleotides (e.g., synthetic polynucleotides) encoding the same, wherein the HVR-H3 comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:223-256.

(11) In another aspect, provided herein are one or more HVR-L1 amino acid sequences, and/or one or more polynucleotides (e.g., synthetic polynucleotides) encoding the same, wherein the HVR-L1 comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:257-264.

(12) In another aspect, provided herein are one or more HVR-L3 amino acid sequences, and/or one or more polynucleotides (e.g., synthetic polynucleotides) encoding the same, wherein the HVR-L3 comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:265-274.

(13) In another aspect, provided herein is a polynucleotide (e.g., a synthetic polynucleotide) encoding an antibody heavy chain variable region comprising a HVR-H1, a HVR-H2, and a HVR-H3, wherein the HVR-H1 comprises an amino acid sequence according to a formula selected from the group consisting of Formula

(I), Formula (II), and Formula (III). In some embodiments, provided herein is a library comprising polynucleotides (e.g., synthetic polynucleotides), wherein at least one (e.g., at least one, at least two, at least three, at least four, at least five, at least ten etc.) of the polynucleotides in the library encodes an antibody heavy chain variable region comprising a HVR-H1, a HVR-H2, and a HVR-H3, wherein the HVR-H1 comprises an amino acid sequence according to a formula selected from the group consisting of Formula (I), Formula (II), and Formula (III). In some embodiments, provided herein is a library comprising polynucleotides (e.g., synthetic polynucleotides), wherein each of the polynucleotides in the library encodes an antibody heavy chain variable region comprising a HVR-H1, HVR-H2, and a HVR-H3, wherein the HVR-H1 comprises an amino acid sequence according to a formula selected from the group consisting of Formula (I), Formula (II), and Formula (III).

(14) In some embodiments, the HVR-H1 comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 1-52 and 137-158. In some embodiments, the HVR-H1 comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 1-52. In some embodiments, the HVR-H1 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 1, 4, 5, 7, 8, 9, 11, 13, 16, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 31, 33, 34, 38, 40, 42, 43, 45, 47, 49, 50, and 51. In some embodiments, the HVR-H1 comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 2, 3, 14, 15, 30, 32, 35, 37, 39, 41, 44, 46, and 48. In some embodiments, the HVR-H1 comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 6, 10, 17, 29, 36, and 52.

(15) In some embodiments that may be combined with any of the preceding embodiments, the heavy chain variable region comprises an HVR-H1, a HVR-H2, and a HVR-H3, wherein the HVR-H3 comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 223-256.

(16) In some embodiments, the heavy chain variable region further comprises a FW-H1 comprising the amino acid sequence of SEQ ID NO:165. In some embodiments, the heavy chain variable region further comprises a FW-H2 comprising the amino acid sequence of SEQ ID NO:166. In some embodiments, the heavy chain variable region further comprises a FW-H3 comprising the amino acid sequence of SEQ ID NO:167. In some embodiments, the heavy chain variable region further comprises a FW-H4 comprising the amino acid sequence of SEQ ID NO:168. In some embodiments, the heavy chain variable region comprises at least two (e.g., at least two, at least three, or all four) of a FW-H1 comprising the amino acid sequence of SEQ ID NO:165, a FW-H2 comprising the amino acid sequence of SEQ ID NO:166, a FW-H3 comprising the amino acid sequence of SEQ ID NO:167, and a FW-H4 comprising the amino acid sequence of SEQ ID NO:168, in any combination. In some embodiments, the FW-H3 sequence comprises an arginine to lysine mutation at R19 of SEQ ID NO:167.

(17) In another aspect, provided herein is a polynucleotide (e.g., a synthetic polynucleotide) encoding an antibody heavy chain variable region comprising a HVR-H1, a HVR-H2, and a HVR-H3, wherein the HVR-H2 comprises an amino acid sequence according to a formula selected from the group consisting of Formula (IV), Formula (V), Formula (VI), Formula (VII), Formula (VIII), Formula (IX), and Formula (X). In some embodiments, provided herein is a library comprising polynucleotides (e.g., synthetic polynucleotides), wherein at least one (e.g., at least one, at least two, at least three, at least four, at least five, at least ten etc.) of the polynucleotides in the library encodes an antibody heavy chain variable region comprising a HVR-H1, a HVR-H2, and a HVR-H3, wherein the HVR-H2 comprises an amino acid sequence according to a formula selected from the group consisting of Formula (IV), Formula (V), Formula (VI), Formula (VII), Formula (VIII), Formula (IX), and Formula (X). In some embodiments, provided herein is a library comprising polynucleotides (e.g., synthetic polynucleotides), wherein each of the polynucleotides in the library encodes an antibody heavy chain variable region comprising a HVR-H1, HVR-H2, and a HVR-H3, wherein the HVR-H2 comprises an amino acid sequence according to a formula selected from the group consisting of Formula (IV), Formula (V), Formula (VI), Formula (VII), Formula (VIII), Formula (IX), and Formula (X).

(18) In some embodiments, provided herein is a polynucleotide (e.g., a synthetic polynucleotide) encoding an antibody heavy chain variable region comprising a HVR-H1, a HVR-H2, and a HVR-H3, wherein the HVR-H2 comprises an amino acid sequence according to a formula selected from the group consisting of Formula (IV), Formula (VII), Formula (VIII), Formula (IX), Formula (XI), Formula (XII), and Formula (XIII). In some embodiments, provided herein is a library comprising polynucleotides (e.g., synthetic polynucleotides), wherein at least one (e.g., at least one, at least two, at least three, at least four, at least five, at least ten etc.) of the polynucleotides in the library encodes an antibody heavy chain variable region comprising a HVR-H1, a HVR-H2, and a HVR-H3, wherein the HVR-H2 comprises an amino acid sequence according to a formula selected from the group consisting of Formula (IV), Formula (VII), Formula (VIII), Formula (IX), Formula

(XI), Formula (XII), and Formula (XIII). In some embodiments, provided herein is a library comprising polynucleotides (e.g., synthetic polynucleotides), wherein each of the polynucleotides in the library encodes an antibody heavy chain variable region comprising a HVR-H1, HVR-H2, and a HVR-H3, wherein the HVR-H2 comprises an amino acid sequence according to a formula selected from the group consisting of Formula (IV), Formula (VII), Formula (VIII), Formula (IX), Formula (XI), Formula (XII), and Formula (XIII).

(19) In some embodiments, the HVR-H2 comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 53-136 and 159-164. In some embodiments, the HVR-H2 comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 53-136. In some embodiments, the HVR-H2 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 53, 60, 63, 65, 66, 67, 70, 82, 89, 93, 95, 105, 109, 110, 117, 121, 122, 123, 124, 128, 129, 130, 131, 132, and 134. In some embodiments, the HVR-H2 comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 55, 56, 59, 61, 62, 64, 68, 69, 71, 73, 74, 75, 76, 77, 78, 79, 72, 81, 83, 86, 90, 91, 99, 100, 103, 106, 107, 108, 112, 113, 116, 118, 126, 135, and 136. In some embodiments, the HVR-H2 comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 54, 57, 58, 80, 84, 85, 87, 88, 92, 94, 96, 97, 98, 101, 102, 104, 111, 114, 115, 119, 120, 125, 127 and 133.

(20) In some embodiments that may be combined with any of the preceding embodiments, the heavy chain variable region comprises an HVR-H1, a HVR-H2, and a HVR-H3, wherein the HVR-H3 comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 223-256.

(21) In some embodiments, the heavy chain variable region further comprises a FW-H1 comprising the amino acid sequence of SEQ ID NO:165. In some embodiments, the heavy chain variable region further comprises a FW-H2 comprising the amino acid sequence of SEQ ID NO:166. In some embodiments, the heavy chain variable region further comprises a FW-H3 comprising the amino acid sequence of SEQ ID NO:167. In some embodiments, the heavy chain variable region further comprises a FW-H4 comprising the amino acid sequence of SEQ ID NO:168. In some embodiments, the heavy chain variable region comprises at least two (e.g., at least two, at least three, or all four) of a FW-H1 comprising the amino acid sequence of SEQ ID NO:165, a FW-H2 comprising the amino acid sequence of SEQ ID NO:166, a FW-H3 comprising the amino acid sequence of SEQ ID NO:167, and a FW-H4 comprising the amino acid sequence of SEQ ID NO:168, in any combination. In some embodiments, the FW-H3 sequence comprises an arginine to lysine mutation at R19 of SEQ ID NO:167.

(22) In another aspect, provided herein is a polynucleotide (e.g., a synthetic polynucleotide) encoding an antibody heavy chain variable region comprising a HVR-H1, a HVR-H2, and a HVR-H3, wherein the HVR-H1 comprises an amino acid sequence according to a formula selected from the group consisting of Formula (I), Formula (II), and Formula (III), and wherein the HVR-H2 comprises an amino acid sequence according to a formula selected from the group consisting of Formula (IV), Formula (V), Formula (VI), Formula (VII), Formula (VIII), Formula (IX), and Formula (X). In some embodiments, provided herein is a library comprising polynucleotides (e.g., synthetic polynucleotides), wherein at least one (e.g., at least one, at least two, at least three, at least four, at least five, at least ten etc.) of the polynucleotides in the library encodes an antibody heavy chain variable region comprising a HVR-H1, a HVR-H2, and a HVR-H3, wherein the HVR-H1 comprises an amino acid sequence according to a formula selected from the group consisting of Formula (I), Formula (II), and Formula (III), and wherein the HVR-H2 comprises an amino acid sequence according to a formula selected from the group consisting of Formula (IV), Formula (V), Formula (VI), Formula (VII), Formula (VIII), Formula (IX), and Formula (X). In some embodiments, provided herein is a library comprising polynucleotides (e.g., synthetic polynucleotides), wherein each of the polynucleotides in the library encodes an antibody heavy chain variable region comprising a HVR-H1, a HVR-H2, and a HVR-H3, wherein the HVR-H1 comprises an amino acid sequence according to a formula selected from the group consisting of Formula (I), Formula (II), and Formula (III), and wherein the HVR-H2 comprises an amino acid sequence according to a formula selected from the group consisting of Formula (IV), Formula (V), Formula (VI), Formula (VII), Formula (VIII), Formula (IX), and Formula (X).

(23) In some embodiments, provided herein is a polynucleotide (e.g., a synthetic polynucleotide) encoding an antibody heavy chain variable region comprising a HVR-H1, a HVR-H2, and a HVR-H3, wherein the HVR-H1 comprises an amino acid sequence according to a formula selected from the group consisting of Formula (I), Formula (II), and Formula (III), and wherein the HVR-H2 comprises an amino acid sequence according to a formula selected from the group consisting of Formula (IV), Formula (VII), Formula (VIII), Formula (IX), Formula (XI), Formula (XII), and Formula (XIII). In some embodiments, provided herein is a library

comprising polynucleotides (e.g., synthetic polynucleotides), wherein at least one (e.g., at least one, at least two, at least three, at least four, at least five, at least ten etc.) of the polynucleotides in the library encodes an antibody heavy chain variable region comprising a HVR-H1, a HVR-H2, and a HVR-H3, wherein the HVR-H1 comprises an amino acid sequence according to a formula selected from the group consisting of Formula (I), Formula (II), and Formula (III), and wherein the HVR-H2 comprises an amino acid sequence according to a formula selected from the group consisting of Formula (IV), Formula (VII), Formula (VIII), Formula (IX), Formula (XI), Formula (XII), and Formula (XIII). In some embodiments, provided herein is a library comprising polynucleotides (e.g., synthetic polynucleotides), wherein each of the polynucleotides in the library encodes an antibody heavy chain variable region comprising a HVR-H1, a HVR-H2, and a HVR-H3, wherein the HVR-H1 comprises an amino acid sequence according to a formula selected from the group consisting of Formula (I), Formula (II), and Formula (III), and wherein the HVR-H2 comprises an amino acid sequence according to a formula selected from the group consisting of Formula (IV), Formula (VII), Formula (VIII), Formula (IX), Formula (XI), Formula (XII), and Formula (XIII).

(24) In some embodiments, the HVR-H1 comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 1-52 and 137-158. In some embodiments, the HVR-H2 comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 53-136 and 159-164. In some embodiments, the HVR-H1 comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 1-52 and 137-158, and the HVR-H2 comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 53-136 and 159-164. In some embodiments, the HVR-H1 comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 1-52. In some embodiments, the HVR-H2 comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 53-136. In some embodiments, the HVR-H1 comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 1-52, and the HVR-H2 comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 53-136. In some embodiments, the HVR-H1 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 1, 4, 5, 7, 8, 9, 11, 13, 16, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 31, 33, 34, 38, 40, 42, 43, 45, 47, 49, 50, and 51, and the HVR-H2 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 53, 60, 63, 65, 66, 67, 70, 82, 89, 93, 95, 105, 109, 110, 117, 121, 122, 123, 124, 128, 129, 130, 131, 132, and 134. In some embodiments, the HVR-H1 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 3, 14, 15, 30, 32, 35, 37, 39, 41, 44, 46, and 48, and the HVR-H2 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 55, 56, 59, 61, 62, 64, 68, 69, 71, 73, 74, 75, 76, 77, 78, 79, 72, 81, 83, 86, 90, 91, 99, 100, 103, 106, 107, 108, 112, 113, 116, 118, 126, 135, and 136. In some embodiments, the HVR-H1 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 6, 10, 17, 29, 36, and 52, and the HVR-H2 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 54, 57, 58, 80, 84, 85, 87, 88, 92, 94, 96, 97, 98, 101, 102, 104, 111, 114, 115, 119, 120, 125, 127 and 133.

(25) In some embodiments, the heavy chain variable region comprises a HVR-H1, a HVR-H2, and a HVR-H3, wherein the HVR-H1 and HVR-H2 are selected from the group consisting of: a HVR-H1 comprising the amino acid sequence of Formula (II) and a HVR-H2 comprising the amino acid sequence of Formula (IX); a HVR-H1 comprising the amino acid sequence of Formula (II) and a HVR-H2 comprising the amino acid sequence of Formula (VII); a HVR-H1 comprising the amino acid sequence of Formula (I) and a HVR-H2 comprising the amino acid sequence of Formula (VII); a HVR-H1 comprising the amino acid sequence of Formula (I) and a HVR-H2 comprising the amino acid sequence of Formula (IX); a HVR-H1 comprising the amino acid sequence of Formula (II) and a HVR-H2 comprising the amino acid sequence of Formula (IV); a HVR-H1 comprising the amino acid sequence of Formula (II) and a HVR-H2 comprising the amino acid sequence of Formula (V); a HVR-H1 comprising the amino acid sequence of Formula (II) and a HVR-H2 comprising the amino acid sequence of Formula (VI); a HVR-H1 comprising the amino acid sequence of Formula (I) and a HVR-H2 comprising the amino acid sequence of Formula (VI); a HVR-H1 comprising the amino acid sequence of Formula (III) and a HVR-H2 comprising the amino acid sequence of Formula (VI); a HVR-H1 comprising the amino acid sequence of Formula (III) and a HVR-H2 comprising the amino acid sequence of Formula (VII); a HVR-H1 comprising the amino acid sequence of Formula (II) and a HVR-H2 comprising the amino acid sequence of Formula (VIII); a HVR-H1 comprising the amino acid sequence of Formula (I) and a HVR-H2 comprising the amino acid sequence of Formula (V); a HVR-H1 comprising the amino acid sequence of Formula (III) and a HVR-H2 comprising the amino acid sequence of Formula (V); and a HVR-H1 comprising the amino acid sequence of Formula (I) and a HVR-H2 comprising the amino acid sequence of Formula (VIII). In some embodiments, the HVR-H1 and HVR-H2 are selected from the

group consisting of: a HVR-H1 comprising the amino acid sequence of Formula (II) and a HVR-H2 comprising the amino acid sequence of Formula (XI); a HVR-H1 comprising the amino acid sequence of Formula (II) and a HVR-H2 comprising the amino acid sequence of Formula (XII); a HVR-H1 comprising the amino acid sequence of Formula (I) and a HVR-H2 comprising the amino acid sequence of Formula (XII); a HVR-H1 comprising the amino acid sequence of Formula (III) and a HVR-H2 comprising the amino acid sequence of Formula (XII); a HVR-H1 comprising the amino acid sequence of Formula (I) and a HVR-H2 comprising the amino acid sequence of Formula (XI); and a HVR-H1 comprising the amino acid sequence of Formula (III) and a HVR-H2 comprising the amino acid sequence of Formula (XI). In some embodiments, the HVR-H1 and HVR-H2 are selected from the group consisting of: a HVR-H1 comprising the amino acid sequence of Formula (I) and a HVR-H2 comprising the amino acid sequence of Formula (IV); a HVR-H1 comprising the amino acid sequence of Formula (III) and a HVR-H2 comprising the amino acid sequence of Formula (IV); a HVR-H1 comprising the amino acid sequence of Formula (II) and a HVR-H2 comprising the amino acid sequence of Formula (X); a HVR-H1 comprising the amino acid sequence of Formula (III) and a HVR-H2 comprising the amino acid sequence of Formula (IX); a HVR-H1 comprising the amino acid sequence of Formula (I) and a HVR-H2 comprising the amino acid sequence of Formula (X); a HVR-H1 comprising the amino acid sequence of Formula (III) and a HVR-H2 comprising the amino acid sequence of Formula (VIII); and a HVR-H1 comprising the amino acid sequence of Formula (III) and a HVR-H2 comprising the amino acid sequence of Formula (X). In some embodiments, the HVR-H1 and HVR-H2 are selected from the group consisting of: a HVR-H1 comprising the amino acid sequence of Formula (II) and a HVR-H2 comprising the amino acid sequence of Formula (XIII); a HVR-H1 comprising the amino acid sequence of Formula (I) and a HVR-H2 comprising the amino acid sequence of Formula (XIII); and a HVR-H1 comprising the amino acid sequence of Formula (III) and a HVR-H2 comprising the amino acid sequence of Formula (XIII).

(26) In some embodiments, the heavy chain variable region comprises a HVR-H1, a HVR-H2, and a HVR-H3, wherein the HVR-H1 and HVR-H2 are selected from the group consisting of: a HVR-H1 comprising the amino acid sequence of SEQ ID NO:157, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:63; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:1, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:122; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:138, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:63; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:154, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:63; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:158, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:161; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:158, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:63; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:145, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:128; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:22, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:61; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:31, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:63; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:153, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:63; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:155, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:67; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:156, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:100; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:51, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:162; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:138, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:123; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:139, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:110; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:8, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:126; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:13, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:129; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:31, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:124; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:25, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:130; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:150, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:132; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:158, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:162; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:12, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:82; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:149, and a HVR-H2 comprising the amino acid

sequence of SEQ ID NO: 117; and a HVR-H1 comprising the amino acid sequence of SEQ ID NO:7, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:134. In some embodiments, the HVR-H1 and HVR-H2 are selected from the group consisting of: a HVR-H1 comprising the amino acid sequence of SEQ ID NO:26, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:53; a HVR-HL comprising the amino acid sequence of SEQ ID NO:151, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:53; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:34, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:63; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:50, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:162; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:158, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:104; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:5, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:121; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:6, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:116; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:7, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:121; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:17, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:63; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:25, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:101; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:25, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:114; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:29, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO: 112; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:152, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:63; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:156, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:89; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:157, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:94; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:48, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:58; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:50, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:89; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:50, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:163; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:158, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:160; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:158, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:87; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:158, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:92; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:158, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:93; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:158, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:97; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:158, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:103; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:158, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:164; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:137, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:54; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:3, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:127; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:4, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:85; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:4, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO: 110; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:139, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:109; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:139, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:121; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:8, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:120; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:140, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:131; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:141, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO: 116; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:142, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:159; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:143, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:116; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:144, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:121; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:146, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:110; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:147, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:133; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:148, and

a HVR-H2 comprising the amino acid sequence of SEQ ID NO:63; and a HVR-H1 comprising the amino acid sequence of SEQ ID NO:13, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:118.
(27) In some embodiments that may be combined with any of the preceding embodiments, the polynucleotides in the library contain less than about 6.5*10.sup.4 (e.g., less than about 6.5*10.sup.4, less than about 5.5*10.sup.4, less than about 2.5*10.sup.4, less than about 1*10.sup.4, less than about 6700, less than about 6660, less than about 5000, less than about 2500, less than about 1000, less than about 690, less than about 500, less than about 100, less than about 50, etc.) unique combinations of HVR-H1 and HVR-H2 sequences. In some embodiments, the polynucleotides in the library (e.g., synthetic polynucleotides) contain about 62272 or less unique combinations of HVR-H1 and HVR-H2 sequences. In some embodiments, the polynucleotides in the library (e.g., synthetic polynucleotides) contain about 60928 or less unique combinations of HVR-H1 and HVR-H2 sequences. In some embodiments, the polynucleotides in the library (e.g., synthetic polynucleotides) contain about 54656 or less unique combinations of HVR-H1 and HVR-H2 sequences. In some embodiments, the polynucleotides in the library (e.g., synthetic polynucleotides) contain about 6660 or less unique combinations of HVR-H1 and HVR-H2 sequences. In some embodiments, the polynucleotides in the library (e.g., synthetic polynucleotides) contain about 690 or less unique combinations of HVR-H1 and HVR-H2 sequences. In some embodiments, at least one of the HVR-H1 and HVR-H2 of the antibody heavy chain variable region adopts multiple conformations, as assayed by structural determination and/or computational modeling.
(28) In some embodiments that may be combined with any of the preceding embodiments, the heavy chain variable region comprises an HVR-H1, a HVR-H2, and a HVR-H3, wherein the HVR-H3 comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 223-256.
(29) In some embodiments, the heavy chain variable region further comprises a FW-H1 comprising the amino acid sequence of SEQ ID NO:165. In some embodiments, the heavy chain variable region further comprises a FW-H2 comprising the amino acid sequence of SEQ ID NO:166. In some embodiments, the heavy chain variable region further comprises a FW-H3 comprising the amino acid sequence of SEQ ID NO:167. In some embodiments, the heavy chain variable region further comprises a FW-H4 comprising the amino acid sequence of SEQ ID NO:168. In some embodiments, the heavy chain variable region comprises at least two (e.g., at least two, at least three, or all four) of a FW-H1 comprising the amino acid sequence of SEQ ID NO:165, a FW-H2 comprising the amino acid sequence of SEQ ID NO:166, a FW-H3 comprising the amino acid sequence of SEQ ID NO:167, and a FW-H4 comprising the amino acid sequence of SEQ ID NO:168, in any combination. In some embodiments, the FW-H3 sequence comprises an arginine to lysine mutation at R19 of SEQ ID NO:167. In some embodiments, the heavy chain variable region comprises a sequence selected from the group consisting of SEQ ID NOs: 169, 171, 173, 175, 177, 179, 181, 183, 185, 187, 189, 191, 193, and 195.
(30) In some embodiments, the polynucleotides in the library encode full-length antibody heavy chains. In some embodiments, the libraries further comprise one or more polynucleotides (e.g., synthetic polynucleotides) that encode antibody light chain variable regions. In some embodiments, the antibody light chain variable regions comprise a HVR-L1, a HVR-L2 and a HVR-L3, wherein the HVR-L1 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 257-264 and/or the HVR-L3 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 265-274. In some embodiments, the polynucleotides that encode antibody light chain variable regions include at least one unique sequence, at least 100 unique sequences, at least 280 unique sequences, at least 10.sup.3 unique sequences, at least 10.sup.4 unique sequences, at least 10.sup.5 unique sequences, at least 10.sup.6 unique sequences, at least 10.sup.7 unique sequences, at least 10.sup.8 unique sequences, or least about 10.sup.9 unique sequences. In some embodiments, the one or more polynucleotides in the library that encodes antibody light chain variable regions encode full-length antibody light chains.
(31) In another aspect, provided herein are polynucleotides (e.g., synthetic polynucleotides) encoding a plurality of unique antibodies, wherein each antibody comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region of each antibody of the plurality comprises an identical sequence and is encoded by any of the polynucleotides encoding a heavy chain variable region as described above. In some embodiments, provided herein are libraries comprising polynucleotides (e.g., synthetic polynucleotides) encoding a plurality of unique antibodies, wherein each antibody comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region of each antibody of the plurality comprises an identical sequence and is encoded by any of the polynucleotides encoding a heavy chain variable region as described above

(32) In some embodiments, the light chain variable regions comprise a HVR-L1, a HVR-L2 and a HVR-L3, wherein the HVR-L1 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 257-264 and/or the HVR-L3 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 265-274. In some embodiments, the light chain variable regions of the antibodies in the library include at least one unique sequence, at least 100 unique sequences, at least 280 unique sequences, at least 10.sup.3 unique sequences, at least 10.sup.4 unique sequences, at least 10.sup.5 unique sequences, at least 10.sup.6 unique sequences, at least 10.sup.7 unique sequences, at least 108 unique sequences, or least about 109 unique sequences.

(33) In another aspect, provided herein is a vector comprising any of the polynucleotides as described above. In some embodiments, provided herein is a library comprising vectors, wherein at least one (e.g., at least one, at least two, at least five, at least 10, at least 25, at least 50, at least 100, at least 250, at least 500, at least 690, at least 750, at least 1000, at least 2500, at least 5000, at least 6000, at least 6500, etc.) of the vectors in the library comprises any of the polynucleotides as described above. In some embodiments, at least two of the vectors in the library comprise a polynucleotide as described above. In some embodiments, at least 100 of the vectors in the library comprise a polynucleotide as described above. In some embodiments, at least 500 of the vectors in the library comprise a polynucleotide as described above. In some embodiments, at least 1000 of the vectors in the library comprise a polynucleotide as described above. In some embodiments, at least 5000 of the vectors in the library comprise a polynucleotide as described above. In some embodiments, at least 6500 of the vectors in the library comprise a polynucleotide as described above. In some embodiments, provided herein is a library comprising vectors, wherein each of the vectors in the library comprises any of the polynucleotides as described above. In some embodiments, the vector is an expression vector. In some embodiments, the vector is a display vector. In some embodiments, the library comprising vectors further comprises at least one (e.g., at least one, at least two, at least five, at least 10, at least 25, at least 50, at least 100, at least 250, at least 500, at least 690, at least 750, at least 1000, at least 2500, at least 5000, at least 6000, at least 6500, etc.) vector that encodes a light chain variable region polypeptide. In some embodiments, the light chain variable regions comprise a HVR-L1, a HVR-L2 and a HVR-L3, wherein the HVR-Li comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 257-264 and/or the HVR-L3 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 265-274. In some embodiments, the at least one vector in the library encodes light chain variable regions which include at least one unique sequence, at least 100 unique sequences, at least 280 unique sequences, at least 10.sup.3 unique sequences, at least 10.sup.4 unique sequences, at least 10.sup.5 unique sequences, at least 10.sup.6 unique sequences, at least 10.sup.7 unique sequences, at least 10.sup.8 unique sequences, or least about 10.sup.9 unique sequences.

(34) In another aspect, provided herein is a cell comprising any of the polynucleotides and/or vectors as described above. In some embodiments, provided herein is a library comprising a population of cells, wherein at least one (e.g., at least one, at least two, at least five, at least 10, at least 100, at least 10.sup.3, at least 10.sup.4, at least 10.sup.5, at least 10.sup.6, at least 10.sup.7, at least 10.sup.8, at least 10.sup.9, etc.) of the cells in the library comprises any of the polynucleotides and/or vectors as described above. In some embodiments, at least two of the cells in the library comprise a polynucleotide and/or vector as described above. In some embodiments, at least 100 of the cells in the library comprise a polynucleotide and/vector as described above. In some embodiments, provided herein is a library comprising a population of cells, wherein each *of the cells in the library comprises any of the polynucleotides and/or vectors as described above. In some embodiments, the cell is a bacterial, yeast, or mammalian cell (e.g., non-human animal cells or isolated human cells).

(35) In another aspect, provided herein is an antibody heavy chain variable region comprising a HVR-H1, a HVR-H2, and a HVR-H3, wherein the HVR-H1 comprises an amino acid sequence according to a formula selected from the group consisting of Formula (I), Formula (II), and Formula (III). In some embodiments, provided herein is a library comprising antibody heavy chain variable regions, wherein at least one (e.g., at least one, at least two, at least three, at least four, at least five, at least ten etc.) of the heavy chain variable regions in the library comprises a HVR-H1, a HVR-H2, and a HVR-H3, wherein the HVR-H1 comprises an amino acid sequence according to a formula selected from the group consisting of Formula (I), Formula (II), and Formula (III). In some embodiments, provided herein is a library comprising antibody heavy chain variable regions, wherein each of the heavy chain variable regions in the library comprises a HVR-H1, HVR-H2, and a HVR-H3, wherein the HVR-H1 comprises an amino acid sequence according to a formula selected from the group consisting of Formula (I), Formula (II), and Formula (III).

(36) In some embodiments, the HVR-H1 comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 1-52 and 137-158. In some embodiments, the HVR-H1 comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 1-52. In some embodiments, the HVR-H1 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 1, 4, 5, 7, 8, 9, 11, 13, 16, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 31, 33, 34, 38, 40, 42, 43, 45, 47, 49, 50, and 51. In some embodiments, the HVR-H1 comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 2, 3, 14, 15, 30, 32, 35, 37, 39, 41, 44, 46, and 48. In some embodiments, the HVR-H1 comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 6, 10, 17, 29, 36, and 52.
(37) In some embodiments that may be combined with any of the preceding embodiments, the heavy chain variable region comprises an HVR-H1, a HVR-H2, and a HVR-H3, wherein the HVR-H3 comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 223-256.
(38) In some embodiments, the heavy chain variable region further comprises a FW-H1 comprising the amino acid sequence of SEQ ID NO:165. In some embodiments, the heavy chain variable region further comprises a FW-H2 comprising the amino acid sequence of SEQ ID NO:166. In some embodiments, the heavy chain variable region further comprises a FW-H3 comprising the amino acid sequence of SEQ ID NO: 167. In some embodiments, the heavy chain variable region further comprises a FW-H4 comprising the amino acid sequence of SEQ ID NO:168. In some embodiments, the heavy chain variable region comprises at least two (e.g., at least two, at least three, or all four) of a FW-H1 comprising the amino acid sequence of SEQ ID NO:165, a FW-H2 comprising the amino acid sequence of SEQ ID NO:166, a FW-H3 comprising the amino acid sequence of SEQ ID NO:167, and a FW-H4 comprising the amino acid sequence of SEQ ID NO:168, in any combination. In some embodiments, the FW-H3 sequence comprises an arginine to lysine mutation at R19 of SEQ ID NO:167.
(39) In another aspect, provided herein is an antibody heavy chain variable region comprising a HVR-H1, a HVR-H2, and a HVR-H3, wherein the HVR-H2 comprises an amino acid sequence according to a formula selected from the group consisting of Formula (IV), Formula (V), Formula (VI), Formula (VII), Formula (VIII), Formula (IX), and Formula (X). In some embodiments, provided herein is a library comprising antibody heavy chain variable regions, wherein at least one (e.g., at least one, at least two, at least three, at least four, at least five, at least ten etc.) of the heavy chain variable regions in the library comprises a HVR-H1, a HVR-H2, and a HVR-H3, wherein the HVR-H2 comprises an amino acid sequence according to a formula selected from the group consisting of Formula (IV), Formula (V), Formula (VI), Formula (VII), Formula (VIII), Formula (IX), and Formula (X). In some embodiments, provided herein is a library comprising antibody heavy chain variable regions, wherein each of the heavy chain variable regions in the library comprises a HVR-H1, HVR-H2, and a HVR-H3, wherein the HVR-H2 comprises an amino acid sequence according to a formula selected from the group consisting of Formula (IV), Formula (V), Formula (VI), Formula (VII), Formula (VIII), Formula (IX), and Formula (X).
(40) In some embodiments, provided herein is an antibody heavy chain variable region comprising a HVR-H1, a HVR-H2, and a HVR-H3, wherein the HVR-H2 comprises an amino acid sequence according to a formula selected from the group consisting of Formula (IV), Formula (VII), Formula (VIII), Formula (IX), Formula (XI), Formula (XII), and Formula (XIII). In some embodiments, provided herein is a library comprising antibody heavy chain variable regions, wherein at least one (e.g., at least one, at least two, at least three, at least four, at least five, at least ten etc.) of the heavy chain variable regions in the library comprises a HVR-H1, a HVR-H2, and a HVR-H3, wherein the HVR-H2 comprises an amino acid sequence according to a formula selected from the group consisting of Formula (IV), Formula (VII), Formula (VIII), Formula (IX), Formula (XI), Formula (XII), and Formula (XIII). In some embodiments, provided herein is a library comprising antibody heavy chain variable regions, wherein each of the heavy chain variable regions in the library comprises a HVR-H1, HVR-H2, and a HVR-H3, wherein the HVR-H2 comprises an amino acid sequence according to a formula selected from the group consisting of Formula (IV), Formula (VII), Formula (VIII), Formula (IX), Formula (XI), Formula (XII), and Formula (XIII).
(41) In some embodiments, the HVR-H2 comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 53-136 and 159-164. In some embodiments, the HVR-H2 comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 53-136. In some embodiments, the HVR-H2 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 53, 60, 63, 65, 66, 67, 70, 82, 89, 93, 95, 105, 109, 110, 117, 121, 122, 123, 124, 128, 129, 130, 131, 132, and 134. In some embodiments, the HVR-H2 comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 55, 56, 59, 61, 62, 64, 68, 69, 71, 73, 74, 75, 76, 77, 78, 79, 72, 81, 83, 86, 90, 91, 99, 100, 103, 106,

107, 108, 112, 113, 116, 118, 126, 135, and 136. In some embodiments, the HVR-H2 comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 54, 57, 58, 80, 84, 85, 87, 88, 92, 94, 96, 97, 98, 101, 102, 104, 111, 114, 115, 119, 120, 125, 127 and 133.

(42) In some embodiments that may be combined with any of the preceding embodiments, the heavy chain variable region comprises an HVR-H1, a HVR-H2, and a HVR-H3, wherein the HVR-H3 comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 223-256.

(43) In some embodiments, the heavy chain variable region further comprises a FW-H1 comprising the amino acid sequence of SEQ ID NO:165. In some embodiments, the heavy chain variable region further comprises a FW-H2 comprising the amino acid sequence of SEQ ID NO:166. In some embodiments, the heavy chain variable region further comprises a FW-H3 comprising the amino acid sequence of SEQ ID NO: 167. In some embodiments, the heavy chain variable region further comprises a FW-H4 comprising the amino acid sequence of SEQ ID NO:168. In some embodiments, the heavy chain variable region comprises at least two (e.g., at least two, at least three, or all four) of a FW-H1 comprising the amino acid sequence of SEQ ID NO:165, a FW-H2 comprising the amino acid sequence of SEQ ID NO:166, a FW-H3 comprising the amino acid sequence of SEQ ID NO:167, and a FW-H4 comprising the amino acid sequence of SEQ ID NO:168, in any combination. In some embodiments, the FW-H3 sequence comprises an arginine to lysine mutation at R19 of SEQ ID NO:167.

(44) In another aspect, provided herein is an antibody heavy chain variable region comprising a HVR-H1, a HVR-H2, and a HVR-H3, wherein the HVR-H1 comprises an amino acid sequence according to a formula selected from the group consisting of Formula (I), Formula (II), and Formula (III), and wherein the HVR-H2 comprises an amino acid sequence according to a formula selected from the group consisting of Formula (IV), Formula (V), Formula (VI), Formula (VII), Formula (VIII), Formula (IX), and Formula (X). In some embodiments, provided herein is a library comprising antibody heavy chain variable regions, wherein at least one (e.g., at least one, at least two, at least three, at least four, at least five, at least ten etc.) of the heavy chain variable regions in the library comprises a HVR-H1, a HVR-H2, and a HVR-H3, wherein the HVR-H1 comprises an amino acid sequence according to a formula selected from the group consisting of Formula (I), Formula (II), and Formula (III), and wherein the HVR-H2 comprises an amino acid sequence according to a formula selected from the group consisting of Formula (IV), Formula (V), Formula (VI), Formula (VII), Formula (VIII), Formula (IX), and Formula (X). In some embodiments, provided herein is a library comprising antibody heavy chain variable regions, wherein each of the heavy chain variable regions in the library comprises a HVR-H1, a HVR-H2, and a HVR-H3, wherein the HVR-H1 comprises an amino acid sequence according to a formula selected from the group consisting of Formula (I), Formula (II), and Formula (III), and wherein the HVR-H2 comprises an amino acid sequence according to a formula selected from the group consisting of Formula (IV), Formula (V), Formula (VI), Formula (VII), Formula (VIII), Formula (IX), and Formula (X).

(45) In some embodiments, provided herein is an antibody heavy chain variable region comprising a HVR-H1, a HVR-H2, and a HVR-H3, wherein the HVR-H1 comprises an amino acid sequence according to a formula selected from the group consisting of Formula (I), Formula (II), and Formula (III), and wherein the HVR-H2 comprises an amino acid sequence according to a formula selected from the group consisting of Formula (IV), Formula (VII), Formula (VIII), Formula (IX), Formula (XI), Formula (XII), and Formula (XIII). In some embodiments, provided herein is a library comprising antibody heavy chain variable regions, wherein at least one (e.g., at least one, at least two, at least three, at least four, at least five, at least ten etc.) of the heavy chain variable regions in the library comprises a HVR-H1, a HVR-H2, and a HVR-H3, wherein the HVR-H1 comprises an amino acid sequence according to a formula selected from the group consisting of Formula (I), Formula (II), and Formula (III), and wherein the HVR-H2 comprises an amino acid sequence according to a formula selected from the group consisting of Formula (IV), Formula (VII), Formula (VIII), Formula (IX), Formula (XI), Formula (XII), and Formula (XIII). In some embodiments, provided herein is a library comprising antibody heavy chain variable regions, wherein each of the heavy chain variable regions in the library comprises a HVR-H1, a HVR-H2, and a HVR-H3, wherein the HVR-H1 comprises an amino acid sequence according to a formula selected from the group consisting of Formula (I), Formula (II), and Formula (III), and wherein the HVR-H2 comprises an amino acid sequence according to a formula selected from the group consisting of Formula (IV), Formula (VII), Formula (VIII), Formula (IX), Formula (XI), Formula (XII), and Formula (XIII).

(46) In some embodiments, the HVR-H1 comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 1-52 and 137-158. In some embodiments, the HVR-H2 comprises an amino acid

sequence selected from the group consisting of SEQ ID NOS: 53-136 and 159-164. In some embodiments, the HVR-H1 comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 1-52 and 137-158, and the HVR-H2 comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 53-136 and 159-164. In some embodiments, the HVR-H1 comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 1-52. In some embodiments, the HVR-H2 comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 53-136. In some embodiments, the HVR-H1 comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 1-52, and the HVR-H2 comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 53-136. In some embodiments, the HVR-H1 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 1, 4, 5, 7, 8, 9, 11, 13, 16, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 31, 33, 34, 38, 40, 42, 43, 45, 47, 49, 50, and 51, and the HVR-H2 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 53, 60, 63, 65, 66, 67, 70, 82, 89, 93, 95, 105, 109, 110, 117, 121, 122, 123, 124, 128, 129, 130, 131, 132, and 134. In some embodiments, the HVR-H1 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 3, 14, 15, 30, 32, 35, 37, 39, 41, 44, 46, and 48, and the HVR-H2 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 55, 56, 59, 61, 62, 64, 68, 69, 71, 73, 74, 75, 76, 77, 78, 79, 72, 81, 83, 86, 90, 91, 99, 100, 103, 106, 107, 108, 112, 113, 116, 118, 126, 135, and 136. In some embodiments, the HVR-H1 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 6, 10, 17, 29, 36, and 52, and the HVR-H2 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 54, 57, 58, 80, 84, 85, 87, 88, 92, 94, 96, 97, 98, 101, 102, 104, 111, 114, 115, 119, 120, 125, 127 and 133.

(47) In some embodiments, the heavy chain variable region comprises a HVR-H1, a HVR-H2, and a HVR-H3, wherein the HVR-H1 and HVR-H2 are selected from the group consisting of: a HVR-H1 comprising the amino acid sequence of Formula (II) and a HVR-H2 comprising the amino acid sequence of Formula (IX); a HVR-H1 comprising the amino acid sequence of Formula (II) and a HVR-H2 comprising the amino acid sequence of Formula (VII); a HVR-H1 comprising the amino acid sequence of Formula (I) and a HVR-H2 comprising the amino acid sequence of Formula (VII); a HVR-H1 comprising the amino acid sequence of Formula (I) and a HVR-H2 comprising the amino acid sequence of Formula (IX); a HVR-H1 comprising the amino acid sequence of Formula (II) and a HVR-H2 comprising the amino acid sequence of Formula (IV); a HVR-H1 comprising the amino acid sequence of Formula (II) and a HVR-H2 comprising the amino acid sequence of Formula (V); a HVR-H1 comprising the amino acid sequence of Formula (II) and a HVR-H2 comprising the amino acid sequence of Formula (VI); a HVR-H1 comprising the amino acid sequence of Formula (I) and a HVR-H2 comprising the amino acid sequence of Formula (VI); a HVR-H1 comprising the amino acid sequence of Formula (III) and a HVR-H2 comprising the amino acid sequence of Formula (VI); a HVR-H1 comprising the amino acid sequence of Formula (III) and a HVR-H2 comprising the amino acid sequence of Formula (VII); a HVR-H1 comprising the amino acid sequence of Formula (II) and a HVR-H2 comprising the amino acid sequence of Formula (VIII); a HVR-H1 comprising the amino acid sequence of Formula (I) and a HVR-H2 comprising the amino acid sequence of Formula (V); a HVR-H1 comprising the amino acid sequence of Formula (III) and a HVR-H2 comprising the amino acid sequence of Formula (V); and a HVR-H1 comprising the amino acid sequence of Formula (I) and a HVR-H2 comprising the amino acid sequence of Formula (VIII). In some embodiments, the HVR-H1 and HVR-H2 are selected from the group consisting of: a HVR-H1 comprising the amino acid sequence of Formula (II) and a HVR-H2 comprising the amino acid sequence of Formula (XI); a HVR-H1 comprising the amino acid sequence of Formula (II) and a HVR-H2 comprising the amino acid sequence of Formula (XII); a HVR-H1 comprising the amino acid sequence of Formula (I) and a HVR-H2 comprising the amino acid sequence of Formula (XII); a HVR-H1 comprising the amino acid sequence of Formula (III) and a HVR-H2 comprising the amino acid sequence of Formula (XII); a HVR-H1 comprising the amino acid sequence of Formula (I) and a HVR-H2 comprising the amino acid sequence of Formula (XI); and a HVR-H1 comprising the amino acid sequence of Formula (III) and a HVR-H2 comprising the amino acid sequence of Formula (XI). In some embodiments, the HVR-H1 and HVR-H2 are selected from the group consisting of: a HVR-H1 comprising the amino acid sequence of Formula (I) and a HVR-H2 comprising the amino acid sequence of Formula (IV); a HVR-H1 comprising the amino acid sequence of Formula (III) and a HVR-H2 comprising the amino acid sequence of Formula (IV); a HVR-H1 comprising the amino acid sequence of Formula (II) and a HVR-H2 comprising the amino acid sequence of Formula (X); a HVR-H1 comprising the amino acid sequence of Formula (III) and a HVR-H2 comprising the amino acid sequence of Formula (IX); a HVR-H1 comprising the amino acid sequence of Formula (I) and a HVR-H2 comprising the amino acid sequence of Formula (X);

a HVR-H1 comprising the amino acid sequence of Formula (III) and a HVR-H2 comprising the amino acid sequence of Formula (VIII); and a HVR-H1 comprising the amino acid sequence of Formula (III) and a HVR-H2 comprising the amino acid sequence of Formula (X). In some embodiments, the HVR-H1 and HVR-H2 are selected from the group consisting of: a HVR-H1 comprising the amino acid sequence of Formula (II) and a HVR-H2 comprising the amino acid sequence of Formula (XIII); a HVR-H1 comprising the amino acid sequence of Formula (I) and a HVR-H2 comprising the amino acid sequence of Formula (XIII); and a HVR-H1 comprising the amino acid sequence of Formula (III) and a HVR-H2 comprising the amino acid sequence of Formula (XIII).

(48) In some embodiments, the heavy chain variable region comprises a HVR-H1, a HVR-H2, and a HVR-H3, wherein the HVR-H1 and HVR-H2 are selected from the group consisting of: a HVR-H1 comprising the amino acid sequence of SEQ ID NO:157, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:63; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:1, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:122; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:138, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:63; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:154, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:63; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:158, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:161; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:158, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:63; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:145, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:128; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:22, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:61; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:31, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:63; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:153, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:63; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:155, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:67; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:156, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:100; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:51, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:162; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:138, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:123; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:139, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:110; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:8, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:126; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:13, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:129; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:31, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:124; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:25, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:130; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:150, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:132; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:158, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:162; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:12, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:82; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:149, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO: 117; and a HVR-H1 comprising the amino acid sequence of SEQ ID NO:7, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:134. In some embodiments, the HVR-H1 and HVR-H2 are selected from the group consisting of: a HVR-H1 comprising the amino acid sequence of SEQ ID NO:26, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:53; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:151, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:53; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:34, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:63; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:50, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:162; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:158, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:104; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:5, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:121; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:6, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:116; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:7, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:121; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:17, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:63; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:25, and a HVR-H2

comprising the amino acid sequence of SEQ ID NO:101; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:25, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO: 114; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:29, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO: 112; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:152, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:63; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:156, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:89; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:157, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:94; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:48, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:58; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:50, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:89; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:50, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:163; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:158, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:160; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:158, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:87; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:158, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:92; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:158, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:93; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:158, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:97; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:158, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:103; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:158, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO: 164; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:137, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:54; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:3, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:127; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:4, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:85; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:4, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:110; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:139, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:109; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:139, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:121; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:8, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:120; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:140, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:131; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:141, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:116; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:142, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:159; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:143, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:116; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:144, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:121; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:146, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:110; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:147, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:133; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:148, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:63; and a HVR-H1 comprising the amino acid sequence of SEQ ID NO:13, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:118.

(49) In some embodiments that may be combined with any of the preceding embodiments, the heavy chain variable region comprises an HVR-H1, a HVR-H2, and a HVR-H3, wherein the HVR-H3 comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 223-256.

(50) In some embodiments, the heavy chain variable region further comprises a FW-H1 comprising the amino acid sequence of SEQ ID NO:165. In some embodiments, the heavy chain variable region further comprises a FW-H2 comprising the amino acid sequence of SEQ ID NO:166. In some embodiments, the heavy chain variable region further comprises a FW-H3 comprising the amino acid sequence of SEQ ID NO:167. In some embodiments, the heavy chain variable region further comprises a FW-H4 comprising the amino acid sequence of SEQ ID NO:168. In some embodiments, the heavy chain variable region comprises at least two (e.g., at least two, at least three, or all four) of a FW-H1 comprising the amino acid sequence of SEQ ID NO:165, a FW-H2 comprising the amino acid sequence of SEQ ID NO:166, a FW-H3 comprising the amino acid sequence of SEQ ID NO:167, and a FW-H4 comprising the amino acid sequence of SEQ ID NO:168, in any combination. In some embodiments, the FW-H3 sequence comprises an arginine to lysine

mutation at R19 of SEQ ID NO:167. In some embodiments, the heavy chain variable region comprises a sequence selected from the group consisting of SEQ ID NOs: 169, 171, 173, 175, 177, 179, 181, 183, 185, 187, 189, 191, 193, and 195.

(51) In some embodiments that may be combined with any of the preceding embodiments, the heavy chain variable regions in the library contain less than about 6.5*10.sup.4 (e.g., less than about 6.5*10.sup.4, less than about 5.5*10.sup.4, less than about 2.5*10.sup.4, less than about 1*10.sup.4, less than about 6700, less than about 6660, less than about 5000, less than about 2500, less than about 1000, less than about 690, less than about 500, less than about 100, less than about 50, etc.) unique combinations of HVR-H1 and HVR-H2 sequences. In some embodiments, the heavy chain variable regions in the library contain about 62272 or less unique combinations of HVR-H1 and HVR-H2 sequences. In some embodiments, the heavy chain variable regions in the library contain about 60928 or less unique combinations of HVR-H1 and HVR-H2 sequences. In some embodiments, the heavy chain variable regions in the library contain about 54656 or less unique combinations of HVR-H1 and HVR-H2 sequences. In some embodiments, the heavy chain variable regions in the library contain about 6660 or less unique combinations of HVR-H1 and HVR-H2 sequences. In some embodiments, the heavy chains variable regions in the library contain about 690 or less unique combinations of HVR-H1 and HVR-H2 sequences. In some embodiments, at least one of the HVR-H1 and HVR-H2 of the antibody heavy chain variable regions adopts multiple conformations, as assayed by structural determination and/or computational modeling.

(52) In another aspect, provided herein is an antibody heavy chain variable region and an antibody light chain variable region, wherein the antibody heavy chain variable region is any of the heavy chain variable regions as described herein. In some embodiments, provided herein is a library comprising antibody heavy chain variable regions and antibody light chain variable regions, wherein at least one (e.g., at least one, at least two, at least five, at least 10, at least 100, etc.) of the antibody heavy chain variable regions in the library is any of the heavy chain variable regions as described herein. In some embodiments, provided herein is a library comprising antibody heavy chain variable regions and antibody light chain variable regions, wherein each of the antibody heavy chain variable regions in the library is any of the heavy chain variable regions as described herein. In some embodiments, the antibody light chain variable region comprises a HVR-L1, a HVR-L2 and a HVR-L3, wherein the HVR-L1 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 257-264 and/or the HVR-L3 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 265-274. In some embodiments, the light chain variable regions in the library include at least one unique sequence, at least 100 unique sequences, at least 280 unique sequences, at least 103 unique sequences, at least 104 unique sequences, at least 105 unique sequences, at least 10.sup.6 unique sequences, at least 107 unique sequences, at least 10.sup.8 unique sequences, or least about 109 unique sequences.

(53) In another aspect, provided herein is an antigen binding domain comprising an antibody heavy chain variable region, wherein the antigen binding domain comprises any of the antibody heavy chain variable regions as described herein. In some embodiments, provided herein is a library comprising antigen binding domains comprising antibody heavy chain variable regions, wherein at least one (e.g., at least one, at least two, at least five, at least 10, at least 100, etc.) of the antigen binding domains in the library comprises any of the heavy chain variable regions as described herein. In some embodiments, provided herein is a library comprising antigen binding domains comprising antibody heavy chain variable regions, wherein each of the antigen binding domains in the library comprises any of the heavy chain variable regions as described herein. In some embodiments, the antigen binding domain further comprises an antibody light chain variable region comprising a HVR-L1, a HVR-L2 and a HVR-L3, wherein the HVR-L1 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 257-264 and/or the HVR-L3 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 265-274. In some embodiments, antigen binding domains comprising the light chain variable regions in the library include light chain variable regions comprising at least one unique sequence, at least 100 unique sequences, at least 280 unique sequences, at least 103 unique sequences, at least 104 unique sequences, at least 105 unique sequences, at least 10.sup.6 unique sequences, at least 107 unique sequences, at least 108 unique sequences, or least about 109 unique sequences.

(54) In another aspect, provided herein is an antibody comprising an antibody heavy chain variable region, wherein the antibody comprises any of the antibody heavy chain variable regions as described herein. In some embodiments, provided herein is a library comprising antibodies, wherein at least one (e.g., at least one, at least two, at least five, at least 10, at least 100, etc.) of the antibodies in the library comprises any of

the antibody heavy chain variable regions as described herein. In some embodiments, provided herein is a library comprising antibodies, wherein each of the antibodies in the library comprises any of the heavy chain variable regions as described herein. In some embodiments, the antibody further comprises an antibody light chain variable region comprising a HVR-L1, a HVR-L2 and a HVR-L3, wherein the HVR-L1 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 257-264 and/or the HVR-L3 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 265-274. In some embodiments, antibodies comprising the light chain variable regions in the library include light chain variable regions comprising at least one unique sequence, at least 100 unique sequences, at least 280 unique sequences, at least 10.sup.3 unique sequences, at least 10.sup.4 unique sequences, at least 10.sup.5 unique sequences, at least 10.sup.6 unique sequences, at least 10.sup.7 unique sequences, at least 10.sup.8 unique sequences, or least about 10.sup.9 unique sequences.

(55) In some embodiments that may be combined with any of the preceding embodiments, the antibodies contain less than about 6.5*10.sup.4 unique combinations of HVR-H1 and HVR-H2 sequences. In some embodiments that may be combined with any of the preceding embodiments, the antibodies contain less than about 5.5*10.sup.4 unique combinations of HVR-H1 and HVR-H2 sequences. In some embodiments, the antibodies contain about 62272 or less unique combinations of HVR-H1 and HVR-H2 sequences. In some embodiments, the antibodies contain about 60928 or less unique combinations of HVR-H1 and HVR-H2 sequences. In some embodiments, the antibodies contain about 54656 or less unique combinations of HVR-H1 and HVR-H2 sequences. In some embodiments, the antibodies contain about 6660 or less unique combinations of HVR-H1 and HVR-H2 sequences. In some embodiments, the antibodies contain about 690 or less unique combinations of HVR-H1 and HVR-H2 sequences. In some embodiments, at least one of the HVR-H1 and HVR-H2 of the antibody heavy chain variable region adopts multiple conformations, as assayed by structural determination and/or computational modeling.

(56) In some embodiments that may be combined with any of the preceding embodiments, the antibody binds at least 1 target with an equilibrium dissociation constant (Kd) of between about 10.sup.−7 and about 10.sup.−11 M. In some embodiments, the antibody has a melting temperature (Tm) of between about 60° C. and about 90° C.

(57) In another aspect, provided herein is a polypeptide (e.g., scaffold polypeptides) comprising one or more (e.g., one or more, two or more, three or more, four or more, five or more etc.) HVRs of the present disclosure. In some embodiments, provided herein are libraries comprising polypeptides, wherein at least one (e.g., at least one, at least two, at least five, at least 10, at least 25, at least 50, at least 100, at least 250, at least 500, at least 750, at least 1000, at least 2500, at least 5000, at least 6000, at least 6500, etc.) of the polypeptides in the library comprises one or more HVRs of the present disclosure. In some embodiments, provided herein are libraries comprising polypeptides, wherein each of the polypeptides in the library comprises one or more HVRs of the present disclosure. In some embodiments, the polypeptide comprises an HVR-H1 comprising an amino acid sequence selected from any HVR-H1 sequence as described herein (e.g., a HVR-H1 according to a formula selected from the group consisting of Formula (I), Formula (II), and Formula (III); and SEQ ID NOS:1-52 and 137-158). In some embodiments, the polypeptide comprises an HVR-H2 comprising an amino acid sequence selected from any HVR-H2 as described herein (e.g., a HVR-H2 according to formula selected from the group consisting of Formula (IV), Formula (V), Formula (VI), Formula (VII), Formula (VIII), Formula (IX), Formula (X), Formula (XI), Formula (XII) and Formula (XIII); and SEQ ID NOS:53-136 and 159-164). In some embodiments, the polypeptide comprises an HVR-H3 comprising an amino acid sequence selected from any HVR-H3 sequence as described herein (e.g., SEQ ID NOs: 223-256). In some embodiments, the polypeptide comprises an HVR-L1 comprising an amino acid sequence selected from any HVR-L1 sequence as described herein (e.g., SEQ ID NOs: 257-264). In some embodiments, the polypeptide comprises an HVR-L3 comprising an amino acid sequence selected from any HVR-L3 sequence as described herein (e.g., SEQ ID NOs: 265-274). In some embodiments, the polypeptide comprises two or more (e.g., two or more, three or more, four or more, or all five) of the HVR-H1, HVR-H2, HVR-H3, HVR-L1, and/or HVR-L3 sequences described herein. In some embodiments, provided herein are polynucleotides and libraries comprising polynucleotides encoding any of the polypeptides as described above.

(58) In another aspect, provided herein is a phage comprising at least one polypeptide on its surface wherein the at least one polypeptide comprises any of the antibody heavy chain variable regions described herein. In some embodiments, the at least one polypeptide is any of the antigen binding domains as described herein. In some embodiments, provided herein is a library of phages, wherein at least one (e.g., at least one, at least

two, at least five, at least 10, at least 25, at least 50, at least 100, at least 250, at least 500, at least 750, at least 1000, at least 2500, at least 5000, at least 6000, at least 6500, etc.) phage in the library comprises at least one polypeptide on its surface comprising any of the antibody heavy chain variable regions described herein. In some embodiments, the at least one phage in the library comprises at least one polypeptide on its surface comprising any of the antigen binding domains as described herein. In some embodiments, provided herein is a library comprising phages, wherein each of the phages in the library comprises at least one polypeptide on its surface comprising any of the antibody heavy chain variable regions described herein. In some embodiments, the at least one polypeptide is any of the antigen binding domains as described herein.

(59) In another aspect, provided herein is a non-human animal comprising at least one polynucleotide encoding any of the antibody heavy chain variable regions described herein (e.g., any of the polynucleotides or polynucleotide libraries described herein). In some embodiments, the non-human animal comprises at least one polynucleotide encoding any of the antibodies described herein. In some embodiments, the non-human animal is a mammal (e.g., a mouse, rat, rabbit, camel, or non-human primate).

(60) In another aspect, provided herein are methods of preparing a library comprising providing and assembling any of the polynucleotide sequences of the libraries as described herein.

(61) In another aspect, provided herein are methods of screening for a polypeptide that binds to a target, comprising incubating any of the libraries comprising polyeptpdies described herein (e.g., a library of antigen binding domains, a library of antibodies, a library of phages, etc.) with a target, and selecting one or more polypeptides from the library that binds to the target.

(62) In another aspect, provided herein are methods of making an antibody library comprising the steps: (a) selecting one, two or three heavy chain HVRs comprising a sequence having multiple conformations; and (b) assembling polynucleotide sequences to produce a library of synthetic polynucleotides encoding a plurality of antibody heavy chain variable region sequences. In some embodiments, at least one of the plurality of antibody heavy chain variable region sequences is any of the heavy chain variable region sequences described herein. In some embodiments, each of the plurality of antibody heavy chain variable region sequences are any of the heavy chain variable region sequences described herein.

(63) In another aspect, provided herein are methods of preparing polypeptides (e.g., heavy chain variable regions, antibody heavy chains, antibodies, scaffold polypeptides, etc.) comprising culturing a cell comprising any of the polynucleotides, polynucleotide libraries, vectors, and/or vector libraries as described above to produce the polypeptide. In some embodiments, the polypeptide is collected from the cultured cell, and is further purified.

(64) In another aspect, provided herein are methods of generating a bispecific antibody comprising two antibody heavy chain variable regions and two identical light chain variable regions, comprising: (a) screening for a first antigen binding domain that binds to a first antigen, wherein the first antigen binding domain comprises a first antibody heavy chain variable region and a first antibody light chain variable region, wherein the first antibody heavy chain variable region comprises any of the heavy chain variable regions described herein; (b) screening for a second antigen binding domain that binds to a second antigen, wherein the second antigen binding domain comprises a second antibody heavy chain variable region and a second antibody light chain variable region, wherein the second antibody heavy chain variable region has the same sequence as the first antibody heavy chain variable region; and (c) producing a bispecific antibody comprising the first antigen binding domain and the second antigen binding domain.

(65) In another aspect, provided herein are bispecific antibodies comprising: (a) a first binding domain comprising a first heavy chain variable region and a first light chain variable region, wherein the first binding domain binds to a first target; (b) a second binding domain comprising a second heavy chain variable region and a second light chain variable region, wherein the second binding domain binds to a second target, wherein the second heavy chain variable region has a sequence identical to the first heavy chain variable region sequence; wherein each of the first and second heavy chain variable regions comprises any of the heavy chain variable regions described herein. In some embodiments, the bispecific antibodies comprise a first light chain and a second light chain, wherein the first light chain comprises the first light chain variable region and the second light chain comprises the second light chain variable region, and both the first and second light chains each comprise a kappa CL domain (e.g., a human kappa C.sub.L domain). In some embodiments, the bispecific antibodies comprise a first light chain and a second light chain, wherein the first light chain comprises the first light chain variable region and the second light chain comprises the second light chain variable region, and both the first and second light chains each comprise a lambda CL domain (e.g., a human lambda CL domain). In some embodiments, the bispecific antibodies comprise a first light

chain and a second light chain, wherein the first light chain comprises the first light chain variable region and a kappa CL domain (e.g., a human kappa CL domain), and the second light chain comprises the second light chain variable region and a lambda C.sub.L domain (e.g., a human lambda C.sub.L domain). In some embodiments, the bispecific antibodies comprise a first light chain and a second light chain, wherein the first light chain comprises the first light chain variable region and a lambda C.sub.L domain (e.g., a human lambda C.sub.L domain), and the second light chain comprises the second light chain variable region and a kappa C.sub.L domain (e.g., a human kappa C.sub.L domain).

(66) In another aspect, provided herein are kits comprising any of the polynucleotides, polynucleotide libraries, vectors, and/or vector libraries (or any cells or population of cells comprising them) as described herein. In some embodiments, provided herein are kits comprising any of the heavy chain variable regions, heavy chain variable region libraries, antigen binding domains, antigen binding domain libraries, antibodies, antibody libraries, polypeptides (e.g., scaffold polypeptides), polypeptide libraries, phages, and/or phage libraries as described herein.

(67) It is to be understood that one, some, or all of the properties of the various embodiments described above and herein may be combined to form other embodiments of the present disclosure. These and other aspects of the present disclosure will become apparent to one of skill in the art. These and other embodiments of the present disclosure are further described by the detailed description that follows.

Description

BRIEF DESCRIPTION OF THE DRAWINGS

(1) FIG. **1**A shows an entropy plot by residue number for the amino acids of a V.sub.Hdomain. 113 V.sub.H structures of human antibodies were used to calculate the entropy.

(2) FIG. **1**B shows the definition of the hyper-variable regions (HVRs) used herein for an exemplary antibody heavy chain variable domain (VH) sequence (SEQ ID NO:197) in comparison to the Kabat definition of the complementarity-determining regions (CDRs) for the same VH sequence.

(3) FIG. **2**A shows the affinity measurements for fabs with confirmed binding to the antigens TAGT-1 to TAGT-12.

(4) FIG. **2**B shows the melting temperature (Tm) measurements for fabs with confirmed binding to the antigens TAGT-1 to TAGT-12.

DETAILED DESCRIPTION

(5) The present disclosure provides libraries containing synthetic (e.g., non-naturally occurring) polynucleotides that encode antibody heavy chains (e.g., heavy chains of a dynamic human antibody). Advantageously, the antibody heavy chains disclosed herein include HVR sequences designed to generate highly flexible loops for more effective substrate binding and/or specificity against multiple substrates of interest. These HVR sequences allow the creation of smaller antibody libraries with broader epitope coverage than existing techniques.

I. General Techniques

(6) The techniques and procedures described or referenced herein are generally well understood and commonly employed using conventional methodology by those skilled in the art, such as, for example, the widely utilized methodologies described in Sambrook et al., Molecular Cloning: A Laboratory Manual 3d edition (2001) Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y.; Current Protocols in Molecular Biology (F. M. Ausubel, et al. eds., (2003)); the series Methods in Enzymology (Academic Press, Inc.): PCR 2: A Practical Approach (M. J. MacPherson, B. D. Hames and G. R. Taylor eds. (1995)), Harlow and Lane, eds. (1988) Antibodies, A Laboratory Manual, and Animal Cell Culture (R.I. Freshney, ed. (1987)); Oligonucleotide Synthesis (M. J. Gait, ed., 1984); Methods in Molecular Biology, Humana Press; Cell Biology: A Laboratory Notebook (J. E. Cellis, ed., 1998) Academic Press; Animal Cell Culture (R.I. Freshney), ed., 1987); Introduction to Cell and Tissue Culture (J.P. Mather and P.E. Roberts, 1998) Plenum Press; Cell and Tissue Culture: Laboratory Procedures (A. Doyle, J.B. Griffiths, and D. G. Newell, eds., 1993-8) J. Wiley and Sons; Handbook of Experimental Immunology (D. M. Weir and C.C. Blackwell, eds.); Gene Transfer Vectors for Mammalian Cells (J. M. Miller and M. P. Calos, eds., 1987); PCR: The Polymerase Chain Reaction, (Mullis et al., eds., 1994); Current Protocols in Immunology (J. E. Coligan et al., eds., 1991); Short Protocols in Molecular Biology (Wiley and Sons, 1999); Immunobiology (C.A. Janeway and P. Travers, 1997); Antibodies (P. Finch, 1997); Antibodies: A Practical Approach (D. Catty., ed.,

IRL Press, 1988-1989); Monoclonal Antibodies: A Practical Approach (P. Shepherd and C. Dean, eds., Oxford University Press, 2000); Using Antibodies: A Laboratory Manual (E. Harlow and D. Lane (Cold Spring Harbor Laboratory Press, 1999); The Antibodies (M. Zanetti and J. D. Capra, eds., Harwood Academic Publishers, 1995); and Cancer: Principles and Practice of Oncology (V. T. DeVita et al., eds., J.B. Lippincott Company, 1993).

II. Definitions

(7) Before describing the present disclosure in detail, it is to be understood that this present disclosure is not limited to particular compositions or biological systems, which can, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting.

(8) As used in this specification and the appended claims, the singular forms “a”, “an” and “the” include plural referents unless the content clearly dictates otherwise. Thus, for example, reference to “a molecule” optionally includes a combination of two or more such molecules, and the like.

(9) The term “about” as used herein refers to the usual error range for the respective value readily known to the skilled person in this technical field. Reference to “about” a value or parameter herein includes (and describes) embodiments that are directed to that value or parameter per se.

(10) It is understood that aspects and embodiments of the present disclosure described herein include “comprising,” “consisting,” and “consisting essentially of” aspects and embodiments.

(11) The term “antibody” is used herein in the broadest sense and specifically covers monoclonal antibodies (including full length monoclonal antibodies), polyclonal antibodies, multispecific antibodies (e.g., bispecific antibodies), and antibody fragments (e.g., a single-chain variable fragment or scFv) so long as they exhibit the desired biological activity.

(12) The basic 4-chain antibody unit is a heterotetrameric glycoprotein composed of two identical light (L) chains and two identical heavy (H) chains. The pairing of a V.sub.H and V.sub.L together forms a single antigen-binding site. For the structure and properties of the different classes of antibodies, see, e.g., *Basic and Clinical Immunology,* 8th Ed., Daniel P. Stites, Abba I. Terr and Tristram G. Parslow (eds.), Appleton & Lange, Norwalk, CT, 1994, page 71 and Chapter 6.

(13) The L chain from any vertebrate species can be assigned to one of two clearly distinct types, called kappa (“u”) and lambda (“2”), based on the amino acid sequences of their constant domains. Depending on the amino acid sequence of the constant domain of their heavy chains (CH), immunoglobulins can be assigned to different classes or isotypes. There are five classes of immunoglobulins: IgA, IgD, IgE, IgG, and IgM, having heavy chains designated alpha (“a”), delta (“6”), epsilon (“c”), gamma (“y”) and mu (“p”), respectively. The y and a classes are further divided into subclasses (isotypes) on the basis of relatively minor differences in the CH sequence and function, e.g., humans express the following subclasses: IgG1, IgG2, IgG3, IgG4, IgA1, and IgA2. The subunit structures and three dimensional configurations of different classes of immunoglobulins are well known and described generally in, for example, Abbas et al., Cellular and Molecular Immunology, 4.sup.th ed. (W. B. Saunders Co., 2000).

(14) The “variable region” or “variable domain” of an antibody refers to the amino-terminal domains of the heavy or light chain of the antibody. The variable domain of the heavy chain may be referred to as “VH.” The variable domain of the light chain may be referred to as “V.sub.L.” These domains are generally the most variable parts of an antibody and contain the antigen-binding sites.

(15) The term “variable domain residue numbering as in Kabat” or “amino acid position numbering as in Kabat,” and variations thereof, refers to the numbering system used for heavy chain variable domains or light chain variable domains of the compilation of antibodies in Kabat et al., supra. Using this numbering system, the actual linear amino acid sequence may contain fewer or additional amino acids corresponding to a shortening of, or insertion into, a FR or HVR of the variable domain. For example, a heavy chain variable domain may include a single amino acid insert (residue 52a according to Kabat) after residue 52 of H2 and inserted residues (e.g. residues 82a, 82b, and 82c, etc. according to Kabat) after heavy chain FR residue 82. The Kabat numbering of residues may be determined for a given antibody by alignment at regions of homology of the sequence of the antibody with a “standard” Kabat numbered sequence.

(16) The Kabat numbering system is generally used when referring to a residue in the variable domain (approximately residues 1-107 of the light chain and residues 1-113 of the heavy chain) (e.g., Kabat et al., Sequences of Immunological Interest. 5th Ed. Public Health Service, National Institutes of Health, Bethesda, Md. (1991)). The “EU numbering system” or “EU index” is generally used when referring to a residue in an immunoglobulin heavy chain constant region (e.g., the EU index reported in Kabat et al., supra). The “EU

index as in Kabat" refers to the residue numbering of the human IgG1 EU antibody.
(17) The term "constant domain" refers to the portion of an immunoglobulin molecule having a more conserved amino acid sequence relative to the other portion of the immunoglobulin, the variable domain, which contains the antigen binding site. The constant domain contains the C.sub.H1, C.sub.H2 and C.sub.H3 domains (collectively, C.sub.H) of the heavy chain and the CHL (or CL) domain of the light chain.
(18) The term "full-length antibody" (the terms "intact" antibody or "whole" antibody may be used interchangeably herein) may refer to an antibody in its substantially intact form, as opposed to an antibody fragment. Similarly, the term "full-length antibody heavy chain" (the terms "intact" antibody heavy chain or "whole" antibody heavy chain may be used interchangeably herein) may refer to an antibody heavy chain in its substantially intact form, as opposed to an antibody heavy chain fragment. Specifically whole antibodies include those with heavy and light chains including an Fc region. The constant domains may be native sequence constant domains (e.g., human native sequence constant domains) or amino acid sequence variants thereof. In some cases, the intact antibody may have one or more effector functions.
(19) The term "monoclonal antibody" as used herein refers to an antibody obtained from a population of substantially homogeneous antibodies, i.e., the individual antibodies comprising the population are identical except for possible naturally occurring mutations and/or post-translation modifications (e.g., isomerizations, amidations) that may be present in minor amounts. Monoclonal antibodies are highly specific, being directed against a single antigenic site. In contrast to polyclonal antibody preparations which typically include different antibodies directed against different determinants (epitopes), each monoclonal antibody is directed against a single determinant on the antigen. The modifier "monoclonal" indicates the character of the antibody as being obtained from a substantially homogeneous population of antibodies, and is not to be construed as requiring production of the antibody by any particular method. For example, the monoclonal antibodies to be used in accordance with the present disclosure may be made by a variety of techniques, including, for example, the hybridoma method (e.g., Kohler and Milstein., *Nature,* 256:495-97 (1975); Hongo et al., *Hybridoma,* 14 (3):253-260 (1995), Harlow et al., *Antibodies: A Laboratory Manual*, (Cold Spring Harbor Laboratory Press, 2d ed. 1988); Hammerling et al., in: *Monoclonal Antibodies* and *T-Cell Hybridomas* 563-681 (Elsevier, N.Y., 1981)), recombinant DNA methods (see, e.g., U.S. Pat. No. 4,816,567), phage-display technologies (see, e.g., Clackson et al., *Nature,* 352:624-628 (1991); Marks et al., *J. Mol. Biol.* 222:581-597 (1992); Sidhu et al., *J. Mol. Biol.* 338(2): 299-310 (2004); Lee et al., *J. Mol. Biol.* 340(5):1073-1093 (2004); Fellouse, *Proc. Nat'l Acad. Sci. USA* 101(34):12467-472 (2004); and Lee et al., J. Immunol. Methods 284(1-2):119-132 (2004), and technologies for producing human or human-like antibodies in animals that have parts or all of the human immunoglobulin loci or genes encoding human immunoglobulin sequences (see, e.g., WO 1998/24893; WO 1996/34096; WO 1996/33735; WO 1991/10741; Jakobovits et al., *Proc. Nat'l Acad. Sci. USA* 90:2551 (1993); Jakobovits et al., *Nature* 362:255-258 (1993); Bruggemann et al., *Year in Immunol.* 7:33 (1993); U.S. Pat. Nos. 5,545,807; 5,545,806; 5,569,825; 5,625,126; 5,633,425; and U.S. Pat. No. 5,661,016; Marks et al., Bio/Technology 10:779-783 (1992); Lonberg et al., *Nature* 368:856-859 (1994); Morrison, *Nature* 368:812-813 (1994); Fishwild et al., *Nature Biotechnol.* 14:845-851 (1996); Neuberger, *Nature Biotechnol.* 14:826 (1996); and Lonberg and Huszar, *Intern. Rev. Immunol.* 13:65-93 (1995).
(20) As used herein, "hypervariable region (HVR)" refers to the regions of an antibody domain which are hypervariable in sequence and/or form structurally defined loops. Generally, antibodies comprise six HVRs; three in the VH (H1, H2, H3), and three in the VL (L1, L2, L3). See, e.g., Xu et al., *Immunity* 13:37-45 (2000); Johnson and Wu, in *Methods in Molecular Biology* 248:1-25 (Lo, ed., Human Press, Totowa, N.J., 2003). Each VH and VL is composed of three HVRs and four framework (FW) regions arranged from amino terminus to carboxy terminus in the following order: FW1-HVR1-FW2-HVR2-FW3-HVR3-FW4. Throughout the present disclosure, the three HVRs of the heavy chain are referred to as HVR-H1, HVR-H2, and HVR-H3. Throughout the present disclosure, the four framework regions of the heavy chain are referred to as FW-H1, FW-H2, FW-H3 and FW-H4. For comparison, the definition of the HVRs (as used herein) is contrasted with the Kabat definition of the complementarity-determining regions (CDRs) (Yvonne Chen et al. (1999) "Selection and Analysis of an Optimized Anti-VEGF Antibody: Crystal Structure of an Affinity-matured Fab in Complex with Antigen", *J. Mol. Biol.* 293, 865-881) for the exemplary antibody heavy chain variable domain shown in FIG. **1**B.
(21) As used herein, "library" refers to a set of two or more entities having a shared class. For example, a library containing polynucleotides may refer to a set of two or more polynucleotides. The term "library" is used herein in the broadest sense and specifically covers sub-libraries that may or may not be combined.

(22) As used herein, “unique” refers to a member of a set that is different from other members of the set. For example, a unique antibody from a library encoding a plurality of polynucleotides encoding antibodies may refer to an antibody having a particular sequence not shared by other antibodies encoded by the library. As a practical matter, it is to be understood that a “unique” member of a physical realization of a library may be present in more than one copy. For example, a library may contain a plurality of “unique” antibodies, with one or more of the “unique” antibody molecules occurring in more than one copy.
(23) As used herein, “diversity” refers to a variety and/or heterogeneity. For example, a diversity of antibodies in a library may refer to a variety of antibodies with unique sequences present in the library.
(24) The terms “polypeptide,” “protein,” and “peptide” are used interchangeably herein and may refer to polymers of two or more amino acids.
(25) “Polynucleotide,” or “nucleic acid,” as used interchangeably herein, refer to polymers of nucleotides of any length, and include DNA and RNA. The nucleotides can be deoxyribonucleotides, ribonucleotides, modified nucleotides or bases, and/or their analogs, or any substrate that can be incorporated into a polymer by DNA or RNA polymerase or by a synthetic reaction. A polynucleotide may comprise modified nucleotides, such as methylated nucleotides and their analogs. If present, modification to the nucleotide structure may be imparted before or after assembly of the polymer. The sequence of nucleotides may be interrupted by non-nucleotide components. A polynucleotide may comprise modification(s) made after synthesis, such as conjugation to a label. Other types of modifications include, for example, “caps,” substitution of one or more of the naturally occurring nucleotides with an analog, internucleotide modifications such as, for example, those with uncharged linkages (e.g., methyl phosphonates, phosphotriesters, phosphoamidates, carbamates, etc.) and with charged linkages (e.g., phosphorothioates, phosphorodithioates, etc.), those containing pendant moieties, such as, for example, proteins (e.g., nucleases, toxins, antibodies, signal peptides, ply-L-lysine, etc.), those with intercalators (e.g., acridine, psoralen, etc.), those containing chelators (e.g., metals, radioactive metals, boron, oxidative metals, etc.), those containing alkylators, those with modified linkages (e.g., alpha anomeric nucleic acids, etc.), as well as unmodified forms of the polynucleotides(s). Further, any of the hydroxyl groups ordinarily present in the sugars may be replaced, for example, by phosphonate groups, phosphate groups, protected by standard protecting groups, or activated to prepare additional linkages to additional nucleotides, or may be conjugated to solid or semi-solid supports. The 5′ and 3′ terminal OH can be phosphorylated or substituted with amines or organic capping group moieties of from 1 to 20 carbon atoms. Other hydroxyls may also be derivatized to standard protecting groups. Polynucleotides can also contain analogous forms of ribose or deoxyribose sugars that are generally known in the art, including, for example, 2′-O-methyl-, 2′-O-allyl-, 2′-fluoro- or 2′-azido-ribose, carbocyclic sugar analogs, α-anomeric sugars, epimeric sugars such as arabinose, xyloses or lyxoses, pyranose sugars, furanose sugars, sedoheptuloses, acyclic analogs, and basic nucleoside analogs such as methyl riboside. One or more phosphodiester linkages may be replaced by alternative linking groups. These alternative linking groups include, but are not limited to, embodiments wherein phosphate is replaced by P(O)S (“thioate”), P(S)S (“dithioate”), (O)NR2 (“amidate”), P(O)R, P(O)OR′, CO, or CH2 (“formacetal”), in which each R or R′ is independently H or substituted or unsubstituted alkyl (1-20 C) optionally containing an ether (—O—) linkage, aryl, alkenyl, cycloalkyl, cycloalkenyl or araldyl. Not all linkages in a polynucleotide need be identical. The preceding description applies to all polynucleotides referred to herein, including RNA and DNA.
(26) A cell (e.g., a cell or population of cells comprising a synthetic polynucleotide or library of synthetic polynucleotides) includes an individual cell or cell culture that can be or has been a recipient for vector(s) for incorporation of polynucleotide inserts. Host cells include progeny of a single host cell, and the progeny may not necessarily be completely identical (in morphology or in genomic DNA complement) to the original parent cell due to natural, accidental, or deliberate mutation. A host cell includes cells transfected in vivo with a polynucleotide(s) (e.g., a synthetic polynucleotide that encodes an antibody heavy chain variable region of the present disclosure).
(27) A “non-human animal” refers to any animal not classified as a human, such as domestic, farm, or zoo animals, sports, pet animals (such as dogs, horses, cats, cows, etc.), as well as animals used in research. Research animals may refer without limitation to nematodes, arthropods, vertebrates, mammals, frogs, rodents (e.g., mice or rats), fish (e.g., zebrafish or pufferfish), birds (e.g., chickens), dogs, cats, and non-human primates (e.g., rhesus monkeys, cynomolgus monkeys, chimpanzees, etc.). In preferred embodiments, the animal is one that produces antibodies.
III. Antibody Libraries and Generation of Libraries

(28) Certain aspects of the present disclosure relate to libraries of polynucleotides, e.g., that encode an antibody heavy chain variable region (V.sub.H) or light chain variable region (V.sub.L). A library of the present disclosure can contain one or more polynucleotides encoding a heavy chain variable region comprising a HVR-H1, a HVR-H2, and a HVR-H3, wherein the HVR-H1 and HVR-H2 are any of the HVR-H1s and/or HVR-H2s described herein.
(29) In some embodiments, a library of the present disclosure contains a smaller number of unique heavy chain HVR sequences and/or unique V.sub.H sequences than typical antibody libraries. Advantageously, such libraries can provide sufficient diversity for the identification of antibodies binding one or more of a number of antigens of interest while also allowing for more efficient screening due to the reduced library size. In some embodiments, a library of the present disclosure includes or consists of polynucleotides containing less than about 10000, less than about 9000, less than about 8000, or less than about 7000 unique combinations of HVR-H1 and HVR-H2 sequences. In certain embodiments, a library of the present disclosure includes or consists of polynucleotides containing about 6600 or less unique combinations of HVR-H1 and HVR-H2 sequences.
(30) In some embodiments, a library contains a plurality of polynucleotides, with at least one of the polynucleotides encoding an antibody heavy chain variable region of the present disclosure (e.g., comprising a HVR-H1 and HVR-H2 of the present disclosure).
(31) In some embodiments, one or more of the polynucleotides encode an antibody heavy chain variable region comprising a HVR-H1, a HVR-H2, and a HVR-H3, wherein the HVR-H1 comprises an amino acid sequence according to a formula selected from the group consisting of (Formula I) X1TFX2X3YX4IHWV, wherein X1 is F or Y, X2 is S or T, X3 is D, G, N, or S, and X4 is A, G, or W(SEQ ID NO:198); (Formula II) YSIX1SGX2X3WX4WI, wherein X1 is S or T, X2 is H or Y, X3 is H or Y, and X4 is A, D, G, N, S, or T (SEQ ID NO:199); and (Formula III) FSLSTX1GVX2VX3WI, wherein X1 is G or S, X2 is A or G, and X3 is A, G, S, or T(SEQ ID NO:200). In some embodiments, one or more of the polynucleotides encode an antibody heavy chain variable region comprising a HVR-H1, a HVR-H2, and a HVR-H3, wherein the HVR-H2 comprises an amino acid sequence according to a formula selected from the group consisting of (Formula IV) LAX1IX2WX3X4DKX5YSX6SLKSRL, wherein X1 is L or R, X2 is D or Y, X3 is A, D, S, or Y, X4 is D or G, X5 is R, S, or Y, and X6 is P or T(SEQ ID NO:201); (Formula V) IGX1IX2X3SGSTYYSPSLKSRV, wherein X1 is A, D, E, S, or Y, X2 is S or Y, and X3 is H or Y(SEQ ID NO:202); (Formula VI) IGX1IYX2SGX3TX4YNPSLKSRV, wherein X1 is D, E, R, S, or Y, X2 is H or Y, X3 is N or S, and X4 is N or Y(SEQ ID NO:203); (Formula VII) VSX1ISGX2GX3X4TYYADSVKGRF, wherein X1 is A, G, S, V, or Y, X2 is A, D, S, or Y, X3 is D, G, or S, and X4 is S or T(SEQ ID NO:204); (Formula VIII) IGX1INPNX2GX3TX4YAQKFQGRV, wherein X1 is I, R, or W, X2 is F or R, X3 is D, G, or S, and X4 is K or N(SEQ ID NO:205); (Formula IX) IGX IIX2PSX3GX4TX5YAQKFQGRV, wherein X1 is I, R, or W, X2 is S or Y, X3 is G or S, X4 is D, G, or S, and X5 is K or N(SEQ ID NO:206); and (Formula X) VGRIX1SKX2X3GX4TTX5YAAX6VKGRF, wherein X1 is K or R, X2 is A or T, X3 is D or Y, X4 is G or Y, X5 is D or E, and X6 is P or S(SEQ ID NO:207). In some embodiments, the HVR-H2 comprises an amino acid sequence according to a formula selected from the group consisting of (Formula XI) IGX1IX2X3SGSTYYSPSLKSRV, wherein X1 is A, D, or E, X2 is S or Y, and X3 is H or Y (SEQ ID NO:208); (Formula XI) IGXIIYX2SGX3TX4YNPSLKSRV, wherein X1 is D, E, or S, X2 is H or Y, X3 is N or S, and X4 is N or Y(SEQ ID NO:209); and (Formula XII) VGRIXISKX2X3GX4TTEYAAX5VKGRF, wherein X1 is K or R, X2 is A or T, X3 is D or Y, X4 is G or Y, and X5 is P or S(SEQ ID NO:210). In some embodiments, one or more of the polynucleotides encode an antibody heavy chain variable region comprising a HVR-H1, a HVR-H2, and a HVR-H3, wherein the HVR-H1 comprises an amino acid sequence according to a formula selected from the group consisting of (Formula I) X1TFX2X3YX4IHWV, wherein X1 is F or Y, X2 is S or T, X3 is D, G, N, or S, and X4 is A, G, or W(SEQ ID NO:198); (Formula II) YSIX1SGX2X3WX4WI, wherein X1 is S or T, X2 is H or Y, X3 is H or Y, and X4 is A, D, G, N, S, or T (SEQ ID NO:199); and (Formula III) FSLSTX1GVX2VX3WI, wherein X1 is G or S, X2 is A or G, and X3 is A, G, S, or T(SEQ ID NO:200); and an HVR-H2 comprises an amino acid sequence according to a formula selected from the group consisting of (Formula IV) LAX1IX2WX3X4DKX5YSX6SLKSRL, wherein X1 is L or R, X2 is D or Y, X3 is A, D, S, or Y, X4 is D or G, X5 is R, S, or Y, and X6 is P or T(SEQ ID NO:201); (Formula V) IGX1IX2X3SGSTYYSPSLKSRV, wherein X1 is A, D, E, S, or Y, X2 is S or Y, and X3 is H or Y(SEQ ID NO:202); (Formula VI) IGXIIYX2SGX3TX4YNPSLKSRV, wherein X1 is D, E, R, S, or Y, X2 is H or Y, X3 is N or S, and X4 is N or Y(SEQ ID NO:203); (Formula VII) VSXIISGX2GX3X4TYYADSVKGRF, wherein X1 is A, G, S, V, or Y, X2 is A, D, S, or Y, X3 is D, G, or S,

and X4 is S or T(SEQ ID NO:204); (Formula VIII) IGX1INPNX2GX3TX4YAQKFQGRV, wherein X1 is I, R, or W, X2 is F or R, X3 is D, G, or S, and X4 is K or N(SEQ ID NO:205); (Formula IX) IGX1IX2PSX3GX4TX5YAQKFQGRV, wherein X1 is I, R, or W, X2 is S or Y, X3 is G or S, X4 is D, G, or S, and X5 is K or N(SEQ ID NO:206); and (Formula X) VGRIXISKX2X3GX4TTX5YAAX6VKGRF, wherein X1 is K or R, X2 is A or T, X3 is D or Y, X4 is G or Y, X5 is D or E, and X6 is P or S(SEQ ID NO:207). In some embodiments, one or more of the polynucleotides encode an antibody heavy chain variable region comprising a HVR-H1, a HVR-H2, and a HVR-H3, wherein the HVR-H1 comprises an amino acid sequence according to a formula selected from the group consisting of (Formula I) X1TFX2X3YX4IHWV, wherein X1 is F or Y, X2 is S or T, X3 is D, G, N, or S, and X4 is A, G, or W(SEQ ID NO:198); (Formula II) YSIX1SGX2X3WX4WI, wherein X1 is S or T, X2 is H or Y, X3 is H or Y, and X4 is A, D, G, N, S, or T (SEQ ID NO:199); and (Formula III) FSLSTX1GVX2VX3WI, wherein X1 is G or S, X2 is A or G, and X3 is A, G, S, or T(SEQ ID NO:200); and an HVR-H2 comprises an amino acid sequence according to a formula selected from the group consisting of (Formula XI) IGX1IX2X3SGSTYYSPSLKSRV, wherein X1 is A, D, or E, X2 is S or Y, and X3 is H or Y (SEQ ID NO:208); (Formula XI) IGXlIYX2SGX3TX4YNPSLKSRV, wherein X1 is D, E, or S, X2 is H or Y, X3 is N or S, and X4 is N or Y(SEQ ID NO:209); and (Formula XII) VGRIXISKX2X3GX4TTEYAAX5VKGRF, wherein X1 is K or R, X2 is A or T, X3 is D or Y, X4 is G or Y, and X5 is P or S(SEQ ID NO:210). In some embodiments, one or more polynucleotides of the library are in a vector (e.g., an expression vector or display vector).

(32) In some embodiments, at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, 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, at least 100, at least 110, at least 120, at least 130, at least 140, at least 150, at least 160, at least 170, at least 180, at least 190, at least 200, at least 225, at least 250, at least 500, at least 1000, at least 1250, at least 1500, at least 1750, at least 2000, at least 2250, at least 2500, at least 2750, at least 3000, at least 3250, at least 3500, at least 3750, at least 4000, at least 4250, at least 4500, at least 4750, at least 5000, at least 5250, at least 5500, at least 5750, at least 6000, at least 6250, or at least 6500 of the polynucleotides encodes an antibody heavy chain variable region comprising a HVR-H1, a HVR-H2 and a HVR-H3, wherein the HVR-H1 comprises an amino acid sequence according to a formula selected from the group consisting of (Formula I) X1TFX2X3YX4IHWV, wherein X1 is F or Y, X2 is S or T, X3 is D, G, N, or S, and X4 is A, G, or W(SEQ ID NO:198); (Formula II) YSIX1SGX2X3WX4WI, wherein X1 is S or T, X2 is H or Y, X3 is H or Y, and X4 is A, D, G, N, S, or T (SEQ ID NO:199); and (Formula III) FSLSTX1GVX2VX3WI, wherein X1 is G or S, X2 is A or G, and X3 is A, G, S, or T(SEQ ID NO:200); and/or an HVR-H2 comprising the amino acid sequence according to a formula selected from the group consisting of (Formula IV) LAX1IX2WX3X4DKX5YSX6SLKSRL, wherein X1 is L or R, X2 is D or Y, X3 is A, D, S, or Y, X4 is D or G, X5 is R, S, or Y, and X6 is P or T(SEQ ID NO:201); (Formula V) IGX1IX2X3SGSTYYSPSLKSRV, wherein X1 is A, D, E, S, or Y, X2 is S or Y, and X3 is H or Y(SEQ ID NO:202); (Formula VI) IGXIIYX2SGX3TX4YNPSLKSRV, wherein X1 is D, E, R, S, or Y, X2 is H or Y, X3 is N or S, and X4 is N or Y(SEQ ID NO:203); (Formula VII) VSX1ISGX2GX3X4TYYADSVKGRF, wherein X1 is A, G, S, V, or Y, X2 is A, D, S, or Y, X3 is D, G, or S, and X4 is S or T(SEQ ID NO:204); (Formula VIII) IGX1INPNX2GX3TX4YAQKFQGRV, wherein X1 is I, R, or W, X2 is F or R, X3 is D, G, or S, and X4 is K or N(SEQ ID NO:205); (Formula IX) IGX1IX2PSX3GX4TX5YAQKFQGRV, wherein X1 is I, R, or W, X2 is S or Y, X3 is G or S, X4 is D, G, or S, and X5 is K or N(SEQ ID NO:206); and (Formula X) VGRIX1SKX2X3GX4TTX5YAAX6VKGRF, wherein X1 is K or R, X2 is A or T, X3 is D or Y, X4 is G or Y, X5 is D or E, and X6 is P or S(SEQ ID NO:207); and/or less than about 6.5*104 (e.g., less than about 6.5*104, less than about 5.5*104, less than about 2.5*104, less than about 1*10.sup.4, less than about 6700, less than about 6660, less than about 5000, less than about 2500, less than about 1000, less than about 690, less than about 500, less than about 100, less than about 50, etc.), less than or equal to 62272, less than or equal to 60928, less than or equal to 54656, or less than or equal to 6660 of the polynucleotides encodes an antibody heavy chain variable region comprising and HVR-H1, HVR-H2, and HVR-H3, wherein the HVR-H1 comprises an amino acid sequence according to a formula selected from the group consisting of (Formula I) X1TFX2X3YX4IHWV, wherein XI is F or Y, X2 is S or T, X3 is D, G, N, or S, and X4 is A, G, or W(SEQ ID NO:198); (Formula II) YSIX1SGX2X3WX4WI, wherein X1 is S or T, X2 is H or Y, X3 is H or Y, and X4 is A, D, G, N, S, or T (SEQ ID NO:199); and (Formula III) FSLSTX1GVX2VX3WI, wherein X1 is G or S, X2 is A or G, and X3 is A, G, S, or T(SEQ ID NO:200); and an HVR-H2 comprising the amino acid

sequence according to a formula selected from the group consisting of (Formula IV) LAX1IX2WX3X4DKX5YSX6SLKSRL, wherein X1 is L or R, X2 is D or Y, X3 is A, D, S, or Y, X4 is D or G, X5 is R, S, or Y, and X6 is P or T(SEQ ID NO:201); (Formula V) IGX1IX2X3SGSTYYSPSLKSRV, wherein X1 is A, D, E, S, or Y, X2 is S or Y, and X3 is H or Y(SEQ ID NO:202); (Formula VI) IGX1IYX2SGX3TX4YNPSLKSRV, wherein X1 is D, E, R, S, or Y, X2 is H or Y, X3 is N or S, and X4 is N or Y(SEQ ID NO:203); (Formula VII) VSX1ISGX2GX3X4TYYADSVKGRF, wherein XI is A, G, S, V, or Y, X2 is A, D, S, or Y, X3 is D, G, or S, and X4 is S or T(SEQ ID NO:204); (Formula VIII) IGX1INPNX2GX3TX4YAQKFQGRV, wherein X1 is I, R, or W, X2 is F or R, X3 is D, G, or S, and X4 is K or N(SEQ ID NO:205); (Formula IX) IGX1IX2PSX3GX4TX5YAQKFQGRV, wherein X1 is I, R, or W, X2 is S or Y, X3 is G or S, X4 is D, G, or S, and X5 is K or N(SEQ ID NO:206); and (Formula X) VGRIX1SKX2X3GX4TTX5YAAX6VKGRF, wherein X1 is K or R, X2 is A or T, X3 is D or Y, X4 is G or Y, X5 is D or E, and X6 is P or S(SEQ ID NO:207). In some embodiments, one or more polynucleotides of the library are in a vector (e.g., an expression vector or display vector).

(33) In some embodiments, at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, 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, at least 100, at least 110, at least 120, at least 130, at least 140, at least 150, at least 160, at least 170, at least 180, at least 190, at least 200, at least 225, at least 250, at least 500, at least 1000, at least 1250, at least 1500, at least 1750, at least 2000, at least 2250, at least 2500, at least 2750, at least 3000, at least 3250, at least 3500, at least 3750, at least 4000, at least 4250, at least 4500, at least 4750, at least 5000, at least 5250, at least 5500, at least 5750, at least 6000, at least 6250, or at least 6500 of the polynucleotides encodes an antibody heavy chain variable region comprising a HVR-H1, a HVR-H2 and a HVR-H3, wherein the HVR-H1 comprises an amino acid sequence according to a formula selected from the group consisting of (Formula I) X1TFX2X3YX4IHWV, wherein XI is F or Y, X2 is S or T, X3 is D, G, N, or S, and X4 is A, G, or W(SEQ ID NO: 198); (Formula II) YSIX1SGX2X3WX4WI, wherein X1 is S or T, X2 is H or Y, X3 is H or Y, and X4 is A, D, G, N, S, or T (SEQ ID NO:199); and (Formula III) FSLSTX1GVX2VX3WI, wherein X1 is G or S, X2 is A or G, and X3 is A, G, S, or T(SEQ ID NO:200); and/or an HVR-H2 comprising the amino acid sequence according to a formula selected from the group consisting of (Formula X1) IGX1IX2X3SGSTYYSPSLKSRV, wherein X1 is A, D, or E, X2 is S or Y, and X3 is H or Y (SEQ ID NO:208); (Formula XI) IGXIIYX2SGX3TX4YNPSLKSRV, wherein X1 is D, E, or S, X2 is H or Y, X3 is N or S, and X4 is N or Y(SEQ ID NO:209); and (Formula XII) VGRIX1SKX2X3GX4TTEYAAX5VKGRF, wherein X1 is K or R, X2 is A or T, X3 is D or Y, X4 is G or Y, and X5 is P or S(SEQ ID NO:210); and/or less than about 6.5*10.sup.4 (e.g., less than about 6.5*104, less than about 5.5*10.sup.4, less than about 2.5*10.sup.4, less than about 1*104, less than about 6700, less than about 6660, less than about 5000, less than about 2500, less than about 1000, less than about 690, less than about 500, less than about 100, less than about 50, etc.), less than or equal to 62272, less than or equal to 60928, less than or equal to 54656, or less than or equal to 6660 of the polynucleotides encodes an antibody heavy chain variable region comprising and HVR-H1, HVR-H2, and HVR-H3, wherein the HVR-H1 comprises an amino acid sequence according to a formula selected from the group consisting of (Formula I) X1TFX2X3YX4IHWV, wherein X1 is F or Y, X2 is S or T, X3 is D, G, N, or S, and X4 is A, G, or W(SEQ ID NO:198); (Formula II) YSIX1SGX2X3WX4WI, wherein X1 is S or T, X2 is H or Y, X3 is H or Y, and X4 is A, D, G, N, S, or T (SEQ ID NO:199); and (Formula III) FSLSTX1GVX2VX3WI, wherein X1 is G or S, X2 is A or G, and X3 is A, G, S, or T(SEQ ID NO:200); and an HVR-H2 comprising the amino acid sequence according to a formula selected from the group consisting of (Formula XI) IGX1IX2X3SGSTYYSPSLKSRV, wherein X1 is A, D, or E, X2 is S or Y, and X3 is H or Y (SEQ ID NO:208); (Formula XI) IGX1IYX2SGX3TX4YNPSLKSRV, wherein X1 is D, E, or S, X2 is H or Y, X3 is N or S, and X4 is N or Y(SEQ ID NO:209); and (Formula XII) VGRIX1SKX2X3GX4TTEYAAX5VKGRF, wherein X1 is K or R, X2 is A or T, X3 is D or Y, X4 is G or Y, and X5 is P or S(SEQ ID NO:210). In some embodiments, one or more polynucleotides of the library are in a vector (e.g., an expression vector or display vector).

(34) In some embodiments, the polynucleotides in the library encodes an antibody heavy chain variable region comprising an HVR-H1 comprising the amino acid sequence according to the formula X1TFX2X3YX4IHWV, wherein X1 is F or Y, X2 is S or T, X3 is D, G, N, or S, and X4 is A, G, or W (SEQ ID NO:198); and an HVR-H2 comprising the amino acid sequence according to a formula selected from the group consisting of (Formula IV) LAX1IX2WX3X4DKX5YSX6SLKSRL, wherein X1 is L or R, X2 is D or Y, X3 is A, D, S, or Y, X4 is D or G, X5 is R, S, or Y, and X6 is P or T(SEQ ID NO:201); (Formula V)

IGX1IX2X3SGSTYYSPSLKSRV, wherein XI is A, D, E, S, or Y, X2 is S or Y, and X3 is H or Y(SEQ ID NO:202); (Formula VI) IGX1IYX2SGX3TX4YNPSLKSRV, wherein X1 is D, E, R, S, or Y, X2 is H or Y, X3 is N or S, and X4 is N or Y(SEQ ID NO:203); (Formula VII) VSX1ISGX2GX3X4TYYADSVKGRF, wherein XI is A, G, S, V, or Y, X2 is A, D, S, or Y, X3 is D, G, or S, and X4 is S or T(SEQ ID NO:204); (Formula VIII) IGX1INPNX2GX3TX4YAQKFQGRV, wherein X1 is I, R, or W, X2 is F or R, X3 is D, G, or S, and X4 is K or N(SEQ ID NO:205); (Formula IX) IGX1IX2PSX3GX4TX5YAQKFQGRV, wherein X1 is I, R, or W, X2 is S or Y, X3 is G or S, X4 is D, G, or S, and X5 is K or N(SEQ ID NO:206); and (Formula X) VGRIX1SKX2X3GX4TTX5YAAX6VKGRF, wherein X1 is K or R, X2 is A or T, X3 is D or Y, X4 is G or Y, X5 is D or E, and X6 is P or S(SEQ ID NO:207).

(35) In some embodiments, the polynucleotides in the library encodes an antibody heavy chain variable region comprising an HVR-H1 comprising the amino acid sequence according to the formula X1TFX2X3YX4IHWV, wherein X1 is F or Y, X2 is S or T, X3 is D, G, N, or S, and X4 is A, G, or W (SEQ ID NO:198); and an HVR-H2 comprising the amino acid sequence according to a formula selected from the group consisting of (Formula XI) IGX1IX2X3SGSTYYSPSLKSRV, wherein XI is A, D, or E, X2 is S or Y, and X3 is H or Y (SEQ ID NO:208); (Formula XI) IGXIIYX2SGX3TX4YNPSLKSRV, wherein X1 is D, E, or S, X2 is H or Y, X3 is N or S, and X4 is N or Y(SEQ ID NO:209); and (Formula XII) VGRIX1SKX2X3GX4TTEYAAX5VKGRF, wherein X1 is K or R, X2 is A or T, X3 is D or Y, X4 is G or Y, and X5 is P or S(SEQ ID NO:210).

(36) In some embodiments, the polynucleotides in the library encodes an antibody heavy chain variable region comprising an HVR-H1 comprising the amino acid sequence according to the formula YSIX1SGX2X3WX4WI, wherein XI is S or T, X2 is H or Y, X3 is H or Y, and X4 is A, D, G, N, S, or T (SEQ ID NO: 19); and an HVR-H2 comprising the amino acid sequence according to a formula selected from the group consisting of (Formula IV) LAX1IX2WX3X4DKX5YSX6SLKSRL, wherein X1 is L or R, X2 is D or Y, X3 is A, D, S, or Y, X4 is D or G, X5 is R, S, or Y, and X6 is P or T(SEQ ID NO:201); (Formula V) IGX1IX2X3SGSTYYSPSLKSRV, wherein X1 is A, D, E, S, or Y, X2 is S or Y, and X3 is H or Y(SEQ ID NO:202); (Formula VI) IGX1IYX2SGX3TX4YNPSLKSRV, wherein X1 is D, E, R, S, or Y, X2 is H or Y, X3 is N or S, and X4 is N or Y(SEQ ID NO:203); (Formula VII) VSX1ISGX2GX3X4TYYADSVKGRF, wherein X1 is A, G, S, V, or Y, X2 is A, D, S, or Y, X3 is D, G, or S, and X4 is S or T(SEQ ID NO:204); (Formula VIII) IGX1INPNX2GX3TX4YAQKFQGRV, wherein X1 is I, R, or W, X2 is F or R, X3 is D, G, or S, and X4 is K or N(SEQ ID NO:205); (Formula IX) IGX1IX2PSX3GX4TX5YAQKFQGRV, wherein X1 is I, R, or W, X2 is S or Y, X3 is G or S, X4 is D, G, or S, and X5 is K or N(SEQ ID NO:206); and (Formula X) VGRIX1SKX2X3GX4TTX5YAAX6VKGRF, wherein X1 is K or R, X2 is A or T, X3 is D or Y, X4 is G or Y, X5 is D or E, and X6 is P or S(SEQ ID NO:207).

(37) In some embodiments, the polynucleotides in the library encodes an antibody heavy chain variable region comprising an HVR-H1 comprising the amino acid sequence according to the formula YSIX1SGX2X3WX4WI, wherein X1 is S or T, X2 is H or Y, X3 is H or Y, and X4 is A, D, G, N, S, or T (SEQ ID NO:199); and an HVR-H2 comprising the amino acid sequence according to a formula selected from the group consisting of (Formula XI) IGX1IX2X3SGSTYYSPSLKSRV, wherein X1 is A, D, or E, X2 is S or Y, and X3 is H or Y (SEQ ID NO:208); (Formula XI) IGX1IYX2SGX3TX4YNPSLKSRV, wherein X1 is D, E, or S, X2 is H or Y, X3 is N or S, and X4 is N or Y(SEQ ID NO:209); and (Formula XII) VGRIX1SKX2X3GX4TTEYAAX5VKGRF, wherein X1 is K or R, X2 is A or T, X3 is D or Y, X4 is G or Y, and X5 is P or S(SEQ ID NO:210).

(38) In some embodiments, the polynucleotides in the library encodes an antibody heavy chain variable region comprising an HVR-H1 comprising the amino acid sequence according to the formula FSLSTX1GVX2VX3WI, wherein X1 is G or S, X2 is A or G, and X3 is A, G, S, or T (SEQ ID NO:200); and an HVR-H2 comprising the amino acid sequence according to a formula selected from the group consisting of (Formula IV) LAX1IX2WX3X4DKX5YSX6SLKSRL, wherein X1 is L or R, X2 is D or Y, X3 is A, D, S, or Y, X4 is D or G, X5 is R, S, or Y, and X6 is P or T(SEQ ID NO:201); (Formula V) IGX1IX2X3SGSTYYSPSLKSRV, wherein X1 is A, D, E, S, or Y, X2 is S or Y, and X3 is H or Y(SEQ ID NO:202); (Formula VI) IGXIIYX2SGX3TX4YNPSLKSRV, wherein X1 is D, E, R, S, or Y, X2 is H or Y, X3 is N or S, and X4 is N or Y(SEQ ID NO:203); (Formula VII) VSX1ISGX2GX3X4TYYADSVKGRF, wherein X1 is A, G, S, V, or Y, X2 is A, D, S, or Y, X3 is D, G, or S, and X4 is S or T(SEQ ID NO:204); (Formula VIII) IGX1INPNX2GX3TX4YAQKFQGRV, wherein X1 is I, R, or W, X2 is F or R, X3 is D, G, or S, and X4 is K or N(SEQ ID NO:205); (Formula IX) IGX1IX2PSX3GX4TX5YAQKFQGRV, wherein X1 is

I, R, or W, X2 is S or Y, X3 is G or S, X4 is D, G, or S, and X5 is K or N(SEQ ID NO:206); and (Formula X) VGRIX1SKX2X3GX4TTX5YAAX6VKGRF, wherein X1 is K or R, X2 is A or T, X3 is D or Y, X4 is G or Y, X5 is D or E, and X6 is P or S(SEQ ID NO:207).

(39) In some embodiments, the polynucleotides in the library encodes an antibody heavy chain variable region comprising an HVR-H1 comprising the amino acid sequence according to the formula FSLSTX1GVX2VX3WI, wherein X1 is G or S, X2 is A or G, and X3 is A, G, S, or T (SEQ ID NO:200); and an HVR-H2 comprising the amino acid sequence according to a formula selected from the group consisting of (Formula XI) IGX1IX2X3SGSTYYSPSLKSRV, wherein X1 is A, D, or E, X2 is S or Y, and X3 is H or Y (SEQ ID NO:208); (Formula XI) IGXIIYX2SGX3TX4YNPSLKSRV, wherein X1 is D, E, or S, X2 is H or Y, X3 is N or S, and X4 is N or Y(SEQ ID NO:209); and (Formula XII) VGRIX1SKX2X3GX4TTEYAAX5VKGRF, wherein X1 is K or R, X2 is A or T, X3 is D or Y, X4 is G or Y, and X5 is P or S(SEQ ID NO:210).

(40) In some embodiments, the polynucleotide library encodes an antibody heavy chain variable region comprising a HVR-H1, HVR-H2, and HVR-H3, wherein the HVR-H1 comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:1-52 and 137-158. In some embodiments, the polynucleotide library encodes an antibody heavy chain variable region comprising a HVR-H1, HVR-H2, and HVR-H3, wherein the HVR-H1 comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:1-52.

(41) In some embodiments, the polynucleotide library encodes an antibody heavy chain variable region comprising a HVR-H1, HVR-H2, and HVR-H3, wherein the HVR-H2 comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:53-136 and 159-164. In some embodiments, the polynucleotide library encodes an antibody heavy chain variable region comprising a HVR-H1, HVR-H2, and HVR-H3, wherein the HVR-H2 comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:53-136.

(42) In some embodiments, the polynucleotide library encodes an antibody heavy chain variable region comprising a HVR-H1, HVR-H2, and HVR-H3, wherein the HVR-H1 comprises an amino acid sequence selected from the group consisting of Formula (I), Formula (II), and Formula (III), or the HVR-H2 comprises an amino acid sequence selected from the group consisting of Formula (IV), Formula (V), Formula (VI), Formula (VII), Formula (VIII), Formula (IX), Formula (X), Formula (XI), Formula (XII), and Formula (XIII). In some embodiments, the polynucleotide library encodes an antibody heavy chain variable region comprising a HVR-H1, a HVR-H2 and a HVR-H3, wherein the HVR-H1 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 1-52, or wherein the HVR-H2 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 53-136. In some embodiments, the HVR-H1 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 1, 4, 5, 7, 8, 9, 11, 13, 16, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 31, 33, 34, 38, 40, 42, 43, 45, 47, 49, 50, and 51, or wherein the HVR-H2 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 53, 60, 63, 65, 66, 67, 70, 82, 89, 93, 95, 105, 109, 110, 117, 121, 122, 123, 124, 128, 129, 130, 131, 132, and 134. In some embodiments, the HVR-H1 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 3, 14, 15, 30, 32, 35, 37, 39, 41, 44, 46, and 48, or wherein the HVR-H2 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 55, 56, 59, 61, 62, 64, 68, 69, 71, 73, 74, 75, 76, 77, 78, 79, 72, 81, 83, 86, 90, 91, 99, 100, 103, 106, 107, 108, 112, 113, 116, 118, 126, 135, and 136. In some embodiments, the HVR-H1 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 6, 10, 17, 29, 36, and 52, or wherein the HVR-H2 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 54, 57, 58, 80, 84, 85, 87, 88, 92, 94, 96, 97, 98, 101, 102, 104, 111, 114, 115, 119, 120,125,127 and 133.

(43) In some embodiments, the polynucleotide library encodes an antibody heavy chain variable region comprising a HVR-H1, HVR-H2, and HVR-H3, wherein the HVR-H3 is any HVR-H3 known in the art. In some embodiments, the HVR-H3 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 223-256.

(44) The heavy chain HVR sequences described herein may be included in any combination in a library of the present disclosure. In some embodiments, a heavy chain variable region comprises an HVR-H1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOS:1-52 and 137-158, and an HVR-H2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOS:53-136 and 159-164. In some embodiments, a heavy chain variable region comprises an HVR-H1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOS:1-52, and an HVR-H2 comprising

an amino acid sequence selected from the group consisting of SEQ ID NOS:53-136. In some embodiments, a heavy chain variable region comprises an HVR-H1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOS:1-52 and 137-158, and an HVR-H3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOS:223-256. In some embodiments, a heavy chain variable region comprises an HVR-H1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOS:1-52, and an HVR-H3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOS:223-256. In some embodiments, a heavy chain variable region comprises an HVR-H2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOS:53-136 and 159-164 and a HVR-H3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 223-256. In some embodiments, a heavy chain variable region comprises an HVR-H2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOS:53-136 and a HVR-H3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 223-256. In some embodiments, a heavy chain variable region comprises an HVR-H1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOS:1-52 and 137-158, an HVR-H2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOS:53-136 and 159-164, and a HVR-H3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 223-256. In some embodiments, a heavy chain variable region comprises an HVR-H1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOS:1-52, an HVR-H2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOS:53-136, and a HVR-H3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 223-256.

(45) In certain embodiments, a heavy chain variable region comprises three of a HVR-H1, a HVR-H2, and a HVR-H3, wherein the HVR-H1 and HVR-H2 are selected from the group consisting of: a HVR-H1 comprising the amino acid sequence of Formula (II) and a HVR-H2 comprising the amino acid sequence of Formula (IX); a HVR-H1 comprising the amino acid sequence of Formula (II) and a HVR-H2 comprising the amino acid sequence of Formula (VII); a HVR-H1 comprising the amino acid sequence of Formula (I) and a HVR-H2 comprising the amino acid sequence of Formula (VII); a HVR-H1 comprising the amino acid sequence of Formula (I) and a HVR-H2 comprising the amino acid sequence of Formula (IX); a HVR-H1 comprising the amino acid sequence of Formula (II) and a HVR-H2 comprising the amino acid sequence of Formula (IV); a HVR-H1 comprising the amino acid sequence of Formula (II) and a HVR-H2 comprising the amino acid sequence of Formula (V); a HVR-H1 comprising the amino acid sequence of Formula (II) and a HVR-H2 comprising the amino acid sequence of Formula (VI); a HVR-H1 comprising the amino acid sequence of Formula (I) and a HVR-H2 comprising the amino acid sequence of Formula (VI); a HVR-H1 comprising the amino acid sequence of Formula (III) and a HVR-H2 comprising the amino acid sequence of Formula (VI); a HVR-H1 comprising the amino acid sequence of Formula (III) and a HVR-H2 comprising the amino acid sequence of Formula (VII); a HVR-H1 comprising the amino acid sequence of Formula (II) and a HVR-H2 comprising the amino acid sequence of Formula (VIII); a HVR-H1 comprising the amino acid sequence of Formula (I) and a HVR-H2 comprising the amino acid sequence of Formula (V); a HVR-H1 comprising the amino acid sequence of Formula (III) and a HVR-H2 comprising the amino acid sequence of Formula (V); and a HVR-H1 comprising the amino acid sequence of Formula (I) and a HVR-H2 comprising the amino acid sequence of Formula (VIII). In some embodiments, the HVR-H1 and HVR-H2 are selected from the group consisting of: a HVR-H1 comprising the amino acid sequence of Formula (II) and a HVR-H2 comprising the amino acid sequence of Formula (XI); a HVR-H1 comprising the amino acid sequence of Formula (II) and a HVR-H2 comprising the amino acid sequence of Formula (XII); a HVR-H1 comprising the amino acid sequence of Formula (I) and a HVR-H2 comprising the amino acid sequence of Formula (XII); a HVR-H1 comprising the amino acid sequence of Formula (III) and a HVR-H2 comprising the amino acid sequence of Formula (XII); a HVR-H1 comprising the amino acid sequence of Formula (I) and a HVR-H2 comprising the amino acid sequence of Formula (XI); and a HVR-H1 comprising the amino acid sequence of Formula (III) and a HVR-H2 comprising the amino acid sequence of Formula (XI). In some embodiments, the HVR-H1 and HVR-H2 are selected from the group consisting of: a HVR-H1 comprising the amino acid sequence of Formula (I) and a HVR-H2 comprising the amino acid sequence of Formula (IV); a HVR-H1 comprising the amino acid sequence of Formula (III) and a HVR-H2 comprising the amino acid sequence of Formula (IV); a HVR-H1 comprising the amino acid sequence of Formula (II) and a HVR-H2 comprising the amino acid sequence of Formula (X); a HVR-H1 comprising the amino acid sequence of Formula (III) and a HVR-H2 comprising the amino acid sequence of Formula (IX); a HVR-H1 comprising the amino acid sequence of Formula (I) and a HVR-H2 comprising the amino acid sequence of Formula (X);

a HVR-H1 comprising the amino acid sequence of Formula (III) and a HVR-H2 comprising the amino acid sequence of Formula (VIII); and a HVR-H1 comprising the amino acid sequence of Formula (III) and a HVR-H2 comprising the amino acid sequence of Formula (X). In some embodiments, the HVR-H1 and HVR-H2 are selected from the group consisting of: a HVR-H1 comprising the amino acid sequence of Formula (II) and a HVR-H2 comprising the amino acid sequence of Formula (XIII); a HVR-H1 comprising the amino acid sequence of Formula (I) and a HVR-H2 comprising the amino acid sequence of Formula (XIII); and a HVR-H1 comprising the amino acid sequence of Formula (III) and a HVR-H2 comprising the amino acid sequence of Formula (XIII).

(46) In certain embodiments, a heavy chain variable region comprises three of a HVR-H1, a HVR-H2, and a HVR-H3, wherein the HVR-H1 and HVR-H2 are selected from the group consisting of: a HVR-H1 comprising the amino acid sequence of SEQ ID NO:157, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:63; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:1, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:122; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:138, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:63; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:154, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:63; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:158, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:161; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:158, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:63; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:145, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:128; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:22, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:61; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:31, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:63; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:153, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:63; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:155, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:67; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:156, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:100; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:51, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:162; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:138, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:123; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:139, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:110; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:8, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:126; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:13, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:129; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:31, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:124; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:25, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:130; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:150, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:132; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:158, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:162; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:12, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:82; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:149, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:117; and a HVR-H1 comprising the amino acid sequence of SEQ ID NO:7, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:134. In some embodiments, the HVR-H1 and HVR-H2 are selected from the group consisting of: a HVR-H1 comprising the amino acid sequence of SEQ ID NO:26, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:53; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:151, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:53; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:34, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:63; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:50, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:162; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:158, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:104; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:5, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:121; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:6, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:116; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:7, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:121; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:17, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:63; a HVR-H1

comprising the amino acid sequence of SEQ ID NO:25, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:101; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:25, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:114; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:29, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:112; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:152, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:63; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:156, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:89; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:157, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:94; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:48, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:58; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:50, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:89; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:50, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:163; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:158, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:160; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:158, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:87; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:158, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:92; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:158, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:93; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:158, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:97; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:158, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:103; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:158, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:164; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:137, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:54; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:3, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:127; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:4, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:85; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:4, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:110; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:139, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:109; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:139, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:121; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:8, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:120; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:140, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:131; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:141, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:116; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:142, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:159; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:143, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:116; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:144, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:121; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:146, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:110; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:147, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:133; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:148, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:63; and a HVR-H1 comprising the amino acid sequence of SEQ ID NO:13, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:118.

(47) In some embodiments, a heavy chain variable region comprises three of a HVR-H1, a HVR-H2, and a HVR-H3, wherein the HVR-H1 and HVR-H2 are listed in Table 1. In some embodiments, the HVR-H3 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 223-256. In some embodiments, a heavy chain variable region comprises a sequence selected from the group consisting of SEQ ID NOS: 169, 171, 173, 175, 177, 179, 181, 183, 185, 187, 189, 191, 193, and 195, or a sequence having at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to a sequence selected from SEQ ID NOS: 169, 171, 173, 175, 177, 179, 181, 183, 185, 187, 189, 191, 193, and 195.

(48) In some embodiments, a heavy chain variable region further comprises variable region heavy chain framework sequences juxtaposed between the HVRs according to the formula: (FW-H1)−(HVR-H1)−(FW-H2)−(HVR-H2)−(FW-H3)−(HVR-H3)−(FW-H4). In some embodiments, one, two, three, or four of the framework sequences is/are the following: FW-H1 is EVQLVESGGGLVQPGGSLRLSCAASG (SEQ ID

NO:165) FW-H2 is RQAPGKGLEW (SEQ ID NO:166) FW-H3 is TISRDNSKNTLYLQLNSLRAEDTAVYYC (SEQ ID NO:167) FW-H4 is WGQGTLVTVSS (SEQ ID NO:168).

(49) In some embodiments, the heavy chain variable region comprises an alternate FW-H3 sequence with an arginine to lysine mutation at R19 of SEQ ID NO:167. In some embodiments, one, two, three, or four of the framework sequences is/are an FW-H1 of SEQ ID NO:165, an FW-H2 of SEQ ID NO:166, an FW-H3 or SEQ ID NO:167 with an arginine to lysine mutation at R19, and an FW-H4 of SEQ ID NO:168.

(50) In some embodiments, a library contains a plurality of polynucleotides, with at least one of the polynucleotides encoding an antibody light chain variable region (e.g., comprising a HVR-L1, HVR-L2, and HVR-L3). In some embodiments, the antibody light chain variable region comprises an HVR-L1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 257-264. In some embodiments, the antibody light chain variable region comprises an HVR-L3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 265-274. In some embodiments, the antibody light chain variable region comprises an HVR-L1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 257-264, and an HVR-L3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 265-274 In some embodiments, a library contains a plurality of polynucleotides that encodes at least one, at least 50, at least 100, at least 250, at least 500, at least 10.sup.3, at least 10.sup.4, at least 10.sup.5, at least 10.sup.6, at least 10.sup.7, at least 10.sup.8, at least 10.sup.9, at least 10.sup.10, at least 10.sup.11, or at least 10.sup.12 unique sequences of antibody light chain variable regions. In some embodiments, a library contains a plurality of polynucleotides that encodes at least 10.sup.3 unique sequences of antibody light chain variable regions. In some embodiments, a library contains a plurality of polynucleotides that encodes at least 10.sup.5 unique sequences of antibody light chain variable regions. In some embodiments, a library contains a plurality of polynucleotides that encodes at least 10.sup.9 unique sequences of antibody light chain variable regions. In other embodiments, a library contains a polynucleotide that encodes one antibody light chain variable region. In some embodiments, a library contains a plurality of polynucleotides that encodes from 1 to about 10.sup.3 unique sequences of antibody light chain variable regions. In some embodiments, the antibody light chain variable region is any of the antibody light chain variable regions found in International Application No. PCT/CN2017/098333 and/or U.S. patent application Ser. No. 16/640,673 (the disclosures of which are each incorporated herein by reference in their entireties). In some embodiments, the antibody light chain variable region comprises any of the HVR-L1, HVR-L2, and/or HVR-L3 sequences found in International Application No. PCT/CN2017/098333 and/or U.S. patent application Ser. No. 16/640,673 (the disclosures of which are each incorporated herein by reference in their entireties).

(51) In some embodiments, one or more of the polynucleotides of a library encode(s) full-length antibody heavy chain(s). In other embodiments, one or more of the polynucleotides of a library encode(s) heavy chain Fab fragment(s). In some embodiments, one or more of the polynucleotides of a library encode(s) single-chain variable fragment(s).

(52) In some embodiments, a library contains a plurality of polynucleotides that encodes a plurality of unique antibodies. In some embodiments, each antibody comprises a heavy chain variable region and a light chain variable region. In some embodiments, the heavy chain variable region of each antibody of the plurality comprises an identical sequence and comprises a HVR-H1, a HVR-H2 and a HVR-H3. In some embodiments, at least one or at least two of the HVR-H1 and HVR-H2 comprise an amino acid sequence selected from a HVR-H1 sequence of the present disclosure (e.g., X1TFX2X3YX4IHWV, wherein X1 is F or Y, X2 is S or T, X3 is D, G, N, or S, and X4 is A, G, or W (SEQ ID NO:198); YSIX1SGX2X3WX4WI, wherein X1 is S or T, X2 is H or Y, X3 is H or Y, and X4 is A, D, G, N, S, or T (SEQ ID NO:199); and FSLSTX1GVX2VX3WI, wherein XI is G or S, X2 is A or G, and X3 is A, G, S, or T (SEQ ID NO:200); and SEQ ID NOS:1-52 and 137-158), and a HVR-H2 sequence of the present disclosure (e.g., LAX1IX2WX3X4DKX5YSX6SLKSRL, wherein X1 is L or R, X2 is D or Y, X3 is A, D, S, or Y, X4 is D or G, X5 is R, S, or Y, and X6 is P or T (SEQ ID NO:201); IGX1IX2X3SGSTYYSPSLKSRV, wherein X1 is A, D, E, S, or Y, X2 is S or Y, and X3 is H or Y(SEQ ID NO:202); IGXIIYX2SGX3TX4YNPSLKSRV, wherein X1 is D, E, R, S, or Y, X2 is H or Y, X3 is N or S, and X4 is N or Y (SEQ ID NO:203); VSX1ISGX2GX3X4TYYADSVKGRF, wherein X1 is A, G, S, V, or Y, X2 is A, D, S, or Y, X3 is D, G, or S, and X4 is S or T (SEQ ID NO:204); IGX1INPNX2GX3TX4YAQKFQGRV, wherein X1 is I, R, or W, X2 is F or R, X3 is D, G, or S, and X4 is K or N (SEQ ID NO:205); IGX1IX2PSX3GX4TX5YAQKFQGRV, wherein X1 is I, R, or W, X2 is S or Y, X3 is G or S, X4 is D, G, or S, and X5 is K or N (SEQ ID NO:206);

VGRIX1SKX2X3GX4TTX5YAAX6VKGRF, wherein X1 is K or R, X2 is A or T, X3 is D or Y, X4 is G or Y, X5 is D or E, and X6 is P or S (SEQ ID NO:207); IGX1IX2X3SGSTYYSPSLKSRV, wherein X1 is A, D, or E, X2 is S or Y, and X3 is H or Y (SEQ ID NO:208); IGX1IYX2SGX3TX4YNPSLKSRV, wherein XI is D, E, or S, X2 is H or Y, X3 is N or S, and X4 is N or Y (SEQ ID NO:209); and VGRIX1SKX2X3GX4TTEYAAX5VKGRF, wherein X1 is K or R, X2 is A or T, X3 is D or Y, X4 is G or Y, and X5 is P or S (SEQ ID NO:210); and SEQ ID NOS:53-136 and 159-164). The heavy chain HVR sequences described herein may be included in any combination in a library of the present disclosure that also includes polynucleotides encoding one or more light chain variable region(s).

(53) In some embodiments, a library of the present disclosure includes one or more vectors encoding one or more polynucleotides (e.g., synthetic polynucleotides) of the present disclosure.

(54) Further provided herein is a method of preparing a library, e.g., by providing and assembling the polynucleotide sequences (e.g., synthetic polynucleotide(s)) of a library of the present disclosure. Further provided herein is a method of making a library, e.g., by selecting one, two, or three heavy chain HVRs (e.g., one or two heavy chain HVRs of the present disclosure) comprising a sequence having multiple conformations and assembling polynucleotide sequences to produce a library of polynucleotides (e.g., synthetic polynucleotides) encoding a plurality of antibody heavy chain variable region sequences. In some embodiments, the antibody heavy chain variable region sequences are human antibody sequences. In some embodiments, the antibody heavy chain variable region comprises a HVR-H1, a HVR-H2 and a HVR-H3, and the HVR-H1 and/or HVR-H2 comprise an amino acid sequence selected from a HVR-H1 sequence of the present disclosure (e.g., X1TFX2X3YX4IHWV, wherein X1 is F or Y, X2 is S or T, X3 is D, G, N, or S, and X4 is A, G, or W (SEQ ID NO:198); YSIX1SGX2X3WX4WI, wherein X1 is S or T, X2 is H or Y, X3 is H or Y, and X4 is A, D, G, N, S, or T (SEQ ID NO:199); and FSLSTX1GVX2VX3WI, wherein X1 is G or S, X2 is A or G, and X3 is A, G, S, or T (SEQ ID NO:200); and SEQ ID NOS:1-52 and 137-158), and a HVR-H2 sequence of the present disclosure (e.g., LAX1IX2WX3X4DKX5YSX6SLKSRL, wherein X1 is L or R, X2 is D or Y, X3 is A, D, S, or Y, X4 is D or G, X5 is R, S, or Y, and X6 is P or T (SEQ ID NO:201); IGX1IX2X3SGSTYYSPSLKSRV, wherein X1 is A, D, E, S, or Y, X2 is S or Y, and X3 is H or Y (SEQ ID NO:202); IGX1IYX2SGX3TX4YNPSLKSRV, wherein X1 is D, E, R, S, or Y, X2 is H or Y, X3 is N or S, and X4 is N or Y (SEQ ID NO:203); VSX1ISGX2GX3X4TYYADSVKGRF, wherein X1 is A, G, S, V, or Y, X2 is A, D, S, or Y, X3 is D, G, or S, and X4 is S or T (SEQ ID NO:204); IGX1INPNX2GX3TX4YAQKFQGRV, wherein X1 is I, R, or W, X2 is F or R, X3 is D, G, or S, and X4 is K or N (SEQ ID NO:205); IGX1IX2PSX3GX4TX5YAQKFQGRV, wherein X1 is I, R, or W, X2 is S or Y, X3 is G or S, X4 is D, G, or S, and X5 is K or N (SEQ ID NO:206); VGRIX1SKX2X3GX4TTX5YAAX6VKGRF, wherein X1 is K or R, X2 is A or T, X3 is D or Y, X4 is G or Y, X5 is D or E, and X6 is P or S (SEQ ID NO:207); IGX1IX2X3SGSTYYSPSLKSRV, wherein X1 is A, D, or E, X2 is S or Y, and X3 is H or Y (SEQ ID NO:208); IGX1IYX2SGX3TX4YNPSLKSRV, wherein X1 is D, E, or S, X2 is H or Y, X3 is N or S, and X4 is N or Y (SEQ ID NO:209); and VGRIX1SKX2X3GX4TTEYAAX5VKGRF, wherein X1 is K or R, X2 is A or T, X3 is D or Y, X4 is G or Y, and X5 is P or S (SEQ ID NO:210); and SEQ ID NOS:53-136 and 159-164).

(55) In some embodiments, at least one of the HVR-H1, HVR-H2, and HVR-H3 of the antibody heavy chain variable region adopts multiple conformations. In some embodiments, the multiple conformations can be assayed or detected using techniques known in the art, including, without limitation, structural determination (e.g., X-ray crystallography or NMR) and/or computational modeling.

(56) Polynucleotides encoding a set of antibody light and/or heavy chain variable regions can be cloned into any suitable vector for expression of a portion or the entire light or heavy chain sequences. In some embodiments, the polynucleotide cloned into a vector allows production of a portion or the entire light or heavy chain sequence fused to all or a portion of a viral coat protein (i.e., creating a fusion protein) and displayed on the surface of a particle or cell. Several types of vectors are available and may be used to practice the present disclosure, for example, phagemid vectors. Phagemid vectors generally contain a variety of components including promoters, signal sequences, phenotypic selection genes, origin of replication sites, and other necessary components as are known to those of ordinary skill in the art. In some embodiments, the polynucleotides encoding a set of antibody light and/or heavy chain variable regions can be cloned into vectors for expression in bacterial cells for bacterial display or in yeast cells for yeast display. Exemplary vectors are described in US PG Pub. No. US20160145604. In some embodiments, the vector is a display vector comprising, from 5′ to 3′, a polynucleotide encoding an amino acid sequence to be displayed on a surface (e.g., a surface of phage, bacteria, yeast, or mammalian cells), a restriction site, a second

polynucleotide encoding a surface peptide capable of being displayed on the surface, and a second restriction site. In some embodiments, the second polynucleotide encodes a phage coat protein, a yeast outer wall protein, a bacterial outer membrane protein, a cell surface tether domain, or an adapter, or a truncation or derivative thereof. In certain embodiments, the second polynucleotide is gene III of filamentous phage M13, or a truncation or derivative thereof. In some embodiments, the surface peptide is for phage display, yeast display, bacterial display or mammalian display, or shuttling display there between. In some embodiments, when expressed, the amino acid sequence and the surface peptide are displayed as a fusion protein on the surface. In some embodiments, the vector further comprises a fusion tag 5′ to the first restriction site or 3′ to the second restriction site.

(57) Certain aspects of the present disclosure relate to a population of cells containing vector(s) described herein. Antibody light and/or heavy chains encoded by polynucleotides generated by any of the techniques described herein, or other suitable techniques, can be expressed and screened to identify antibodies having desired structure and/or activity. Expression of the antibodies can be carried out, for example, using cell-free extracts (e.g., ribosome display), phage display, prokaryotic cells (e.g., bacterial display), or eukaryotic cells (e.g., yeast display). In some embodiments, the cells are bacterial cells, yeast cells, or mammalian cells. Methods for transfecting bacterial cells, yeast cells, or mammalian cells are known in the art and described in the references cited herein. Expression (e.g., from a library of the present disclosure) of polypeptides (e.g., antibody chains) in these cell types, as well as screening for antibodies of interest, are described in more detail below.

(58) Alternatively, the polynucleotides can be expressed in an *E. coli* expression system, such as that described by Pluckthun and Skerra. (Meth. Enzymol., 1989, 178: 476; Biotechnology, 1991, 9: 273). The mutant proteins can be expressed for secretion in the medium and/or in the cytoplasm of the bacteria, as described by Better and Horwitz, Meth. Enzymol., 1989, 178: 476. In some embodiments, the single domains encoding V.sub.H and VL are each attached to the 3′ end of a sequence encoding a signal sequence, such as the ompA, phoA or pe1B signal sequence (Lei et al., J. Bacteriol., 1987, 169: 4379). These gene fusions are assembled in a dicistronic construct, so that they can be expressed from a single vector and secreted into the periplasmic space of *E. coli* where they will refold and can be recovered in active form. (Skerra et al., Biotechnology, 1991, 9: 273). For example, antibody heavy chain genes can be concurrently expressed with antibody light chain genes to produce antibodies or antibody fragments.

(59) In other embodiments, the antibody sequences are expressed on the membrane surface of a prokaryote, e.g., *E. coli*, using a secretion signal and lipidation moiety as described, e.g., in US20040072740; US20030100023; and US20030036092.

(60) Alternatively, antibodies can be expressed and screened by anchored periplasmic expression (APEx 2-hybrid surface display), as described, for example, in Jeong et al., PNAS, 2007, 104: 8247 or by other anchoring methods as described, for example, in Mazor et al., Nature Biotechnology, 2007, 25: 563.

(61) Higher eukaryotic cells, such as mammalian cells, for example myeloma cells (e.g., NS/0 cells), hybridoma cells, Chinese hamster ovary (CHO), and human embryonic kidney (HEK) cells, can also be used for expression of the antibodies of the present disclosure. Typically, antibodies expressed in mammalian cells are designed to be secreted into the culture medium, or expressed on the surface of the cell. The antibody or antibody fragments can be produced, for example, as intact antibody molecules or as individual V.sub.H and V.sub.L fragments, Fab fragments, single domains, or as single chains (scFv).

(62) In other embodiments, antibodies can be selected using mammalian cell display (Ho et al., PNAS, 2006, 103: 9637). In some embodiments, as described above and exemplified below, antibodies can be selected after production of a portion or the entire light or heavy chain sequence fused to all or a portion of a viral coat protein (i.e., creating a fusion protein) and displayed on the surface of a particle or cell, e.g., using phage display.

(63) Certain aspects of the present disclosure relate to a non-human animal comprising a polynucleotide library of the present disclosure. For example, a non-human animal of the present disclosure may be modified such that its genome includes a polynucleotide encoding a heavy chain variable region of the present disclosure. In a non-limiting example, a transgenic mouse is generated that includes a heavy chain immunoglobulin locus modified to express one or more of the heavy chain variable regions of the present disclosure. In some embodiments, the transgenic animal (e.g., mouse) expresses antibodies or heavy chains encoded by the polynucleotides. Techniques for modifying one or more immunoglobulin loci of a non-human animal are known in the art (e.g., methods used to generate Xenomouse™).

(64) The screening of the antibodies derived from the libraries of the present disclosure can be carried out by

any appropriate means known in the art. For example, binding activity can be evaluated by standard immunoassay and/or affinity chromatography. Screening of the antibodies of the present disclosure for catalytic function, e.g., proteolytic function can be accomplished using a standard assays, e.g., a hemoglobin plaque assay. Determining binding affinity of an antibody to a target can be assayed in vitro using a variety of well-known techniques, e.g., a BIACORE™ instrument, which measures binding rates of an antibody to a given target or antigen based on surface plasmon resonance, or Bio-Layer Interferometry (BLI), as exemplified below using the ForteBio Octet@RED96 platform (Pall Life Sciences). In vivo assays can be conducted using any of a number of animal models and then subsequently tested, as appropriate, in humans. Cell-based biological assays are also contemplated. The antibodies or antigen binding fragments can be further selected for functional activity, for example, antagonist or agonist activity. Exemplary screening methods are described herein. For example, in some embodiments, affinity of binding between fab fragment(s) and one or more target(s) is measured using BLI by tagging antigens with human IgG1-Fc tag and capture by Anti-hIgG-Fc Capture (AHC) Biosensor. Fabs can be tagged at their C-terminus of the CH1 domain with a His6 tag, over-expressed in a host cell such as *E. coli*, and purified, e.g., using a Ni-NTA resin. Affinity can then be measured using AHC sensors (anti-human IgG-Fc capture dip and read biosensors) dipped into wells containing the purified fabs diluted, e.g., to 5-10 μg/mL with kinetic buffer.

(65) After binders are identified by binding to the target or antigen, and/or functional assays the nucleic acid can be extracted. Extracted DNA can then be used directly to transform *E. coli* host cells or alternatively, the encoding sequences can be amplified, for example using PCR with suitable primers, and sequenced by any typical sequencing method. Variable domain DNA of the binders can be restriction enzyme digested and then inserted into a vector for protein expression.

IV. Antibodies and Antibody Production

(66) Provided herein are antibodies identified and selected from the libraries described herein. Certain aspects of the present disclosure relate to antibody light chain or heavy chain HVRs, variable regions comprising the HVRs, and/or polynucleotide(s) encoding the same. In some embodiments, the HVRs and/or variable regions are part of an antibody fragment, full-length antibody, or single-chain variable fragment (scFv).

(67) In some embodiments, a heavy chain variable region comprises an HVR-H1, HVR-H2, and HVR-H3, wherein the HVR-H1 comprises an amino acid sequence according to a formula selected from the group consisting of (Formula I) X1TFX2X3YX4IHWV, wherein X1 is F or Y, X2 is S or T, X3 is D, G, N, or S, and X4 is A, G, or W (SEQ ID NO:198); (Formula II) YSIX1SGX2X3WX4WI, wherein X1 is S or T, X2 is H or Y, X3 is H or Y, and X4 is A, D, G, N, S, or T (SEQ ID NO: 199); and (Formula III) FSLSTX1GVX2VX3WI, wherein X1 is G or S, X2 is A or G, and X3 is A, G, S, or T (SEQ ID NO:200). In some embodiments, a heavy chain variable region comprises an HVR-H1, HVR-H2, and HVR-H3, wherein the HVR-H2 comprises an amino acid sequence according to a formula selected from the group consisting of (Formula IV) LAX1IX2WX3X4DKX5YSX6SLKSRL, wherein X1 is L or R, X2 is D or Y, X3 is A, D, S, or Y, X4 is D or G, X5 is R, S, or Y, and X6 is P or T (SEQ ID NO:201); (Formula V) IGX1IX2X3SGSTYYSPSLKSRV, wherein X1 is A, D, E, S, or Y, X2 is S or Y, and X3 is H or Y (SEQ ID NO:202); (Formula VI) IGX1IYX2SGX3TX4YNPSLKSRV, wherein X1 is D, E, R, S, or Y, X2 is H or Y, X3 is N or S, and X4 is N or Y (SEQ ID NO:203); (Formula VII) VSXlISGX2GX3X4TYYADSVKGRF, wherein X1 is A, G, S, V, or Y, X2 is A, D, S, or Y, X3 is D, G, or S, and X4 is S or T (SEQ ID NO:204); (Formula VIII) IGX1INPNX2GX3TX4YAQKFQGRV, wherein X1 is I, R, or W, X2 is F or R, X3 is D, G, or S, and X4 is K or N (SEQ ID NO:205); (Formula IX) IGX1IX2PSX3GX4TX5YAQKFQGRV, wherein X1 is I, R, or W, X2 is S or Y, X3 is G or S, X4 is D, G, or S, and X5 is K or N (SEQ ID NO: 206); and (Formula X) VGRIX1SKX2X3GX4TTX5YAAX6VKGRF, wherein X1 is K or R, X2 is A or T, X3 is D or Y, X4 is G or Y, X5 is D or E, and X6 is P or S (SEQ ID NO:207). In some embodiments, the HVR-H2 comprises an amino acid sequence according to a formula selected from the group consisting of (Formula XI) IGX1IX2X3SGSTYYSPSLKSRV, wherein XI is A, D, or E, X2 is S or Y, and X3 is H or Y (SEQ ID NO:208); (Formula XII) IGX1IYX2SGX3TX4YNPSLKSRV, wherein X1 is D, E, or S, X2 is H or Y, X3 is N or S, and X4 is N or Y (SEQ ID NO:209); and (Formula XII) VGRIX1SKX2X3GX4TTEYAAX5VKGRF, wherein X1 is K or R, X2 is A or T, X3 is D or Y, X4 is G or Y, and X5 is P or S (SEQ ID NO:210). In some embodiments, a heavy chain variable region comprises an HVR-H1, HVR-H2, and HVR-H3, wherein the HVR-H1 comprises the amino acid sequence according to a formula selected from the group consisting of (Formula I) X1TFX2X3YX4IHWV, wherein X1 is F or Y, X2 is S or T, X3 is D, G, N, or S, and X4 is A, G, or W (SEQ ID NO:198); (Formula II) YSIX1SGX2X3WX4WI, wherein X1 is S or T, X2 is H or Y, X3 is H

or Y, and X4 is A, D, G, N, S, or T (SEQ ID NO: 199); and (Formula III) FSLSTX1GVX2VX3WI, wherein X1 is G or S, X2 is A or G, and X3 is A, G, S, or T (SEQ ID NO:200); and an HVR-H2 comprising the amino acid sequence according to a formula selected from the group consisting of (Formula IV) LAX1IX2WX3X4DKX5YSX6SLKSRL, wherein X1 is L or R, X2 is D or Y, X3 is A, D, S, or Y, X4 is D or G, X5 is R, S, or Y, and X6 is P or T (SEQ ID NO:201); (Formula V) IGX1IX2X3SGSTYYSPSLKSRV, wherein X1 is A, D, E, S, or Y, X2 is S or Y, and X3 is H or Y (SEQ ID NO:202); (Formula VI) IGXIIYX2SGX3TX4YNPSLKSRV, wherein X1 is D, E, R, S, or Y, X2 is H or Y, X3 is N or S, and X4 is N or Y (SEQ ID NO:203); (Formula VII) VSX1ISGX2GX3X4TYYADSVKGRF, wherein X1 is A, G, S, V, or Y, X2 is A, D, S, or Y, X3 is D, G, or S, and X4 is S or T (SEQ ID NO:204); (Formula VIII) IGX1INPNX2GX3TX4YAQKFQGRV, wherein X1 is I, R, or W, X2 is F or R, X3 is D, G, or S, and X4 is K or N (SEQ ID NO:205); (Formula IX) IGX1IX2PSX3GX4TX5YAQKFQGRV, wherein X1 is I, R, or W, X2 is S or Y, X3 is G or S, X4 is D, G, or S, and X5 is K or N (SEQ ID NO: 206); and (Formula X) VGRIX1SKX2X3GX4TTX5YAAX6VKGRF, wherein X1 is K or R, X2 is A or T, X3 is D or Y, X4 is G or Y, X5 is D or E, and X6 is P or S (SEQ ID NO:207). In some embodiments, a heavy chain variable region comprises an HVR-H1, HVR-H2, and HVR-H3, wherein the HVR-H1 comprises the amino acid sequence according to a formula selected from the group consisting of (Formula I) X1TFX2X3YX4IHWV, wherein X1 is F or Y, X2 is S or T, X3 is D, G, N, or S, and X4 is A, G, or W (SEQ ID NO:198); (Formula II) YSIX1SGX2X3WX4WI, wherein X1 is S or T, X2 is H or Y, X3 is H or Y, and X4 is A, D, G, N, S, or T (SEQ ID NO: 199); and (Formula III) FSLSTX1GVX2VX3WI, wherein X1 is G or S, X2 is A or G, and X3 is A, G, S, or T (SEQ ID NO:200); and an HVR-H2 comprising the amino acid sequence according to a formula selected from the group consisting of (Formula XI) IGX1IX2X3SGSTYYSPSLKSRV, wherein X1 is A, D, or E, X2 is S or Y, and X3 is H or Y (SEQ ID NO:208); (Formula XII) IGX1IYX2SGX3TX4YNPSLKSRV, wherein X1 is D, E, or S, X2 is H or Y, X3 is N or S, and X4 is N or Y (SEQ ID NO:209); and (Formula XII) VGRIX1SKX2X3GX4TTEYAAX5VKGRF, wherein X1 is K or R, X2 is A or T, X3 is D or Y, X4 is G or Y, and X5 is P or S (SEQ ID NO:210).

(68) In some embodiments, the heavy chain variable region comprises an HVR-H1 comprising the amino acid sequence according to the formula X1TFX2X3YX4IHWV, wherein X1 is F or Y, X2 is S or T, X3 is D, G, N, or S, and X4 is A, G, or W (SEQ ID NO:198); and an HVR-H2 comprising an amino acid sequence according to a formula selected from the group consisting of (Formula IV) LAX1IX2WX3X4DKX5YSX6SLKSRL, wherein X1 is L or R, X2 is D or Y, X3 is A, D, S, or Y, X4 is D or G, X5 is R, S, or Y, and X6 is P or T (SEQ ID NO:201); (Formula V) IGX1IX2X3SGSTYYSPSLKSRV, wherein X1 is A, D, E, S, or Y, X2 is S or Y, and X3 is H or Y (SEQ ID NO:202); (Formula VI) IGX1IYX2SGX3TX4YNPSLKSRV, wherein X1 is D, E, R, S, or Y, X2 is H or Y, X3 is N or S, and X4 is N or Y (SEQ ID NO:203); (Formula VII) VSX1ISGX2GX3X4TYYADSVKGRF, wherein X1 is A, G, S, V, or Y, X2 is A, D, S, or Y, X3 is D, G, or S, and X4 is S or T (SEQ ID NO:204); (Formula VIII) IGX1INPNX2GX3TX4YAQKFQGRV, wherein X1 is I, R, or W, X2 is F or R, X3 is D, G, or S, and X4 is K or N (SEQ ID NO:205); (Formula IX) IGX1IX2PSX3GX4TX5YAQKFQGRV, wherein X1 is I, R, or W, X2 is S or Y, X3 is G or S, X4 is D, G, or S, and X5 is K or N (SEQ ID NO: 206); and (Formula X) VGRIX1SKX2X3GX4TTX5YAAX6VKGRF, wherein XI is K or R, X2 is A or T, X3 is D or Y, X4 is G or Y, X5 is D or E, and X6 is P or S (SEQ ID NO:207).

(69) In some embodiments, the heavy chain variable region comprises an HVR-H1 comprising the amino acid sequence according to the formula X1TFX2X3YX4IHWV, wherein X1 is F or Y, X2 is S or T, X3 is D, G, N, or S, and X4 is A, G, or W (SEQ ID NO:198); and an HVR-H2 comprising an amino acid sequence according to a formula selected from the group consisting of (Formula XI) IGX1IX2X3SGSTYYSPSLKSRV, wherein X1 is A, D, or E, X2 is S or Y, and X3 is H or Y (SEQ ID NO:208); (Formula XII) IGX1IYX2SGX3TX4YNPSLKSRV, wherein X1 is D, E, or S, X2 is H or Y, X3 is N or S, and X4 is N or Y (SEQ ID NO:209); and (Formula XII) VGRIX1SKX2X3GX4TTEYAAX5VKGRF, wherein X1 is K or R, X2 is A or T, X3 is D or Y, X4 is G or Y, and X5 is P or S (SEQ ID NO:210).

(70) In some embodiments, the heavy chain variable region comprises an HVR-H1 comprising the amino acid sequence according to the formula YSIX1SGX2X3WX4WI, wherein X1 is S or T, X2 is H or Y, X3 is H or Y, and X4 is A, D, G, N, S, or T (SEQ ID NO:199); and an HVR-H2 comprising an amino acid sequence according to a formula selected from the group consisting of (Formula IV) LAX1IX2WX3X4DKX5YSX6SLKSRL, wherein X1 is L or R, X2 is D or Y, X3 is A, D, S, or Y, X4 is D or G, X5 is R, S, or Y, and X6 is P or T (SEQ ID NO:201); (Formula V) IGX1IX2X3SGSTYYSPSLKSRV, wherein X1 is A, D, E, S, or Y, X2 is S or Y, and X3 is H or Y (SEQ ID NO:202); (Formula VI)

IGXIIYX2SGX3TX4YNPSLKSRV, wherein X1 is D, E, R, S, or Y, X2 is H or Y, X3 is N or S, and X4 is N or Y (SEQ ID NO:203); (Formula VII) VSXIISGX2GX3X4TYYADSVKGRF, wherein X1 is A, G, S, V, or Y, X2 is A, D, S, or Y, X3 is D, G, or S, and X4 is S or T (SEQ ID NO:204); (Formula VIII) IGXIINPNX2GX3TX4YAQKFQGRV, wherein X1 is I, R, or W, X2 is F or R, X3 is D, G, or S, and X4 is K or N (SEQ ID NO:205); (Formula IX) IGX1IX2PSX3GX4TX5YAQKFQGRV, wherein X1 is I, R, or W, X2 is S or Y, X3 is G or S, X4 is D, G, or S, and X5 is K or N (SEQ ID NO: 206); and (Formula X) VGRIX1SKX2X3GX4TTX5YAAX6VKGRF, wherein X1 is K or R, X2 is A or T, X3 is D or Y, X4 is G or Y, X5 is D or E, and X6 is P or S (SEQ ID NO:207).

(71) In some embodiments, the heavy chain variable region comprises an HVR-H1 comprising the amino acid sequence according to the formula YSIX1SGX2X3WX4WI, wherein X1 is S or T, X2 is H or Y, X3 is H or Y, and X4 is A, D, G, N, S, or T (SEQ ID NO:199); and an HVR-H2 comprising an amino acid sequence according to a formula selected from the group consisting of (Formula XI) IGX1IX2X3SGSTYYSPSLKSRV, wherein X1 is A, D, or E, X2 is S or Y, and X3 is H or Y (SEQ ID NO:208); (Formula XII) IGX1IYX2SGX3TX4YNPSLKSRV, wherein X1 is D, E, or S, X2 is H or Y, X3 is N or S, and X4 is N or Y (SEQ ID NO:209); and (Formula XII) VGRIX1SKX2X3GX4TTEYAAX5VKGRF, wherein X1 is K or R, X2 is A or T, X3 is D or Y, X4 is G or Y, and X5 is P or S (SEQ ID NO:210).

(72) In some embodiments, the heavy chain variable region comprises an HVR-H1 comprising the amino acid sequence according to the formula FSLSTX1GVX2VX3WI, wherein X1 is G or S, X2 is A or G, and X3 is A, G, S, or T (SEQ ID NO:200); and an HVR-H2 comprising an amino acid sequence according to a formula selected from the group consisting of (Formula IV) LAX1IX2WX3X4DKX5YSX6SLKSRL, wherein X1 is L or R, X2 is D or Y, X3 is A, D, S, or Y, X4 is D or G, X5 is R, S, or Y, and X6 is P or T (SEQ ID NO:201); (Formula V) IGX1IX2X3SGSTYYSPSLKSRV, wherein X1 is A, D, E, S, or Y, X2 is S or Y, and X3 is H or Y (SEQ ID NO:202); (Formula VI) IGXIIYX2SGX3TX4YNPSLKSRV, wherein X1 is D, E, R, S, or Y, X2 is H or Y, X3 is N or S, and X4 is N or Y (SEQ ID NO:203); (Formula VII) VSX1ISGX2GX3X4TYYADSVKGRF, wherein X1 is A, G, S, V, or Y, X2 is A, D, S, or Y, X3 is D, G, or S, and X4 is S or T (SEQ ID NO:204); (Formula VIII) IGX1INPNX2GX3TX4YAQKFQGRV, wherein X1 is I, R, or W, X2 is F or R, X3 is D, G, or S, and X4 is K or N (SEQ ID NO:205); (Formula IX) IGX1IX2PSX3GX4TX5YAQKFQGRV, wherein X1 is I, R, or W, X2 is S or Y, X3 is G or S, X4 is D, G, or S, and X5 is K or N (SEQ ID NO: 206); and (Formula X) VGRIX1SKX2X3GX4TTX5YAAX6VKGRF, wherein X1 is K or R, X2 is A or T, X3 is D or Y, X4 is G or Y, X5 is D or E, and X6 is P or S (SEQ ID NO:207).

(73) In some embodiments, the heavy chain variable region comprises an HVR-H1 comprising the amino acid sequence according to the formula FSLSTX1GVX2VX3WI, wherein X1 is G or S, X2 is A or G, and X3 is A, G, S, or T (SEQ ID NO:200); and an HVR-H2 comprising an amino acid sequence according to a formula selected from the group consisting of (Formula XI) IGX1IX2X3SGSTYYSPSLKSRV, wherein X1 is A, D, or E, X2 is S or Y, and X3 is H or Y (SEQ ID NO:208); (Formula XII) IGX1IYX2SGX3TX4YNPSLKSRV, wherein X1 is D, E, or S, X2 is H or Y, X3 is N or S, and X4 is N or Y (SEQ ID NO:209); and (Formula XII) VGRIX1SKX2X3GX4TTEYAAX5VKGRF, wherein X1 is K or R, X2 is A or T, X3 is D or Y, X4 is G or Y, and X5 is P or S (SEQ ID NO:210).

(74) In some embodiments, the heavy chain variable region comprises HVR-H1, HVR-H2, and HVR-H3, wherein the HVR-H1 and/or HVR-H2 comprise an amino acid sequence listed in Table 1 below.

(75) TABLE-US-00001 TABLE 1 Heavy chain HVR sequences SEQ ID NO. Designed Sequence HVR-H1 1 FTFTDYGIHWV 2 FTFTGYAIHWV 3 FTFTNYGIHWV 4 YTFSDYAIHWV 5 YTFSDYGIHWV 6 YTFSGYAIHWV 7 YTFSGYGIHWV 8 YTFSNYGIHWV 9 YTFSSYGIHWV 10 YTFSGYWIHWV 11 YTFSNYWIHWV 12 FTFSGYWIHWV 13 FTFSNYWIHWV 14 YTFSDYWIHWV 15 YSISSGHHWAWI 16 YSISSGHYWNWI 17 YSISSGHYWSWI 18 YSISSGHYWTWI 19 YSISSGYHWAWI 20 YSISSGYHWDWI 21 YSISSGYHWGWI 22 YSISSGYHWNWI 23 YSISSGYHWSWI 24 YSISSGHHWDWI 25 YSISSGYYWDWI 26 YSISSGYYWNWI 27 YSISSGYYWTWI 28 YSITSGHHWAWI 29 YSITSGHHWDWI 30 YSITSGHHWGWI 31 YSITSGHHWNWI 32 YSITSGHHWSWI 33 YSISSGHHWGWI 34 YSITSGHYWAWI 35 YSITSGHYWDWI 36 YSITSGHYWGWI 37 YSITSGHYWNWI 38 YSITSGHYWSWI 39 YSITSGYHWAWI 40 YSITSGYHWGWI 41 YSISSGHHWNWI 42 YSITSGYHWNWI 43 YSITSGYHWSWI 44 YSITSGYYWDWI 45 YSISSGHHWTWI 46 YSISSGHYWDWI 47 FSLSTSGVAVSWI 48 FSLSTGGVAVGWI 49 FSLSTGGVAVSWI 50 FSLSTGGVGVAWI 51 FSLSTGGVGVSWI 52

FSLSTSGVAVAWI 137 FTFSDYAIHWV 138 FTFSDYGIHWV 139 YTFSNYAIHWV 140
YTFSSYAIHWV 141 YTFTDYAIHWV 142 YTFTDYGIHWV 143 YTFTNYAIHWV 144
YTFTNYGIHWV 145 FTFSGYGIHWV 146 FTFSNYAIHWV 147 FTFSSYGIHWV 148
FTFSDYWIHWV 149 FTFTSYWIHWV 150 YSISSGYYWGWI 151 YSITSGYYWNWI 152
YSITSGYYWSWI 153 YSISSGHYWAWI 154 YSISSGHYWGWI 155 FSLSTSGVAVGWI 156
FSLSTSGVGVAWI 157 FSLSTSGVGVGWI 158 FSLSTGGVGVGWI HVR-H2 53
LARIDWDDDKRYSPSLKSRL 54 LALIDWDDDKRYSPSLKSRL 55
LALIDWDDDKRYSTSLKSRL 56 LALIDWDDDKYYSPSLKSRL 57
LALIDWADDKYYSPSLKSRL 58 LALIDWAGDKSYSTSLKSRL 59
LARIDWDDDKYYSPSLKSRL 60 LARIDWDDDKYYSTSLKSRL 61
LARIDWDGDKYYSTSLKSRL 62 IGDIYHSGSTYYSPSLKSRV 63 IGEIYHSGSTYYSPSLKSRV
64 IGEIYYSGSTYYSPSLKSRV 65 IGSIYHSGNTNYNPSLKSRV 66
IGEIYHSGNTYYNPSLKSRV 67 IGEIYHSGSTYYNPSLKSRV 68 IGEIYYSGSTYYNPSLKSRV
69 IGDIYHSGNTYYNPSLKSRV 70 IGDIYHSGSTYYNPSLKSRV 71
VSAISGYGDTTYYADSVKGRF 72 VSAISGYGGSTYYADSVKGRF 73
VSAISGYGGTTYYADSVKGRF 74 VSGISGAGDTTYYADSVKGRF 75
VSGISGDGDTTYYADSVKGRF 76 VSGISGDGGSTYYADSVKGRF 77
VSGISGYGDTTYYADSVKGRF 78 VSGISGYGGTTYYADSVKGRF 79
VSVISGDGDTTYYADSVKGRF 80 VSVISGYGGSTYYADSVKGRF 81
VSGISGDGSTTYYADSVKGRF 82 VSGISGYGSTTYYADSVKGRF 83
VSVISGSGSTTYYADSVKGRF 84 VSVISGYGSSTYYADSVKGRF 85
VSVISGYGSTTYYADSVKGRF 86 VSAISGYGSTTYYADSVKGRF 87
VSSISGYGDTTYYADSVKGRF 88 VSSISGYGGSTYYADSVKGRF 89
VSSISGYGGTTYYADSVKGRF 90 VSYISGAGDTTYYADSVKGRF 91
VSSISGAGDTTYYADSVKGRF 92 VSYISGAGGTTYYADSVKGRF 93
VSYISGDGDTTYYADSVKGRF 94 VSYISGDGGSTYYADSVKGRF 95
VSYISGDGGTTYYADSVKGRF 96 VSYISGSGDTTYYADSVKGRF 97
VSSISGAGGSTYYADSVKGRF 98 VSYISGYGDTTYYADSVKGRF 99
VSYISGYGGTTYYADSVKGRF 100 VSSISGAGGTTYYADSVKGRF 101
VSSISGDGDTTYYADSVKGRF 102 VSSISGDGGTTYYADSVKGRF 103
VSSISGAGSSTYYADSVKGRF 104 VSSISGAGSTTYYADSVKGRF 105
VSSISGDGSSTYYADSVKGRF 106 VSSISGDGSTTYYADSVKGRF 107
VSSISGYGSSTYYADSVKGRF 108 VSSISGYGSTTYYADSVKGRF 109
IGWINPNRGDTKYAQKFQGRV 110 IGWINPNRGDTNYAQKFQGRV 111
IGWINPNRGGTKYAQKFQGRV 112 IGWINPNRGGTNYAQKFQGRV 113
IGWINPNRGSTKYAQKFQGRV 114 IGWINPNRGSTNYAQKFQGRV 115
IGRINPNFGDTNYAQKFQGRV 116 IGWINPNFGDTNYAQKFQGRV 117
IGWINPNFGSTKYAQKFQGRV 118 IGWINPNFGSTNYAQKFQGRV 119
IGIINPNRGDTKYAQKFQGRV 120 IGIINPNRGDTNYAQKFQGRV 121 IGIINPNFGDTNYAQKFQGRV
122 IGWISPSGGGTKYAQKFQGRV 123 IGWISPSGGGTNYAQKFQGRV 124
IGWISPSSGGTKYAQKFQGRV 125 IGWISPSSGGTNYAQKFQGRV 126
IGWIYPSGGGTKYAQKFQGRV 127 IGWIYPSGGGTNYAQKFQGRV 128
IGWISPSGGSTNYAQKFQGRV 129 IGWISPSSGSTKYAQKFQGRV 130
IGWISPSSGSTNYAQKFQGRV 131 IGWISPSGGSTKYAQKFQGRV 132 IGIIYPSGGGTNYAQKFQGRV
133 IGIISPSGGGTKYAQKFQGRV 134 IGIISPSGGGTNYAQKFQGRV 135
IGIIYPSGGSTNYAQKFQGRV 136 VGRIKSKTDGYTTEYAAPVKGRF 159
VSAISGSGSTTYYADSVKGRF 160 VSSISGSGDTTYYADSVKGRF 161
VSSISGSGGSTYYADSVKGRF 162 VSSISGSGGTTYYADSVKGRF 163
VSSISGDGGSTYYADSVKGRF 164 VSSISGSGSTTYYADSVKGRF

(76) In some embodiments, the heavy chain variable region comprises HVR-H1, HVR-H2, and HVR-H3, wherein the HVR-H3 is any HVR-H3 known in the art. In some embodiments, the HVR-H3 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 223-256.

(77) In some embodiments, provided herein is an antibody heavy chain with a heavy chain variable region comprising an HVR-H1, HVR-H2, and HVR-H3, wherein the HVR-H1 and/or HVR-H2 are any of the HVR-H1s and/or HVR-H2s described herein. In some embodiments, the HVR-H1 comprises an amino acid

sequence selected from any HVR-H1 sequence of the present disclosure (e.g., X1TFX2X3YX4IHWV, wherein X1 is F or Y, X2 is S or T, X3 is D, G, N, or S, and X4 is A, G, or W (SEQ ID NO:198); YSIX1SGX2X3WX4WI, wherein X1 is S or T, X2 is H or Y, X3 is H or Y, and X4 is A, D, G, N, S, or T (SEQ ID NO:199); and FSLSTX1GVX2VX3WI, wherein X1 is G or S, X2 is A or G, and X3 is A, G, S, or T (SEQ ID NO:200); and SEQ ID NOS:1-52 and 137-158). In some embodiments, the HVR-H2 comprises an amino acid sequence selected from any HVR-H2 of the present disclosure (e.g., LAX1IX2WX3X4DKX5YSX6SLKSRL, wherein X1 is L or R, X2 is D or Y, X3 is A, D, S, or Y, X4 is D or G, X5 is R, S, or Y, and X6 is P or T (SEQ ID NO:201); IGX1IX2X3SGSTYYSPSLKSRV, wherein X1 is A, D, E, S, or Y, X2 is S or Y, and X3 is H or Y (SEQ ID NO:202); IGX1IYX2SGX3TX4YNPSLKSRV, wherein X1 is D, E, R, S, or Y, X2 is H or Y, X3 is N or S, and X4 is N or Y (SEQ ID NO:203); VSX1ISGX2GX3X4TYYADSVKGRF, wherein X1 is A, G, S, V, or Y, X2 is A, D, S, or Y, X3 is D, G, or S, and X4 is S or T (SEQ ID NO:204); IGX1INPNX2GX3TX4YAQKFQGRV, wherein X1 is I, R, or W, X2 is F or R, X3 is D, G, or S, and X4 is K or N (SEQ ID NO:205); IGX1IX2PSX3GX4TX5YAQKFQGRV, wherein X1 is I, R, or W, X2 is S or Y, X3 is G or S, X4 is D, G, or S, and X5 is K or N (SEQ ID NO:206); VGRIX1SKX2X3GX4TTX5YAAX6VKGRF, wherein X1 is K or R, X2 is A or T, X3 is D or Y, X4 is G or Y, X5 is D or E, and X6 is P or S (SEQ ID NO:207); IGX1IX2X3SGSTYYSPSLKSRV, wherein X1 is A, D, or E, X2 is S or Y, and X3 is H or Y (SEQ ID NO:208); IGXIIYX2SGX3TX4YNPSLKSRV, wherein X1 is D, E, or S, X2 is H or Y, X3 is N or S, and X4 is N or Y (SEQ ID NO:209); and VGRIXISKX2X3GX4TTEYAAX5VKGRF, wherein X1 is K or R, X2 is A or T, X3 is D or Y, X4 is G or Y, and X5 is P or S (SEQ ID NO:210); and SEQ ID NOS:53-136 and 159-164).

(78) In some embodiments, provided herein is an antibody heavy chain with a heavy chain variable region comprising an HVR—H1, HVR-H2, and HVR-H3, wherein the HVR-H1 comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:1-52 and 137-158. In some embodiments, the HVR-H1 comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:1-52.

(79) In some embodiments, provided herein is an antibody heavy chain with a heavy chain variable region comprising an HVR-H1, HVR-H2, and HVR-H3, wherein the HVR-H2 comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:53-136 and 159-164. In some embodiments, the HVR-H2 comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:53-136.

(80) In some embodiments, provided herein is an antibody heavy chain with a heavy chain variable region comprising a HVR-H1, HVR-H2, and HVR-H3, wherein the HVR-H1 comprises an amino acid sequence selected from the group consisting of Formula (I), Formula (II), and Formula (III), or the HVR-H2 comprises an amino acid sequence selected from the group consisting of Formula (IV), Formula (V), Formula (VI), Formula (VII), Formula (VIII), Formula (IX), Formula (X), Formula (XI), Formula (XII), and Formula (XIII). In some embodiments, provided herein is an antibody heavy chain with a heavy chain variable region comprising a HVR-H1, a HVR-H2 and a HVR-H3, wherein the HVR-H1 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 1-52, or wherein the HVR-H2 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 53-136. In some embodiments, the HVR-H1 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 1, 4, 5, 7, 8, 9, 11, 13, 16, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 31, 33, 34, 38, 40, 42, 43, 45, 47, 49, 50, and 51, or wherein the HVR-H2 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 53, 60, 63, 65, 66, 67, 70, 82, 89, 93, 95, 105, 109, 110, 117, 121, 122, 123, 124, 128, 129, 130, 131, 132, and 134. In some embodiments, the HVR-H1 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 3, 14, 15, 30, 32, 35, 37, 39, 41, 44, 46, and 48, or wherein the HVR-H2 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 55, 56, 59, 61, 62, 64, 68, 69, 71, 73, 74, 75, 76, 77, 78, 79, 72, 81, 83, 86, 90, 91, 99, 100, 103, 106, 107, 108, 112, 113, 116, 118, 126, 135, and 136. In some embodiments, the HVR-H1 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 6, 10, 17, 29, 36, and 52, or wherein the HVR-H2 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 54, 57, 58, 80, 84, 85, 87, 88, 92, 94, 96, 97, 98, 101, 102, 104, 111, 114, 115, 119, 120, 125, 127 and 133.

(81) In some embodiments, provided herein is an antibody heavy chain with a heavy chain variable region comprising an HVR-H1, HVR-H2, and HVR-H3, wherein the HVR-H1 comprises an amino acid sequence selected from SEQ ID NOS:1-52 and 137-158, and the HVR-H2 comprises an amino acid sequence selected from SEQ ID NOS:53-136 and 159-164. In some embodiments, the HVR-H1 comprises an amino acid sequence selected from SEQ ID NOS:1-52, and the HVR-H2 comprises an amino acid sequence selected from SEQ ID NOS:53-136.

(82) In certain embodiments, a heavy chain variable region comprises three of a HVR-H1, a HVR-H2, and a HVR-H3, wherein the HVR-H1 and HVR-H2 are selected from the group consisting of: a HVR-H1 comprising the amino acid sequence of Formula (II) and a HVR-H2 comprising the amino acid sequence of Formula (IX); a HVR-H1 comprising the amino acid sequence of Formula (II) and a HVR-H2 comprising the amino acid sequence of Formula (VII); a HVR-H1 comprising the amino acid sequence of Formula (I) and a HVR-H2 comprising the amino acid sequence of Formula (VII); a HVR-H1 comprising the amino acid sequence of Formula (I) and a HVR-H2 comprising the amino acid sequence of Formula (IX); a HVR-H1 comprising the amino acid sequence of Formula (II) and a HVR-H2 comprising the amino acid sequence of Formula (IV); a HVR-H1 comprising the amino acid sequence of Formula (II) and a HVR-H2 comprising the amino acid sequence of Formula (V); a HVR-H1 comprising the amino acid sequence of Formula (II) and a HVR-H2 comprising the amino acid sequence of Formula (VI); a HVR-H1 comprising the amino acid sequence of Formula (I) and a HVR-H2 comprising the amino acid sequence of Formula (VI); a HVR-H1 comprising the amino acid sequence of Formula (III) and a HVR-H2 comprising the amino acid sequence of Formula (VI); a HVR-H1 comprising the amino acid sequence of Formula (III) and a HVR-H2 comprising the amino acid sequence of Formula (VII); a HVR-H1 comprising the amino acid sequence of Formula (II) and a HVR-H2 comprising the amino acid sequence of Formula (VIII); a HVR-H1 comprising the amino acid sequence of Formula (I) and a HVR-H2 comprising the amino acid sequence of Formula (V); a HVR-H1 comprising the amino acid sequence of Formula (III) and a HVR-H2 comprising the amino acid sequence of Formula (V); and a HVR-H1 comprising the amino acid sequence of Formula (I) and a HVR-H2 comprising the amino acid sequence of Formula (VIII). In some embodiments, the HVR-H1 and HVR-H2 are selected from the group consisting of: a HVR-H1 comprising the amino acid sequence of Formula (II) and a HVR-H2 comprising the amino acid sequence of Formula (XI); a HVR-H1 comprising the amino acid sequence of Formula (II) and a HVR-H2 comprising the amino acid sequence of Formula (XII); a HVR-H1 comprising the amino acid sequence of Formula (I) and a HVR-H2 comprising the amino acid sequence of Formula (XII); a HVR-H1 comprising the amino acid sequence of Formula (III) and a HVR-H2 comprising the amino acid sequence of Formula (XII); a HVR-H1 comprising the amino acid sequence of Formula (I) and a HVR-H2 comprising the amino acid sequence of Formula (XI); and a HVR-H1 comprising the amino acid sequence of Formula (III) and a HVR-H2 comprising the amino acid sequence of Formula (XI). In some embodiments, the HVR-H1 and HVR-H2 are selected from the group consisting of: a HVR-H1 comprising the amino acid sequence of Formula (I) and a HVR-H2 comprising the amino acid sequence of Formula (IV); a HVR-H1 comprising the amino acid sequence of Formula (III) and a HVR-H2 comprising the amino acid sequence of Formula (IV); a HVR-H1 comprising the amino acid sequence of Formula (II) and a HVR-H2 comprising the amino acid sequence of Formula (X); a HVR-H1 comprising the amino acid sequence of Formula (III) and a HVR-H2 comprising the amino acid sequence of Formula (IX); a HVR-H1 comprising the amino acid sequence of Formula (I) and a HVR-H2 comprising the amino acid sequence of Formula (X); a HVR-H1 comprising the amino acid sequence of Formula (III) and a HVR-H2 comprising the amino acid sequence of Formula (VIII); and a HVR-H1 comprising the amino acid sequence of Formula (III) and a HVR-H2 comprising the amino acid sequence of Formula (X). In some embodiments, the HVR-H1 and HVR-H2 are selected from the group consisting of: a HVR-H1 comprising the amino acid sequence of Formula (II) and a HVR-H2 comprising the amino acid sequence of Formula (XIII); a HVR-H1 comprising the amino acid sequence of Formula (I) and a HVR-H2 comprising the amino acid sequence of Formula (XIII); and a HVR-H1 comprising the amino acid sequence of Formula (III) and a HVR-H2 comprising the amino acid sequence of Formula (XIII).

(83) The heavy chain HVR sequences described herein may be included in any combination in an antibody heavy chain or heavy chain variable region of the present disclosure. In some embodiments, a heavy chain variable region comprises an HVR-H1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOS: 1-52 and 137-158, and a HVR-H2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOS:53-136 and 159-164. In some embodiments, a heavy chain variable region comprises an HVR-H1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOS: 1-52, and a HVR-H2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOS:53-136. In some embodiments, a heavy chain variable region comprises an HVR-H1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOS:1-52 and 137-158, and an HVR-H3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOS:223-256. In some embodiments, a heavy chain variable region comprises an HVR-H1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOS:1-52, and an HVR-H3 comprising

an amino acid sequence selected from the group consisting of SEQ ID NOS:223-256. In some embodiments, a heavy chain variable region comprises an HVR-H2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOS:53-136 and 159-164 and a HVR-H3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 223-256. In some embodiments, a heavy chain variable region comprises an HVR-H2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOS:53-136 and a HVR-H3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 223-256. In some embodiments, a heavy chain variable region comprises an HVR-H1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOS:1-52 and 137-158, an HVR-H2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOS:53-136 and 159-164, and a HVR-H3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 223-256. In some embodiments, a heavy chain variable region comprises an HVR-H1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOS:1-52, an HVR-H2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOS:53-136, and a HVR-H3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 223-256.

(84) In certain embodiments, a heavy chain variable region comprises three of a HVR-H1, a HVR-H2, and a HVR-H3, wherein the HVR-H1 and HVR-H2 are selected from the group consisting of: a HVR-H1 comprising the amino acid sequence of SEQ ID NO:157, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:63; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:1, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:122; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:138, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:63; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:154, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:63; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:158, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:161; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:158, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:63; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:145, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:128; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:22, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:61; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:31, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:63; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:153, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:63; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:155, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:67; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:156, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:100; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:51, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:162; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:138, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:123; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:139, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:110; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:8, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:126; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:13, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:129; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:31, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:124; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:25, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:130; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:150, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:132; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:158, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:162; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:12, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:82; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:149, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO: 117; and a HVR-H1 comprising the amino acid sequence of SEQ ID NO:7, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:134. In some embodiments, the HVR-H1 and HVR-H2 are selected from the group consisting of: a HVR-H1 comprising the amino acid sequence of SEQ ID NO:26, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:53; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:151, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:53; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:34, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:63; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:50, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:162; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:158, and a HVR-H2

comprising the amino acid sequence of SEQ ID NO:104; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:5, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:121; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:6, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:116; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:7, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:121; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:17, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:63; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:25, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:101; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:25, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO: 114; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:29, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:112; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:152, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:63; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:156, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:89; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:157, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:94; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:48, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:58; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:50, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:89; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:50, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:163; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:158, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:160; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:158, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:87; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:158, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:92; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:158, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:93; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:158, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:97; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:158, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:103; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:158, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:164; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:137, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:54; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:3, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:127; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:4, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:85; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:4, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:110; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:139, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:109; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:139, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:121; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:8, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:120; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:140, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:131; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:141, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:116; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:142, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:159; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:143, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO: 116; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:144, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:121; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:146, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:110; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:147, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:133; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:148, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:63; and a HVR-H1 comprising the amino acid sequence of SEQ ID NO:13, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:118.

(85) In some embodiments, a heavy chain variable region comprises three of a HVR-H1, a HVR-H2, and a HVR-H3, wherein the HVR-H1 and HVR-H2 are listed in Table 1. In some embodiments, the HVR-H3 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs:223-256. In some embodiments, a heavy chain variable region comprises a sequence selected from SEQ ID NOS: 169, 171, 173, 175, 177, 179, 181, 183, 185, 187, 189, 191, 193, and 195, or a sequence having at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least

97%, at least 98%, or at least 99% sequence identity to a sequence selected from SEQ ID NOS: 169, 171, 173, 175, 177, 179, 181, 183, 185, 187, 189, 191, 193, and 195.

(86) In some embodiments, a heavy chain variable region further comprises variable region heavy chain framework sequences juxtaposed between the HVRs according to the formula: (FW-H1)−(HVR-H1)−(FW-H2)−(HVR-H2)−(FW-H3)−(HVR-H3)−(FW-H4). In some embodiments, one, two, three, or four of the framework sequences is/are the following:

(87) TABLE-US-00002 (SEQ ID NO: 165) FW-H1 is EVQLVESGGGLVQPGGSLRLSCAASG (SEQ ID NO: 166) FW-H2 is RQAPGKGLEW (SEQ ID NO: 167) FW-H3 is TISRDNSKNTLYLQLNSLRAEDTAVYYC (SEQ ID NO: 168) FW-H4 is WGQGTLVTVSS.

(88) In some embodiments, the heavy chain variable region comprises an alternate FW-H3 sequence with an arginine to lysine mutation at R19 of SEQ ID NO:167. In some embodiments, one, two, three, or four of the framework sequences is/are an FW-H1 of SEQ ID NO:165, an FW-H2 of SEQ ID NO:166, an FW-H3 or SEQ ID NO:167 with an arginine to lysine mutation at R19, and an FW-H4 of SEQ ID NO:168.

(89) In some embodiments, further provided herein is an antibody comprising a heavy chain and a light chain, where the heavy chain includes a heavy chain variable region of the present disclosure, and where the light chain includes any light chain variable region (e.g., comprising a HVR-L1, HVR-L2, and HVR-L3) known in the art. In some embodiments, the antibody light chain variable region comprises an HVR-L1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 257-264. In some embodiments, the antibody light chain variable region comprises an HVR-L3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 265-274. In some embodiments, the antibody light chain variable region comprises an HVR-L1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 257-264, and an HVR-L3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 265-274. In some embodiments, the antibody light chain comprises any of the antibody light chain variable regions found in International Application No. PCT/CN2017/098333 and/or U.S. patent application Ser. No. 16/640,673 (the disclosures of which are each incorporated herein by reference in their entireties). In some embodiments, the antibody light chain comprises a light chain variable region comprising any of the HVR-L1, HVR-L2, and/or HVR-L3 sequences found in International Application No. PCT/CN2017/098333 and/or U.S. patent application Ser. No. 16/640,673 (the disclosures of which are each incorporated herein by reference in their entireties).

(90) IgG-derived scaffolds such as Fab and single chain Fv (scFv), as well as stabilized Fv or scFv, have been designed and prepared with the ability to specifically recognize and tightly bind antigens. Alternative protein scaffolds, or non-IgG like scaffolds, have been explored for analogous applications. Several protein families with non-Ig architecture such as the protein A, fibronectin, the ankyrin repeat, Adnectins, Affibodies, Anticalins, DARPins, engineered Kunitz inhibitors or the lipocalins, cyclic and polycyclic peptides can be empowered with novel binding sites by employing methods of combinatorial engineering, such as site-directed random mutagenesis in combination with phage display, yeast display, or other molecular selection techniques. These novel alternative binding reagents are collectively called engineered protein scaffolds, illustrating the fact that a rigid natural protein structure is used to modify an existing—or to implement a new—binding site for a prescribed target using the dynamic binding motifs or units introduced here. Compared with antibodies or their recombinant fragments, these protein scaffolds often provide practical advantages including elevated stability and high production yield in microbial expression systems. As these novel binding proteins are obtained by means of a biomolecular engineering process in order to achieve tight target-binding activity, they may also be subjected to further selection schemes focused at other desired properties (such as solubility, thermal stability, protease resistance etc.). Consequently, engineered protein scaffolds have become attractive for many applications in biotechnology and biomedical research, especially for multi-specific binding motifs. The effort to generate such an alternative binding protein with beneficial properties are directed toward therapeutic use with special emphasis on biomolecular structure and function as well as on approaches toward clinical application.

(91) In some embodiments, further provided herein is one or more polypeptides (e.g., a scaffold polypeptide, including IgG-derived scaffold polypeptides (such as Fabs, single chain Fvs, and stabilized Fvs) or non-IgG-derived scaffold polypeptides (such as protein A, fibronectin, ankyrin repeat, Adnectins, Affibodies, Anticalins, DARPins, engineered Kunitz inhibitors or the lipocalins, cyclic and polycyclic peptides)) comprising one or more HVRs described herein. In some embodiments, the polypeptide comprises an HVR-H1 comprising an amino acid sequence selected from any HVR-H1 sequence of the present disclosure (e.g., X1TFX2X3YX4IHWV, wherein X1 is F or Y, X2 is S or T, X3 is D, G, N, or S, and X4 is A, G, or W (SEQ

ID NO:198); YSIX1SGX2X3WX4WI, wherein X1 is S or T, X2 is H or Y, X3 is H or Y, and X4 is A, D, G, N, S, or T (SEQ ID NO:199); and FSLSTX1GVX2VX3WI, wherein X1 is G or S, X2 is A or G, and X3 is A, G, S, or T (SEQ ID NO:200); and SEQ ID NOS:1-52 and 137-158). In some embodiments, the polypeptide comprises an HVR-H2 comprising an amino acid sequence selected from any HVR-H2 of the present disclosure (e.g., LAX1IX2WX3X4DKX5YSX6SLKSRL, wherein X1 is L or R, X2 is D or Y, X3 is A, D, S, or Y, X4 is D or G, X5 is R, S, or Y, and X6 is P or T (SEQ ID NO:201); IGX1IX2X3SGSTYYSPSLKSRV, wherein X1 is A, D, E, S, or Y, X2 is S or Y, and X3 is H or Y (SEQ ID NO:202); IGXIIYX2SGX3TX4YNPSLKSRV, wherein XI is D, E, R, S, or Y, X2 is H or Y, X3 is N or S, and X4 is N or Y (SEQ ID NO:203); VSX1ISGX2GX3X4TYYADSVKGRF, wherein X1 is A, G, S, V, or Y, X2 is A, D, S, or Y, X3 is D, G, or S, and X4 is S or T (SEQ ID NO:204); IGX1INPNX2GX3TX4YAQKFQGRV, wherein X1 is I, R, or W, X2 is F or R, X3 is D, G, or S, and X4 is K or N (SEQ ID NO:205); IGX1IX2PSX3GX4TX5YAQKFQGRV, wherein X1 is I, R, or W, X2 is S or Y, X3 is G or S, X4 is D, G, or S, and X5 is K or N (SEQ ID NO:206); VGRIX1SKX2X3GX4TTX5YAAX6VKGRF, wherein X1 is K or R, X2 is A or T, X3 is D or Y, X4 is G or Y, X5 is D or E, and X6 is P or S (SEQ ID NO:207); IGX1IX2X3SGSTYYSPSLKSRV, wherein XI is A, D, or E, X2 is S or Y, and X3 is H or Y (SEQ ID NO:208); IGXIIYX2SGX3TX4YNPSLKSRV, wherein X1 is D, E, or S, X2 is H or Y, X3 is N or S, and X4 is N or Y (SEQ ID NO:209); and VGRIX1SKX2X3GX4TTEYAAX5VKGRF, wherein X1 is K or R, X2 is A or T, X3 is D or Y, X4 is G or Y, and X5 is P or S (SEQ ID NO:210); and SEQ ID NOS:53-136 and 159-164). In some embodiments, the polypeptide comprises an HVR-H3 comprising an amino acid sequence selected from any HVR-H3 sequence of the present disclosure (e.g., SEQ ID NOs: 223-256). In some embodiments, the polypeptide comprises an HVR-L1 comprising an amino acid sequence selected from any HVR-L1 sequence of the present disclosure (e.g., SEQ ID NOs: 257-264). In some embodiments, the polypeptide comprises an HVR-L3 comprising an amino acid sequence selected from any HVR-L3 sequence of the present disclosure (e.g., SEQ ID NOs: 265-274).

(92) In some embodiments, the polypeptide comprises two or more (e.g., two or more, three or more, four or more, or all five) of the HVR-H1, HVR-H2, HVR-H3, HVR-L1, and/or HVR-L3 sequences described herein. In some embodiments, the polypeptide comprises two of the HVR-H1, HVR-H2, HVR-H3, HVR-L1, and/or HVR-L3 sequences described herein, wherein the two are a HVR-H1 and a HVR-H2; a HVR-H1 and a HVR-H3; a HVR-H1 and a HVR-L1; a HVR-H1 and a HVR-L3; a HVR-H2 and a HVR-H3; a HVR-H2 and a HVR-L1; a HVR-H2 and a HVR-L3; a HVR-H3 and a HVR-L1; a HVR-H3 and a HVR-L3; or a HVR-L1 and a HVR-L3. In some embodiments, the polypeptide comprises three of the HVR—H1, HVR-H2, HVR-H3, HVR-L1, and/or HVR-L3 sequences described herein, wherein the three are a HVR-H1, a HVR-H2, and a HVR-H3; a HVR-H1, a HVR-H2, and a HVR-L1; a HVR-H1, a HVR-H2, and a HVR-L3; a HVR-H1, a HVR-H3, and a HVR-L1; a HVR-H1, a HVR-H3, and a HVR-L3; a HVR-H1, a HVR-L1 and a HVR-L3; a HVR-H2, a HVR-H3, and a HVR-L1; a HVR-H2, a HVR-H3, and a HVR-L3; a HVR-H2, a HVR-L1, and a HVR-L3; or a HVR-H3, a HVR-L1, and a HVR-L3. In some embodiments, the polypeptide comprises four of the HVR-H1, HVR-H2, HVR-H3, HVR-L1, and/or HVR-L3 sequences described herein, wherein the four are a HVR-H1, a HVR-H2, a HVR-H3, and a HVR-L1; a HVR-H1, a HVR-H2, a HVR-H3, and a HVR-L3; a HVR-H1, a HVR-H2, a HVR-L1, and a HVR-L3; a HVR-H1, a HVR-H3, a HVR-L1, and a HVR-L3; or a HVR-H2, a HVR-H3, a HVR-L1, and a HVR-L3. In some embodiments, the polypeptide comprises five of the HVR-H1, HVR-H2, HVR-H3, HVR-L1, and/or HVR-L3 sequences described herein, wherein the five are a HVR-H1, a HVR-H2, a HVR-H3, a HVR-L1, and a HVR-L3.

(93) In some embodiments, further provided herein is an antibody fragment or scFv comprising a light chain variable region and a heavy chain variable region of the present disclosure.

(94) In some embodiments, an antibody or antibody fragment of the present disclosure binds at least 1 target (e.g., a target protein or an epitope) or at least two targets with particular binding affinities. For example, in some embodiments, an antibody or antibody fragment of the present disclosure binds at least 1 target or at least two targets with an equilibrium dissociation constant (Kd) of about 10.sup.−7 M or less, 10.sup.−8 M or less, 10.sup.−9 M or less, 10.sup.−10 M or less, or 10.sup.−11 M or less. In some embodiments, an antibody or antibody fragment of the present disclosure binds at least 1 target or at least two targets with an equilibrium dissociation constant (Kd) of between about 10.sup.−7 and about 10.sup.−11 M. Exemplary assays for determining binding affinity are described and exemplified infra (See e.g., the ForteBio assay of Example 4 below).

(95) In some embodiments, an antibody or antibody fragment of the present disclosure has a melting temperature (Tm) of at least 60° C. For example, in some embodiments, an antibody or antibody fragment of

the present disclosure has a Tm of between about 60° C. and about 90° C., between about 65° C. and about 90° C., between about 70° C. and about 90° C., between about 75° C. and about 90° C., between about 80° C. and about 90° C., between about 85° C. and about 90° C., or at least about 65° C., at least about 70° C., at least about 72° C., at least about 75° C., at least about 80° C., or at least about 85° C. In some embodiments, an antibody or antibody fragment of the present disclosure has a Tm of between about 60° C. and about 90° C. Various methods of measuring Tm for an antibody or antibody fragment are known in the art. Exemplary assays for determining antibody Tm are described and exemplified infra (See e.g., the DSF assay of Example 4 below).

(96) Antibodies of the present disclosure may be produced using recombinant methods and compositions, e.g., as described in U.S. Pat. No. 4,816,567. In some embodiments, isolated nucleic acids encoding any antibody described herein are provided. Such nucleic acids may encode an amino acid sequence comprising the V.sub.L and/or an amino acid sequence comprising the VH of the antibodies (e.g., the light and/or heavy chains of the antibodies). In some embodiments, one or more vectors (e.g., expression vectors) comprising such nucleic acids are provided herein. In some embodiments, a host cell comprising such nucleic acids is provided. In one such embodiment, a host cell comprises (e.g., has been transformed with): (1) a vector comprising a nucleic acid that encodes an amino acid sequence comprising the V.sub.L of the antibody and an amino acid sequence comprising the V.sub.H of the antibody, or (2) a first vector comprising a nucleic acid that encodes an amino acid sequence comprising the V.sub.L of the antibody and a second vector comprising a nucleic acid that encodes an amino acid sequence comprising the VH of the antibody. In some embodiments, the host cell is eukaryotic, e.g. a Chinese Hamster Ovary (CHO) cell or lymphoid cell (e.g., Y0, NS0, Sp20 cell). In some embodiments, a method of making an antibody is provided, wherein the method comprises culturing a host cell comprising a nucleic acid encoding the antibody, as provided above, under conditions suitable for expression of the antibody, and optionally recovering the antibody from the host cell (or host cell culture medium).

(97) For recombinant production of antibodies of the present disclosure, nucleic acid encoding an antibody, e.g., as described above, is isolated and inserted into one or more vectors for further cloning and/or expression in a host cell. Such nucleic acid may be readily isolated and sequenced using conventional procedures (e.g., by using oligonucleotide probes that are capable of binding specifically to genes encoding the heavy and light chains of the antibody).

(98) Suitable host cells for cloning or expression of antibody-encoding vectors include prokaryotic or eukaryotic cells. For example, antibodies may be produced in bacteria, in particular when glycosylation and Fc effector function are not needed. For expression of antibody fragments and polypeptides in bacteria, see, e.g., U.S. Pat. Nos. 5,648,237, 5,789,199, and 5,840,523. (See also Charlton, *Methods in Molecular Biology, Vol.* 248 (B.K.C. Lo, ed., Humana Press, Totowa, NJ, 2003), pp. 245-254, describing expression of antibody fragments in *E. coli*.) After expression, the antibody may be isolated from the bacterial cell paste in a soluble fraction and may be further purified.

(99) In addition to prokaryotes, eukaryotic microbes such as filamentous fungi or yeast are suitable cloning or expression hosts for antibody-encoding vectors, including fungi and yeast strains whose glycosylation pathways have been “humanized,” resulting in the production of an antibody with a partially or fully human glycosylation pattern. See Gerngross, Nat. Biotech. 22:1409-1414 (2004), and Li et al., Nat. Biotech. 24:210-215 (2006).

(100) Suitable host cells for the expression of glycosylated antibody are also derived from multicellular organisms (invertebrates and vertebrates). Examples of invertebrate cells include plant and insect cells. Numerous baculoviral strains have been identified which may be used in conjunction with insect cells, particularly for transfection of *Spodoptera frugiperda* cells.

(101) Plant cell cultures can also be utilized as hosts. See, e.g., U.S. Pat. Nos. 5,959,177, 6,040,498, 6,420,548, 7,125,978, and 6,417,429 (describing PLANTIBODIES™ technology for producing antibodies in transgenic plants).

(102) Vertebrate cells may also be used as hosts. For example, mammalian cell lines that are adapted to grow in suspension may be useful. Other examples of useful mammalian host cell lines are monkey kidney CV1 line transformed by SV40 (COS-7); human embryonic kidney line (293 or 293 cells as described, e.g., in Graham et al., *J. Gen Virol.* 36:59 (1977)); baby hamster kidney cells (BHK); mouse sertoli cells (TM4 cells as described, e.g., in Mather, *Biol. Reprod.* 23:243-251 (1980)); monkey kidney cells (CV1); African green monkey kidney cells (VERO-76); human cervical carcinoma cells (HELA); canine kidney cells (MDCK; buffalo rat liver cells (BRL 3A); human lung cells (W138); human liver cells (Hep G2); mouse mammary

tumor (MMT 060562); TRI cells, as described, e.g., in Mather et al., *Annals N.Y. Acad. Sci.* 383:44-68 (1982); MRC 5 cells; and FS4 cells. Other useful mammalian host cell lines include Chinese hamster ovary (CHO) cells, including DHFR-CHO cells (Urlaub et al., *Proc. Natl. Acad. Sci. USA* 77:4216 (1980)); and myeloma cell lines such as Y0, NS0 and Sp2/0. For a review of certain mammalian host cell lines suitable for antibody production, see, e.g., Yazaki and Wu, *Methods in Molecular Biology, Vol.* 248 (B.K.C. Lo, ed., Humana Press, Totowa, NJ), pp. 255-268 (2003).

(103) Bispecific Antibodies with Identical/Common/Single Heavy Chains

(104) Further provided herein is a bispecific antibody having an identical heavy chain variable region of the present disclosure (e.g., having two light chain variable regions with different binding specificities and two identical heavy chain variable regions). In some embodiments, the bispecific antibody comprises two different light chains, wherein the first light chain comprises a kappa C.sub.L domain (e.g., a human kappa C.sub.L domain), and the second light chain comprises a lambda C.sub.L domain (e.g., a human lambda C.sub.L domain). Methods of making and/or purifying bispecific antibodies comprising a kappa C.sub.L domain and a lambda CL domain are known in the art (See e.g., Fischer et al. (2015), *Nat. Commun.* 6:6113; US20140179547). For example, a bispecific antibody comprising: a) two identical heavy chain variable regions (e.g., any one of the heavy chain variable regions described herein), b) a first light chain comprising a first light chain variable region and a kappa C.sub.L domain, and c) a second light chain comprising a second light chain variable region and a lambda CL domain (e.g., the constant region of a second light chain comprising a kappa C.sub.L domain is switched with a lambda C.sub.L domain) may be constructed and expressed (e.g., cloned into one or more expression vectors and expressed in one or more suitable host cells). The resulting bispecific IgG constructed in this way (e.g., comprising both a kappa and a lambda C.sub.L domain) may be purified using the following steps: first, total IgGs are recovered from the culture supernatant using protein A or IgG-C.sub.H1 Capture Select affinity chromatography, resulting in the elimination of free light chains and other contaminants; next, IgGs containing a kappa C.sub.Ldomain are captured using KappaSelect affinity resin, and monospecific IgGs with light chains containing only lambda CL domains are eliminated in the column flow through; finally, pure bispecific kappa-lambda-bodies are recovered using LambdaFabSelect affinity resin, and separated from the monospecific IgGs with light chains containing only kappa C.sub.L domains that do not bind to the resin. Alternatively, the bispecific common heavy chain IgG (e.g., as described above) can be purified by protein A and resolved using resins specific to each light chain C.sub.L domain based on differences in one or more biophysical properties of the differing light chains (such as different molecular weights, different isoelectric points (pI), etc.).

(105) In some embodiments, the bispecific antibody comprises two antibody light chain variable regions and two identical heavy chain variable regions, where the bispecific antibody includes: a first binding domain that binds to a first target or antigen and comprises a first antibody light chain variable region and a first heavy chain variable region; and a second binding domain that binds to a second target or antigen and comprises a second antibody light chain variable region and a second antibody heavy chain variable region; where the second antibody heavy chain variable region has a sequence identical to the first antibody heavy chain variable region sequence. In some embodiments, the first and second binding domains bind to different target biomolecules. In some embodiment, the first and second binding domains bind to different epitopes on a same biomolecule. In some embodiments, the first antibody heavy chain variable region is part of a first antibody heavy chain comprising the first heavy chain variable region and a first heavy chain constant region (e.g., comprising CH1, hinge, CH2 and CH3). In some embodiments, the second antibody heavy chain variable region is part of a second antibody heavy chain comprising the second heavy chain variable region and a second heavy chain constant region (e.g., comprising CH1, hinge, CH2 and CH3). In some embodiments, the first antibody light chain variable region is part of a first antibody light chain comprising the first light chain variable region and a first light chain constant region. In some embodiments, the second antibody light chain variable region is part of a second antibody light chain comprising the second light chain variable region and a second light chain constant region. In some embodiments, the first and the second antibody heavy chains have sequences identical to a heavy chain of the present disclosure.

(106) Further provided herein is a method of generating a bispecific antibody having an identical heavy chain variable region of the present disclosure (e.g., having two light chain variable regions with different binding specificities and two identical heavy chain variable regions). In some embodiments, the method includes (a) selecting a first antigen binding domain that binds to a first antigen and comprises a first antibody light chain variable region and a first heavy chain variable region of the present disclosure; (b) selecting a second antigen binding domain that binds to a second antigen and comprises a second antibody light chain variable

region and a second heavy chain variable region of the present disclosure, where the second antibody heavy chain variable region has a sequence identical to the first antibody heavy chain variable region sequence; and (c) producing the bispecific antibody comprising a light chain variable region comprising the amino acid sequence of the first antibody light chain variable region, a light chain variable region comprising the amino acid sequence of the second antibody light chain variable region, a heavy chain variable region comprising the amino acid sequence of the first antibody heavy chain variable region sequence, and a heavy chain variable region comprising the amino acid sequence of the second antibody heavy chain variable region sequence. In some embodiments, the first heavy chain variable region is encoded by a polynucleotide from a library of the present disclosure.

(107) In some embodiments, bispecific antibodies described herein may have additional specificities. For example, one of the antigen or target binding sites of the bispecific antibody may bind to more than one target specifically.

(108) Methods for making/generating bispecific antibodies are known in the art. Production of full length bispecific antibodies can be based on the co-expression of two immunoglobulin heavy chain-light chain pairs, where the two chains have different specificities (Millstein et al., Nature, 305:537-539 (1983)). Because of the random assortment of immunoglobulin heavy and light chains, these hybridomas (quadromas) produce a potential mixture of 10 different antibody molecules, of which only one has the correct bispecific structure. Purification of the correct molecule, which is usually done by affinity chromatography steps, is rather cumbersome, and the product yields are low. Similar procedures are disclosed in WO 93/08829, and in Traunecker et al., *EMBO J.,* 10:3655-3659 (1991).

V. Kits

(109) In another aspect, provided herein is a kit comprising a library of polynucleotides of the present disclosure. In some embodiments, the kit further comprises a package insert comprising instructions for expressing, modifying, screening, or otherwise using the library, e.g., to identify an antibody HVR or variable region of interest. In some embodiments, the kit further comprises one or more buffers, e.g., for storing, transferring, transfecting, or otherwise using one or more of the polynucleotides (e.g., synthetic polynucleotides). In some embodiments, the kit further comprises one or more containers for storing one or more of the polynucleotides. In some embodiments, the kit further comprises one or more vectors, e.g., for transfection of a host cell with one or more of the polynucleotides.

EXAMPLES

(110) The present disclosure will be more fully understood by reference to the following examples. The examples should not, however, be construed as limiting the scope of the present disclosure. It is understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and scope of the appended claims.

Example 1: Identification of the Minimal Set of Dynamic Motifs on Hypervariable Regions

(111) To understand variability of antibody variable domains at a structural level, an algorithm was developed to map the geometric alignment for antibody variable domains, and further, to calculate the structural and sequence entropy based upon the geometric alignment. Taking such an approach combines the classical theory of antibody diversity being determined by the well-established process of V(D)J recombination coupled with conformational diversity from dynamic units (template-directed conformational selection by Linus Pauling; See e.g., James, L. and Tawfik, D. “Conformational diversity and protein evolution—a 60-year-old hypothesis revisited”, Trends Biochem Sci. 2003 July; 28(7):361-8) to allow sampling of an almost infinite epitope space by selection and adaptation of antibody binding sites. As an example, this algorithm was used to analyze the structural and sequence variability of 113 high-resolution crystal structures of human antibody variable heavy chain domains. Entropy was calculated and plotted for every position of the variable heavy chain domain, (FIG. **1**A; structural entropy in bold line, sequence entropy in dotted line). The results obtained by calculating the structural and sequence entropy based upon geometric alignment were used to locate the hyper-variable (HVR) regions, and to identify the critical positions on these variable regions. For comparison, the HVRs (as defined by the methodology described above) and CDRs (as defined by Kabat) were identified for an exemplary antibody heavy chain variable domain sequence (FIG. **1**B).

(112) Interestingly, variability as assessed by structural alignments was generally lower than the variability observed with sequence alignments. While variability was generally lower as assessed by structural alignments, there were a number of sites/regions with dramatic structural variation, suggesting these variable

sites may play critical roles in antibody function. Furthermore, some of those hyper-variable regions showed high flexibility with multiple conformations. The identification of regions of highly variable residues gave a more comprehensive picture of the conservation and variability of antibody variable domains that could be exploited in new antibody designs. The identification of the dynamic motif made it possible to cover a wide range of structural diversity with a reduced number of amino acid sequences. The surprising advantage of this approach to antibody design was that a more limited number of dynamic motifs could be employed in the variable regions to cover a wide range of antibody structural diversity and provide broad flexibility in these antibodies which may allow binding to multiple antigens of interest. As such, dynamic heavy chain libraries were constructed using single human germline or germline-derived sequences for the invariant residues, while a limited number of dynamic motifs (as compared to 10.sup.6, 10.sup.10 or more) were used in the hyper-variable regions HVR_H1 and HVR_H2 to capture the wide range of structural variability identified in these two regions.

Example 2: Construction of the Common Heavy Chain Libraries

(113) Construction of the Heavy Chain Libraries

(114) To begin construction of the heavy chain libraries, 3 groups of degenerate oligos were designed for the variable region HVR-H1 based on the formulas shown in Table 2, resulting in 112 unique HVR-H1 sequences. 7 groups of degenerate oligos were designed for the variable region HVR-H2 based on the formulas shown in Table 2, resulting in 565 unique HVR-H2 sequences. The synthesized degenerate oligos were converted into double stranded DNA through the following protocol: 0.75 pL of 0.2 μM template oligos were mixed with 10 pL 5× PrimeSTAR buffer, 4 μL dNTP mixture, 1 μL of 100 μM forward primer, 1 μL of 100 μM reverse primer, 0.5 μL of PrimeSTAR HS DNA Polymerase (2.5 U/μL), and 33 μL of water. The PCR solutions were preheated at 96° C. for 5 minutes, then 14 cycles (96° C. for 15 seconds, 60° C. for 15 seconds, 72° C. for six seconds) were performed, followed by extension at 72° C. for three minutes. The VH_vr1s were amplified using the primer pair F_1999 (CGTTTGTCCTGTGCAGCTTCCGG) (SEQ ID NO:211) and R_1999 (CGAGGCCCTTACCCGGGGCCTGACG) (SEQ ID NO:212), while VH_vr2s were amplified using the primer pair F_2003 (CCGGGTAAGGGCCTCGAGTGG) (SEQ ID NO:213) and R_2003 (GAGCACGTCCGTTCGAATTGTCGCGACTTATAG) (SEQ ID NO:214).

(115) The double stranded VH_vr1s and VH_vr2s were joined together through overlapping sequences at their 5′ or 3′ ends. The protocol used was as follows: 20 ng of VH_vr1 and 20 ng of VH_vr2 templates were mixed with 10 μL 5× PrimeSTAR buffer, 4 μL dNTP mixture, 1 μL of 100 μM F_1999 primer, 1 μL of 100 μM R_2003 primer, 0.5 μL of PrimeSTAR HS DNA Polymerase (2.5 U/μL), and water (up to 50 μL), and the mixtures were preheated at 96° C. for 5 minutes, then 14 cycles (96° C. for 15 seconds, 60° C. for 15 seconds, 72° C. for 10 seconds) were performed, followed by extension at 72° C. for three minutes. These PCR fragments were then purified through gel electrophoresis (GENEray Gel Extraction kit), digested with BspEI and BstBI (Thermo Scientific), and subsequently cloned into a filter vector FTV014 digested with the same two enzymes. The ligation mixture was transformed into DH10B cells by electroporation, and the number of colonies exceeding 10 fold of calculated diversity was collected for plasmid preparation. The purified plasmids constituted library VH-vr12

(116) TABLE-US-00003 TABLE 2 formulas for HVR-H1 and HVR-H2 designed variant sequences X.sub.1 X.sub.2 X.sub.3 X.sub.4 X.sub.5 X.sub.6 Amino Acid Sequence Residue Residue Residue Residue Residue Residue Variant Group Formula Identity Identity Identity Identity Identity identity HVR-H1_A X1TFX2X3YX4IHWV F, Y S, T D, G, N, A, G, W n/a n/a (SEQ ID NO: 198) S HVR-H1_B YSIX1SGX2X3WX4WI S, T H, Y H, Y A, D, G, n/a n/a (SEQ ID NO: 199) N, S, T HVR-H1_C FSLSTX1GVX2VX3WI G, S A, G A, G, S, n/a n/a n/a (SEQ ID NO: 200) T HVR-H2_A LAX1IX2WX3X4DKX5Y L, R D, Y A, D, S, D, G R, S, Y P, T (SEQ ID NO: 201) SX6SLKSRL Y HVR-H2_B IGX1IX2X3SGSTYYSPS A, D, E, S, Y H, Y n/a n/a n/a (SEQ ID NO: 202) LKSRV S, Y HVR-H2_C IGX1IYX2SGX3TX4YNP D, E, R, H, Y N, S N, Y n/a n/a (SEQ ID NO: 203) SLKSRV S, Y HVR-H2_D VSX1ISGX2GX3X4TYY A, G, S, A, D, S, D, G, S S, T n/a n/a (SEQ ID NO: 204) ADSVKGRF V, Y Y HVR-H2_E IGX1INPNX2GX3TX4YA I, R, W F, R D, G, S K, N n/a n/a (SEQ ID NO: 205) QKFQGRV HVR-H2_F IGX1IX2PSX3GX4TX5Y I, R, W S, Y G, S D, G, S K, N n/a (SEQ ID NO: 206) AQKFQGRV HVR-H2_G VGRIX1SKX2X3GX4TT K, R A, T D, Y G, Y D, E P, S (SEQ ID NO: 207) X5YAAX6VKGRF n/a, not applicable.

(117) Hundreds of degenerate oligos encoding the VH_vr3 with sequence diversity approaching 10.sup.5 were designed and synthesized, and converted into double strand DNA through the following protocol: 0.75

μL of 0.2 μM template oligos were mixed with 10 μL 5× PrimeSTAR buffer, 4 μL dNTP mixture, 1 μL of 100 μM forward primer, 1 μL of 100 μM reverse primer, 0.5 μL of PrimeSTAR HS DNA Polymerase (2.5 U/pL), and 33 μL of water. The PCR solutions were preheated at 96° C. for 5 minutes, then 14 cycles (96° C. for 15 seconds, 60° C. for 15 seconds, 72° C. for six seconds) were performed, followed by extension at 72° C. for three minutes. The forward primer was S1089 (ACAACTGAACAGCTTAAGAGCTGAGGACACTGCCGTCTATTATTG) (SEQ ID NO:215) and the reverse primer was S1090 (GAGGAGACGGTGACTAGTGTTCCTTGACCCCA) (SEQ ID NO:216). The resulting synthesized DNAs were then purified through gel electrophoresis (GENEray Gel Extraction kit), digested with AflII and SpeI (Thermo Scientific), and subsequently cloned into the filter vector FTV012 digested with the same two restriction enzymes. The ligation mixture was transformed into DH10B cells by electroporation, and the number of colonies exceeding 10 fold of calculated diversity was collected for plasmid preparation. The purified plasmids constituted library VH-vr3.

(118) To assemble the full length VH library, the purified VH-vr3 library plasmid mixture was digested with AflII and SpeI (NEB), and the vr3-encoding fragments were purified through gel electrophoresis (GENEray Gel Extraction kit), and cloned into the VH-vr12 library plasmid mixture digested with the same two restriction enzymes. The ligation products were desalted (QIAquick® PCR Purification Kit (QIAGEN)) before rolling circle amplification (RCA) was performed. RCA was carried out as follows: 40 ng ligation products were mixed with 10 μL 10× NEBuffer 4, 50 μL of 100 μM pd(N)8, and water (up to 88.5 tL), heated to 95° C. for three minutes, and annealed for 65 cycles (30 second each cycle) with each cycle decreasing by 1° C. The annealed reactions were incubated overnight at 30° C. after the addition of 10 μL of 10 mM dNTP mix, 1 μL of 100× BSA, and 0.5 μL of Phi29 DNA polymerase. The RCA products were first digested with NotI, DNA fragments were purified (QIAquick® PCR Purification Kit), and further digested with XhoI. The digested products were then ligated with T4 DNA ligase (Thermo Scientific). After purification through ethanol precipitation, the ligation products were transformed into DH10B cells by electroporation. The purified plasmids constituted library VH-vr123. These constructs each shared the same framework regions, namely FW-H1 (SEQ ID NO:165), FW-H2 (SEQ ID NO:166), FW-H3 (SEQ ID NO:167), and FW-H4 (SEQ ID NO:168).

(119) The above-mentioned mixtures of plasmids for the two heavy chain libraries were digested with PvuI and Acc65I, and ligated into the phagemid vector Fad40 that was also digested with the same two restriction enzymes. The ligation mixtures were transformed into DH10B cells, the resulting libraries were purified, quantified, and stored for the assembly of the complete phagemid library.

(120) Construction of the VL Library

(121) To begin construction of the light chain libraries, 18 groups of degenerate oligos and 5 defined oligos were designed for the variable region VL_vr1 and VL_vr2 respectively. They were converted into double stranded DNA through the following protocol: 0.75 μL of 0.2 μM template oligos were mixed with 10 μL 5× PrimeSTAR buffer, 4 μL dNTP mixture, 1 μL of 100 μM forward primer, 1 μL of 100 μM reverse primer, 0.5 μL of PrimeSTAR HS DNA Polymerase (2.5 U/μL), and 33 μL of water. The PCR solutions were preheated at 96° C. for 5 minutes, then 14 cycles (96° C. for 15 seconds, 60° C. for 15 seconds, 72° C. for six seconds) were performed, followed by extension at 72° C. for three minutes. The VL_vr1s were amplified using the primer pair F_2898 (TACTTATGTAGGCGATCGGGTCACCATCACCTGC) (SEQ ID NO:217) and R_2898 (CGGAGCTTTTCCTGGTTTCTGTTGATAC) (SEQ ID NO:218), while VL_vr2s were amplified using the primer pair F_2013 (GAAACCAGGAAAAGCTCCGAAG) (SEQ ID NO:219) and R_2013 (CGTCCCGGAACCGGATCCAGAGAAGCGAG) (SEQ ID NO:220).

(122) The double stranded VL_vr1s and VL_vr2s were joined together through overlapping sequences at their 5′ or 3′ ends. The protocol used was as follows: 20 ng of VL_vr1 and 20 ng of VL_vr2 templates were mixed with 10 μL 5× PrimeSTAR buffer, 4 μL dNTP mixture, 1 μL of 100 μM F_2898 primer, 1 μL of 100 μM R_2013 primer, 0.5 μL of PrimeSTAR HS DNA Polymerase (2.5 U/μL), and water (up to 50 μL), and the mixtures were preheated at 96° C. for 5 minutes, then 14 cycles (96° C. for 15 seconds, 60° C. for 15 seconds, 72° C. for 10 seconds) were performed, followed by extension at 72° C. for three minutes. These PCR fragments were then purified through gel electrophoresis (GENEray Gel Extraction kit), digested with PvuI and BamHI (Thermo Scientific), and subsequently cloned into a filter vector FTV015 digested with the same two enzymes. The ligation mixture was transformed into DH10B cells by electroporation, and the number of colonies exceeding 10 fold of calculated diversity was collected for plasmid preparation. The purified plasmids constituted library VL-vr12.

(123) 22 groups of degenerate oligos encoding VL_vr3 were designed, synthesized, and converted into

double stranded DNA through the following protocol: 0.75 μL of 0.2 μM template oligos were mixed with 10 μL 5× PrimeSTAR buffer, 4 μL dNTP mixture, 1 μL of 100 μM forward primer F2929 (ACCATCAGCAGTCTGCAGCCGGAAGACTTCGCAAC) (SEQ ID NO:221), 1 μL of 100 μM reverse primer R2929 (GATCTCCACCTTGGTACCCTGTCCGAA) (SEQ ID NO:222), 0.5 μL of PrimeSTAR HS DNA Polymerase (2.5 U/μL), and 33 μL of water. The PCR solutions were preheated at 96° C. for 5 minutes, then 14 cycles (96° C. for 15 seconds, 60° C. for 15 seconds, 72° C. for six seconds) were performed, followed by extension at 72° C. for three minutes. The double stranded DNAs encoding the VL_vr3 were then purified through gel electrophoresis (GENEray Gel Extraction kit), digested with PstI and Acc65I (Thermo Scientific), and subsequently cloned into the filter vector FTVO13 digested with the same two restriction enzymes. The ligation mixture was transformed into DH10B cells by electroporation, and the number of colonies exceeding 10 fold of calculated diversity was collected for plasmid preparation. The purified plasmids constituted library VL-vr3.

(124) To assemble the full length VL library, the purified VL-vr3 library plasmid mixture was digested with PstI and Acc65I (NEB), and the vr3-encoding fragments were purified through gel electrophoresis (GENEray Gel Extraction kit), and subsequently cloned into VL-vrl2 library plasmid mixture that had been digested with the same two restriction enzymes. The ligation products were transformed into DH10B cells by electroporation, and the number of colonies exceeding 10 fold of calculated diversity was collected for plasmid preparation. The purified plasmids constituted library VL-vr123. The vr123 inserts from the library plasmids VL-vr123 were then moved into the phagemid vector Fad40, using the restriction enzymes PvuI and Acc65I. The size of the library containing Fad40-vr123 reached 4*10.sup.7.

(125) Construction of the Complete Dynamic Library

(126) The dynamic library was composed of the heavy chain library derived from the VH-vr123 library and the light chain library derived from the Fad40-vr123 library. Both the VH-vr123 library plasmids and the Fad40-vr123 library plasmids were digested with BspEI and SpeI (Thermo Scientific). The DNA fragments encoding the heavy chain derived from the VH-vr123 library were cloned into the vector backbones derived from Fad40-vr123 library. The ligation products were desalted (QIAquick® PCR Purification Kit (QIAGEN)) before rolling circle amplification (RCA). RCA was carried out as follows: 40 ng ligation products were mixed with 10 μL 10× NEBuffer 4, 50 μL of 100 μM pd(N)8, and water (up to 88.5 μL), heated to 95° C. for three minutes, and annealed for 65 cycles (30 second each cycle) with each cycle decreasing by 1° C. The annealed reactions were incubated overnight at 30° C. after the addition of 10 μL of 10 mM dNTP mix, 1 μL of 100× BSA, and 0.5 μL of Phi29 DNA polymerase. The RCA products were first digested with NotI, DNA fragments were purified (QIAquick® PCR Purification Kit), and further digested with Acc65I. The digested products were then ligated with T4 DNA ligase (Thermo Scientific). After purification through ethanol precipitation, the ligation products were transformed into ER2738 cells by electroporation. A total number of 1.4*10.sup.10 colonies were collected from plates (2×YT, 1% glucose, 100 μg/mL ampicillin) to make the DPL6 library.

Example 3: Screening the Common Heavy Chain Libraries to Isolate Antibodies of Interest

(127) Preparation of Dynamic Library Phagemid Particles

(128) To prepare the dynamic library phagemid particles for antigen panning, 5.0 liters of ER2738 cells harboring the dynamic library (described in Example 2 above) were inoculated in media containing 2×YT, 2% glucose, 100 μg/mL ampicillin and 12.5 g/mL tetracycline at a starting OD.sub.600 of 0.1. The cultures were grown at 37° C., shaking at 250 rpm, until they reached OD.sub.600 of 0.6-0.8. The cells were then infected with M13KO7 helper phages at a multiplicity of infection (MOI) of 10 for 30 minutes at 37° C. The infected ER2738 cells were grown overnight at 22° C. in 3.2 liters of media containing 2×YT, 100 μg/mL ampicillin and 50 μg/mL kanamycin. Culture supernatants were then harvested by centrifugation at 10,000 rpm for 15 minutes, and filtered through a 0.45 μm low-binding membrane filter (Corning). The phagemid particles were then precipitated from the filtered supernatant using PEG/NaCl, and resuspended in PBS. An additional round of PEG/NaCl precipitation, followed by resuspension in PBS, was conducted. Phage titers were determined by OD.sub.268 measurement (assuming 1 unit at OD.sub.268 is approximately 1*10.sup.13 phage particles/mL) and confirmed by plaque assay. Library phagemid particles were stocked in 20% glycerol at −80° C.

(129) Phage Library Panning

(130) Antigen proteins at a concentration of 1-30 μg/ml were coated on Maxisorp strips (Thermo Scientific, Cat. No. 446469) overnight at 4° C. Multiple wells of antigens were prepared for each library. The coated wells were first blocked with 5% milk in PBS for 1-2 hours at room temperature and washed with PBS. Then

1,100 μL/well of phagemid particle solution (typically 1-5*10.sup.12 phages in 2% milk-PBS) was added into 4 parallel wells and incubated for 1-2 hours. Wells were then washed several times with PBS with increasing concentrations of Tween 20 (from 0.1% to 0.3%), and finally with PBS alone. The bound phagemid particles were eluted from the wells with 100 μL of 0.2 M glycine-HCl for 10 minutes at room temperature. The eluted phages were immediately neutralized with 18 μL of 1M Tris-HCl (pH 9.1)
(131) Alternatively, phagemid library panning was performed using Dynabeads (M280, Streptavidin, Invitrogen, Cat. No. 60210) through KingFisher (Thermo Scientific) according to the manufacturer's instructions. 300 μL of Dynabeads were washed with PBS and incubated with biotinylated anti-human Fc for 20 minutes at room temperature. The beads were then blocked with 5% BSA in PBS for one hour at room temperature. Fc-fusion antigens (70-100 pmols) were captured by one hour incubation at room temperature. The beads were then washed once with PBS, and incubated with 1 mL of phage library solution (typically 5*10.sup.12 to 1*10.sup.13 phage particles in 5% BSA-PBS) for 1-2 hours. The beads were then washed several times with PBS/Tween (0.1% to 0.3%) and PBS, and the bound phages were eluted from the beads with 100 μL of 0.2 M glycine-HCl for 10 minutes at room temperature. The eluted phages were immediately neutralized with 18 μL of 1 M Tris-HCl (pH 9.1). A total of three or four rounds of panning were conducted against each of the antigens, and more than 10 fold excess of purified human Fc was included to reduce background binding.
(132) For some of the antigens tested, 2 mL of antigens (10-30 μg/mL) were used to coat immune-tubes overnight at 4° C. The volume of blocking, washing, and elution solutions were increased accordingly.
(133) Amplification of Enriched Phage
(134) The eluted, enriched phage pool was further amplified as follows: ER2738 cells were infected with the eluted phagemid particles at 37° C. for 30 minutes. The infected cells were then plated out on 2×YT agar plates with 2% glucose, 100 μg/mL ampicillin and 12.5 μg/mL tetracycline. The colonies were harvested from plates, grown in 100 ml of 2% glucose, 100 μg/mL ampicillin and 12.5 g/mL tetracycline, and infected with M13KO7 helper phage. The amplified phages were purified and quantified by the processes described above. Usually, the eluted phages after the final round of panning were used to infect ER2738 cells, and the resulting ER2738 colonies were picked for supernatant ELISA screening assays.
(135) Supernatant Sandwich EELISA Assay
(136) A sensitive sandwich Elisa assay was developed to measure the Fabs present in bacterial supernatant. Microplates were coated with polyclonal anti-human IgG (Fab specific) (Sigma 15260) to capture Fabs present in the bacterial supernatant, and then HRP labeled goat anti-human Fc was used to detect the amount of Fabs captured. The A.sub.450 of each well was measured to determine the Fab binding activity. The primary hits were defined as those whose ELISA signals were at least twice that of background, and were further characterized in the following example (Example 4).
(137) Twelve human targets (TAGT-1, TAGT-2, TAGT-3, TAGT-4, TAGT-5, TAGT-6, TAGT-7, TAGT-8H, TAGT-9, TAGT-10H, TAGT-11, and TAGT-12), as well as two corresponding mouse targets (TAGT-8M and TAGT-10M), were screened with the constructed libraries. With these 14 antigens, a total of 690 unique positive hits with high affinity were identified. Most of the variant groups (Table 2) could form antibodies that bound to different target antigens, or were cross reactive between two species (e.g., bound TAGT-8H and TAGT-8M). The variant groups from confirmed binders were subsets of the designed variant groups shown in Table 2. A majority of the designed variants were also found in the confirmed binders (Table 3). (See the designed formulas of Table 2 vs. the formulas from the positive hits of Table 3).
(138) TABLE-US-00004 TABLE 3 formulas for HVR-H1 and HVR-H2 designed variant sequences from positive hits X.sub.1 X.sub.2 X.sub.3 X.sub.4 X.sub.5 X.sub.6 Amino Acid Sequence Residue Residue Residue Residue Residue Residue Variant Group Formula Identity Identity Identity Identity Identity Identity HVR-H1_1 X1TFX2X3YX4IHWV F, Y S, T D, G, N, A, G, W n/a n/a (SEQ ID NO: 198) S HVR-H1_2 YSIX1SGX2X3WX4WI S, T H, Y H, Y A, D, G, n/a n/a (SEQ ID NO: 199) N, S, T HVR-H1_3 FSLSTX1GVX2VX3WI G, S A, G A, G, S, n/a n/a n/a (SEQ ID NO: 200) T HVR-H2_1 LAX1IX2WX3X4DKX5Y L, R D, Y A, D, S, D, G R, S, Y P, T (SEQ ID NO: 201) SX6SLKSRL Y HVR-H2_2 IGX1IX2X3SGSTYYSPS A, D, E S, Y H, Y n/a n/a n/a (SEQ ID NO: 208) LKSRV HVR-H2_3 IGX1IYX2SGX3TX4YNP D, E, S H, Y N, S N, Y n/a n/a (SEQ ID NO: 209) SLKSRV HVR-H2_4 VSX1ISGX2GX3X4TYY A, G, S, A, D, S, D, G, S S, T n/a n/a (SEQ ID NO: 204) ADSVKGRF V, Y Y HVR-H2_5 IGX1INPNX2GX3TX4YA I, R, W F, R D, G, S K, N n/a n/a (SEQ ID NO: 205) QKFQGRV HVR-H2_6 IGX1IX2PSX3GX4TX5Y I, R, W S, Y G, S D, G, S K, N n/a (SEQ

ID NO: 206) AQKFQGRV HVR-H2_7 VGRIX1SKX2X3GX4TT K, R A, T D, Y G, Y P, S n/a (SEQ ID NO: 210) EYAAX5VKGRF n/a, not applicable.

Example 4: Characterization of Antibodies In Vitro

(139) The Fabs corresponding to the primary hits identified in Example 3 above, which were tagged at their C-terminus of the CH1 domain with a His6 tag, were over-expressed in *E. coli*, and were purified through Ni-NTA resin (Thermo Fisher Scientific) according to the manufacturer's instructions. Their affinities were measured by the ForteBio Octet RED96 System. Briefly, the AHC sensors (anti-human IgG-Fc capture dip and read biosensors) were used to capture antigen Fc-His fusion protein (Sino Biological #10039-H03H) were used, and dipped into wells containing the purified Fabs that were diluted to 5-10 μg/mL with kinetic buffer (See also, ForteBio, Anti-human IgG Capture (AHC) Biosensors, Product Insert 41-0072-PD (2008); Yang et al. (2016), Anal. Biochem. 508:78-96). The acquired ForteBio data were processed with Data Acquisition software 7.1, and kinetic data were fitted to a 1:1 Langmuir binding model. Fab melting temperatures were measured by Differential Scanning Fluorimetry (DSF) assay. Briefly, the temperature and fluorescence monitoring was done using a qPCR machine (real time PCR). SYPRO® Orange was diluted from a 5000× stock 50 fold to 100× with PBS buffers; 16 μl of each Fab (˜0.5 mg/ml) was added to each well in a 96-well microplate and mixed with 4 μl of 100× SYPRO® Orange. A LightCycler® 480 System was used to measure fluorescence intensity. The excitation wavelength was set at 483 nm, and the emission wavelength was set at 568 nm. The temperature was increased from 25° C. to 90° C. at an increment of 1.2 to 1.3° C. per minute, and an equilibration time of 15 seconds at each measurement temperature was applied. The data were analyzed using the LightCycler®480 Software. The midpoint of hydrophobic exposure, Tm, was defined as the temperature corresponding to the maximum value of the first derivative of the first fluorescence transition. (See also, Lavinder et al. (2009), J. Am. Chem. Soc.131: 3794-3795; Ericsson et al. (2006), Analytical Biochemistry 357: 289-298; Phillips and Hernandez de la Pena (2011), Current Protocols in Mol. Biol. 94: 10.28.1-10.28.15).

(140) The 12 human target antigens (TAGT-1, TAGT-2, TAGT-3, TAGT-4, TAGT-5, TAGT-6, TAGT-7, TAGT-8H, TAGT-9, TAGT-10H, TAGT-11 and TAGT-12) were unrelated proteins sharing sequence identity lower than 26%. The sequence identity between human antigen TAGT-8H and mouse antigen TAGT-8M was 70%, while the sequence identity between human antigen TAGT-10H and mouse antigen TAGT-10M was 60%. Multiple antibodies targeting 14 different antigens with high affinity could be successfully identified and selected from the dynamic libraries. The affinities of most binders were in the nanomolar range, and some even reached the sub-nanomolar range (FIG. **2**A). In addition, the confirmed binders demonstrated good stability, with Tm ranges shown in FIG. **2**B.

Example 5: Application of the Dynamic Heavy Chain Libraries

(141) To further examine the robustness and flexibility of the heavy chain libraries, the libraries were screened against the 14 target antigens described in Example 4 above by pairing the heavy chains with different light chain libraries having a diversity varying from 10.sup.7 to 280, and all the way to a single light chain (i.e., a common light chain). The limit of the diversity design in both the heavy and light chain libraries was explored by trimming the physical size of their respective pairing partners (e.g., light chain libraries with a diversity ranging from 10.sup.7 to 280, 20, and to a single light chain) while exploring the flexibility and/or the dynamic diversity of the light chain itself. The capacity of these dynamic light chain libraries in pairing with the dynamic heavy chain libraries provided a strong rational for the library design when generating and engineering the diverse antibody hits/leads against known and challenging target antigens. Positive hits having high affinity were identified from each of the libraries tested, and a total of 690 unique positive hits were measured and confirmed with affinity data (Table 4). Their ability for binding different targets, as well as their epitope variation (including, but not limited to, the fine differences in epitope recognition between two species, as shown by the cross-species reactivity with human and murine targets with sequence identity around 60%) were examined. Positive hits using each combination of HVR-H1_1, HVR-H1_2, or HVRH-1_3, and HVR-H2_1, HVR-H2_2, or HVRH-2_3, HVR-H2_4, HVR-H_5, HVRH-2_6, or HVR-H2_7 were observed. These results indicate the power and potential of using these dynamic hypervariable region units for making antibody and protein libraries that recognize a wide range of targets for therapeutic, diagnostic and/or research reagents when they are grafted on or designed into antibody (and/or alternative protein) scaffolds. The dynamic nature of these heavy chain hypervariable region units in designing and constructing antibody (and/or non-antibody) scaffolds, when paired with light chain libraries having a wide diversity (e.g., ranging from 107 to 280, down to a single unique sequence), is a strong validation of the dynamic antibody design concept for creating novel binding reagents useful in therapeutic, diagnostic and/or research settings.

(142) TABLE-US-00005 TABLE 4 Affinity data for confirmed hits HVR-H1 and H2 Usage Hit ID Target ID Kd (M) HVR-H1_1 and 3757 TAGT-6 1.84E−08 HVR-H2_6 3762 TAGT-6 3.04E−08 3780 TAGT-8 1.47E−09 3865 TAGT-11 9.48E−09 3869 TAGT-11 2.35E−08 3898 TAGT-11 1.83E−08 4030 TAGT-8 4.90E−09 4033 TAGT-8 8.75E−10 4043 TAGT-8 2.69E−09 4050 TAGT-10 1.65E−08 4084 TAGT-8 2.94E−09 4101 TAGT-8 2.12E−09 4103 TAGT-8 3.59E−10 4163 TAGT-8 1.37E−08 4614 TAGT-8 3.53E−10 4615 TAGT-8 2.28E−10 4617 TAGT-8 2.88E−10 4618 TAGT-8 1.08E−09 4620 TAGT-8 3.48E−10 4622 TAGT-8 2.74E−10 4623 TAGT-8 4.85E−10 4624 TAGT-8 1.00E−12 4625 TAGT-8 4.02E−10 4627 TAGT-8 1.82E−10 4630 TAGT-8 2.67E−10 4631 TAGT-8 1.83E−10 4633 TAGT-8 3.22E−10 4634 TAGT-8 2.07E−10 4638 TAGT-8 3.14E−10 4642 TAGT-8 1.89E−10 4644 TAGT-8 2.48E−10 4645 TAGT-8 2.96E−10 4650 TAGT-8 3.57E−10 4651 TAGT-8 3.01E−10 4652 TAGT-8 2.94E−10 4653 TAGT-8 3.27E−10 4654 TAGT-8 2.32E−10 4658 TAGT-8 1.42E−10 4659 TAGT-8 2.12E−10 4661 TAGT-8 1.62E−09 4662 TAGT-8 8.98E−10 4665 TAGT-8 3.69E−10 4666 TAGT-8 1.17E−09 4668 TAGT-8 5.79E−10 4670 TAGT-8 8.21E−10 4673 TAGT-8 3.23E−10 4674 TAGT-8 5.02E−10 4675 TAGT-8 1.00E−12 4676 TAGT-8 1.62E−10 4678 TAGT-8 5.98E−10 4681 TAGT-8 5.43E−10 4683 TAGT-8 8.97E−10 4684 TAGT-8 6.69E−10 4685 TAGT-8 4.78E−10 4686 TAGT-8 4.78E−10 4687 TAGT-8 4.08E−10 4689 TAGT-8 1.63E−10 4690 TAGT-8 4.67E−10 4792 TAGT-10 7.39E−09 5103 TAGT-10 2.67E−09 5149 TAGT-11 2.91E−09 5159 TAGT-11 4.09E−09 5160 TAGT-11 8.07E−09 5162 TAGT-11 9.87E−09 5163 TAGT-11 1.71E−08 5165 TAGT-11 4.06E−09 5709 TAGT-11 1.93E−08 5740 TAGT-11 7.26E−09 5752 TAGT-11 6.33E−09 5935 TAGT-12 8.78E−09 5970 TAGT-12 1.35E−08 5994 TAGT-12 1.58E−08 5997 TAGT-12 8.51E−09 6008 TAGT-12 5.10E−08 6032 TAGT-2 1.63E−08 6531 TAGT-3 1.08E−08 7030 TAGT-8 3.47E−08 7035 TAGT-8 3.04E−09 7038 TAGT-8 2.33E−08 7043 TAGT-8 1.34E−08 7044 TAGT-8 1.12E−09 7045 TAGT-8 1.11E−09 7055 TAGT-8 7.57E−10 7213 TAGT-12 8.87E−09 7215 TAGT-12 1.61E−08 7222 TAGT-12 1.26E−09 7231 TAGT-12 3.38E−09 7232 TAGT-12 8.06E−09 7243 TAGT-12 4.95E−09 7357 TAGT-3 6.14E−08 BH3002 TAGT-8 2.51E−10 BH3004 TAGT-8 3.00E−10 BH3005 TAGT-8 3.46E−10 BH3006 TAGT-8 1.94E−10 HVR-H1_1 and 4025 TAGT-8 2.89E−09 HVR-H2_5 4031 TAGT-8 1.06E−09 4054 TAGT-10 1.58E−08 4055 TAGT-10 1.07E−08 4060 TAGT-10 1.10E−08 4061 TAGT-10 3.42E−08 4065 TAGT-10 4.31E−08 4066 TAGT-10 4.76E−08 4181 TAGT-10 4.27E−08 4182 TAGT-10 4.24E−09 4693 TAGT-10 4.87E−10 4696 TAGT-10 4.58E−10 4697 TAGT-10 6.21E−10 4698 TAGT-10 5.70E−10 4700 TAGT-10 2.62E−10 4701 TAGT-10 5.60E−10 4702 TAGT-10 5.02E−10 4703 TAGT-10 2.85E−10 4704 TAGT-10 6.65E−10 4705 TAGT-10 3.02E−10 4706 TAGT-10 2.50E−10 4707 TAGT-10 4.29E−10 4708 TAGT-10 5.29E−10 4710 TAGT-10 6.26E−10 4714 TAGT-10 4.46E−10 4717 TAGT-10 4.61E−10 4718 TAGT-10 5.32E−10 4722 TAGT-10 7.46E−10 4725 TAGT-10 4.84E−10 4729 TAGT-10 8.80E−10 4731 TAGT-10 4.67E−10 4732 TAGT-10 3.33E−10 4738 TAGT-10 5.34E−10 4741 TAGT-10 1.66E−09 4743 TAGT-10 7.40E−09 4744 TAGT-10 3.73E−10 4748 TAGT-10 3.92E−10 4749 TAGT-10 2.55E−10 4750 TAGT-10 7.86E−10 4752 TAGT-10 3.34E−09 4753 TAGT-10 3.43E−10 4759 TAGT-10 6.59E−10 4766 TAGT-10 4.09E−10 4788 TAGT-10 2.88E−10 4794 TAGT-10 5.56E−10 4798 TAGT-10 4.35E−09 4803 TAGT-10 1.88E−10 4805 TAGT-10 4.26E−10 4808 TAGT-10 8.28E−10 4909 TAGT-10 2.90E−10 5126 TAGT-8 9.54E−09 5129 TAGT-8 1.12E−09 5132 TAGT-8 3.06E−09 5145 TAGT-8 7.00E−09 5295 TAGT-9 2.21E−09 6179 TAGT-10 1.99E−09 6180 TAGT-10 6.11E−09 6183 TAGT-10 2.70E−09 6184 TAGT-10 <1.0E−12 6185 TAGT-10 1.57E−09 6187 TAGT-10 2.74E−08 6188 TAGT-10 8.76E−09 6189 TAGT-10 2.38E−10 6190 TAGT-10 2.55E−09 6191 TAGT-10 6.58E−11 6193 TAGT-10 3.18E−09 6194 TAGT-10 2.49E−10 6195 TAGT-10 4.30E−09 6196 TAGT-10 <1.0E−12 6197 TAGT-10 8.56E−09 6198 TAGT-10 2.85E−09 6202 TAGT-10 1.03E−09 6203 TAGT-10 1.05E−08 6204 TAGT-10 6.46E−09 6206 TAGT-10 3.44E−09 6208 TAGT-10 3.50E−09 6209 TAGT-10 3.35E−09 6210 TAGT-10 5.17E−10 6212 TAGT-10 2.25E−09 6214 TAGT-10 1.51E−09 6216 TAGT-10 6.58E−10 6217 TAGT-10 4.99E−09 6219 TAGT-10 3.15E−09 6220 TAGT-10 3.45E−09 6539 TAGT-4 3.45E−09 7025 TAGT-8 4.87E−08 7036 TAGT-8 1.59E−08 7037 TAGT-8 2.10E−08 7047 TAGT-8 2.15E−08 7066 TAGT-8 1.80E−08 7067 TAGT-8 3.41E−08 7068 TAGT-8 1.11E−08 7073 TAGT-8 3.19E−09 HVR-H1_3 and 4074 TAGT-6 1.95E−08 HVR-H2_4 4131 TAGT-6 <1.0E−12 4132 TAGT-6 <1.0E−12 4200 TAGT-6 5.68E−08 4216 TAGT-6 2.59E−08 4878 TAGT-12 4.07E−09 5291 TAGT-1 6.57E−09 5312 TAGT-6 4.50E−07 5326 TAGT-6 7.84E−07 5345 TAGT-6 1.02E−08 5346 TAGT-6 1.61E−08 5347 TAGT-6 1.21E−08 5348 TAGT-6 1.02E−08 5355 TAGT-6 8.71E−10 5364 TAGT-6 7.26E−09 5367 TAGT-6 1.49E−08 5371 TAGT-6 3.97E−09 5405 TAGT-6 1.01E−08 5415 TAGT-6 1.64E−08 5417 TAGT-6 4.04E−08 5418 TAGT-6 2.02E−08 5905 TAGT-12 3.83E−08 5910 TAGT-12 3.30E−08 5911 TAGT-12 3.35E−08 5912 TAGT-12 1.68E−08 5914 TAGT-12 3.30E−08 5915 TAGT-12 1.82E−08 5918 TAGT-12

3.46E−08 5919 TAGT-12 2.38E−08 5920 TAGT-12 1.88E−08 5922 TAGT-12 1.95E−08 5923 TAGT-12
1.60E−08 5927 TAGT-12 4.35E−08 5929 TAGT-12 3.20E−08 5961 TAGT-12 2.41E−08 5962 TAGT-12
8.06E−08 5963 TAGT-12 2.07E−08 5964 TAGT-12 1.40E−08 5974 TAGT-12 5.02E−08 5976 TAGT-12
2.88E−08 5977 TAGT-12 2.70E−08 5978 TAGT-12 3.25E−08 5996 TAGT-12 2.21E−08 5999 TAGT-12
6.29E−08 6000 TAGT-12 7.86E−08 6004 TAGT-12 5.50E−08 6543 TAGT-3 6.78E−08 7077 TAGT-6
1.88E−08 7078 TAGT-6 2.52E−08 7079 TAGT-6 2.99E−08 7080 TAGT-6 2.44E−08 7081 TAGT-6
4.31E−08 7087 TAGT-6 6.96E−08 7088 TAGT-6 4.36E−08 7090 TAGT-6 5.55E−08 7100 TAGT-6
3.50E−08 7105 TAGT-6 3.33E−08 7107 TAGT-6 1.22E−07 7109 TAGT-6 3.20E−08 7120 TAGT-6
3.45E−08 7128 TAGT-6 3.97E−08 7131 TAGT-6 3.04E−08 7133 TAGT-6 4.03E−08 7135 TAGT-6
3.17E−08 7190 TAGT-6 1.03E−08 7201 TAGT-6 3.26E−08 7209 TAGT-12 9.36E−09 7210 TAGT-12
9.85E−09 7211 TAGT-12 1.26E−08 7216 TAGT-12 1.88E−08 7218 TAGT-12 1.49E−08 7219 TAGT-12
1.44E−08 7220 TAGT-12 9.12E−09 7225 TAGT-12 9.53E−09 7226 TAGT-12 7.57E−09 7235 TAGT-12
2.18E−08 7237 TAGT-12 2.13E−08 7240 TAGT-12 1.17E−08 7241 TAGT-12 6.43E−09 7242 TAGT-12
1.71E−08 7245 TAGT-12 1.38E−08 7246 TAGT-12 6.22E−09 7247 TAGT-12 8.93E−09 7251 TAGT-12
2.69E−08 7252 TAGT-12 9.56E−09 7253 TAGT-12 1.62E−08 7255 TAGT-12 1.20E−08 7256 TAGT-12
7.08E−09 7257 TAGT-12 1.11E−08 7420 TAGT-9 1.38E−08 7425 TAGT-9 1.77E−08 HVR-H1_2 and 3761
TAGT-6 9.65E−08 HVR-H2_4 3763 TAGT-6 9.30E−09 4029 TAGT-8 1.89E−09 4034 TAGT-8 4.27E−09
4045 TAGT-8 1.10E−09 4073 TAGT-6 <1.0E−12 4075 TAGT-6 <1.0E−12 4076 TAGT-6 7.44E−09 4077
TAGT-6 <1.0E−12 4123 TAGT-6 5.98E−09 4124 TAGT-6 4.43E−09 4125 TAGT-6 <1.0E−12 4126 TAGT-6
7.27E−09 4127 TAGT-6 <1.0E−12 4129 TAGT-6 <1.0E−12 4133 TAGT-6 3.90E−10 4135 TAGT-6
<1.0E−12 4137 TAGT-6 <1.0E−12 4140 TAGT-6 <1.0E−12 4141 TAGT-6 <1.0E−12 4201 TAGT-6
1.41E−08 4217 TAGT-6 9.67E−08 4218 TAGT-6 2.85E−08 4222 TAGT-6 5.55E−08 4816 TAGT-12
5.32E−09 4842 TAGT-12 4.01E−10 4895 TAGT-7 6.20E−09 4903 TAGT-12 1.91E−09 5212 TAGT-1
9.19E−09 5218 TAGT-1 6.04E−09 5225 TAGT-1 3.10E−10 5235 TAGT-1 1.41E−08 5236 TAGT-1
1.49E−08 5272 TAGT-1 2.49E−08 5275 TAGT-1 9.65E−09 5282 TAGT-1 1.07E−08 5298 TAGT-6
3.41E−07 5301 TAGT-6 2.61E−07 5316 TAGT-6 1.14E−08 5317 TAGT-6 3.34E−07 5320 TAGT-6
6.13E−07 5321 TAGT-6 7.16E−07 5328 TAGT-6 3.42E−07 5329 TAGT-6 2.84E−06 5336 TAGT-6
6.04E−07 5341 TAGT-6 2.93E−08 5349 TAGT-6 6.20E−09 5351 TAGT-6 7.29E−09 5357 TAGT-6
7.14E−09 5360 TAGT-6 2.41E−08 5363 TAGT-6 9.87E−09 5369 TAGT-6 2.05E−08 5399 TAGT-9
3.62E−08 5403 TAGT-6 8.26E−09 5408 TAGT-6 2.36E−08 5409 TAGT-6 1.70E−08 5411 TAGT-6 1.25E−08
5416 TAGT-6 1.09E−08 5420 TAGT-6 1.41E−08 5431 TAGT-9 1.19E−08 5437 TAGT-9 1.92E−08 5694
TAGT-11 9.45E−09 5716 TAGT-11 8.14E−09 5732 TAGT-11 5.24E−09 5906 TAGT-12 1.50E−08 5926
TAGT-12 3.23E−08 5933 TAGT-12 3.13E−08 5983 TAGT-12 2.09E−08 5992 TAGT-12 1.70E−08 5993
TAGT-12 1.13E−08 5995 TAGT-12 1.42E−08 6473 TAGT-4 2.30E−08 6555 TAGT-3 4.18E−08 7097 TAGT-
6 2.43E−08 7183 TAGT-6 1.48E−08 7262 TAGT-5 2.63E−09 7264 TAGT-5 3.17E−09 7312 TAGT-5
3.11E−09 7315 TAGT-5 5.15E−09 7426 TAGT-9 1.12E−08 7427 TAGT-9 5.58E−09 HVR-H1_1 and 3760
TAGT-6 1.26E−08 HVR-H2_4 4048 TAGT-10 3.24E−09 4049 TAGT-10 9.37E−09 4051 TAGT-10
1.80E−08 4056 TAGT-10 1.09E−08 4058 TAGT-10 1.13E−08 4062 TAGT-10 2.11E−08 4063 TAGT-10
1.90E−08 4067 TAGT-10 1.97E−08 4080 TAGT-6 <1.0E−12 4130 TAGT-6 1.00E−09 4138 TAGT-6
1.60E−08 4139 TAGT-6 1.65E−09 4723 TAGT-10 9.11E−10 4733 TAGT-10 3.05E−10 4734 TAGT-10
5.72E−10 4767 TAGT-10 2.77E−10 4771 TAGT-10 7.23E−10 4797 TAGT-10 5.63E−10 4807 TAGT-10
1.17E−09 4829 TAGT-12 3.36E−09 5194 TAGT-1 1.29E−08 5200 TAGT-1 1.53E−08 5210 TAGT-1
3.41E−09 5297 TAGT-6 1.77E−06 5300 TAGT-6 1.53E−08 5315 TAGT-6 2.10E−06 5353 TAGT-6
1.61E−08 5354 TAGT-6 4.96E−09 5438 TAGT-9 9.30E−09 5510 TAGT-2 2.62E−09 5513 TAGT-2
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6.83E−09 5554 TAGT-2 2.88E−09 5557 TAGT-2 3.24E−09 5558 TAGT-2 2.43E−09 5561 TAGT-2
1.64E−08 5565 TAGT-2 3.02E−09 5568 TAGT-2 1.14E−09 5600 TAGT-2 5.33E−09 5612 TAGT-2
7.85E−09 5614 TAGT-2 5.29E−09 5622 TAGT-2 3.06E−09 5642 TAGT-2 3.84E−09 5710 TAGT-11
1.01E−08 5739 TAGT-11 1.29E−08 5745 TAGT-11 1.06E−08 5746 TAGT-11 5.00E−09 5754 TAGT-11
9.52E−09 6221 TAGT-10 6.92E−10 6471 TAGT-4 3.05E−08 6536 TAGT-4 2.03E−09 6537 TAGT-4
1.85E−09 6540 TAGT-4 8.08E−09 7204 TAGT-5 2.33E−09 7212 TAGT-12 1.70E−08 7260 TAGT-5
2.30E−09 7271 TAGT-5 3.13E−08 7276 TAGT-5 1.02E−08 7311 TAGT-5 9.20E−09 7317 TAGT-5 2.02E−08
7323 TAGT-5 3.23E−09 7365 TAGT-5 1.82E−09 7366 TAGT-5 3.76E−09 7369 TAGT-5 2.46E−09 7371
TAGT-5 2.31E−08 7373 TAGT-5 5.13E−09 7374 TAGT-5 1.97E−08 7378 TAGT-5 5.66E−09 7411 TAGT-4
3.82E−08 7415 TAGT-4 9.33E−08 7418 TAGT-9 3.41E−08 7419 TAGT-9 1.72E−08 7429 TAGT-9

2.12E−08 7431 TAGT-9 3.53E−08 HVR-H1_2 and 4027 TAGT-8 1.55E−09 HVR-H2_6 4027 TAGT-8M 3.81E−09 4032 TAGT-8 5.11E−09 4032 TAGT-8M 4.84E−09 4038 TAGT-8 2.98E−09 4204 TAGT-10 6.83E−09 4204 TAGT-10M 6.89E−09 4813 TAGT-12 2.45E−10 4828 TAGT-12 1.10E−09 4849 TAGT-12 8.40E−10 4850 TAGT-12 1.23E−09 4874 TAGT-12 4.19E−09 4925 TAGT-7 1.32E−08 4928 TAGT-7 3.26E−08 5012 TAGT-8 1.76E−09 5012 TAGT-8M 2.03E−09 5014 TAGT-8 2.43E−09 5014 TAGT-8M 3.87E−09 5016 TAGT-8 3.56E−09 5016 TAGT-8M 2.84E−09 5020 TAGT-8 8.78E−10 5020 TAGT-8M 7.00E−09 5022 TAGT-8 3.68E−09 5022 TAGT-8M 3.03E−09 5023 TAGT-8 9.46E−10 5023 TAGT-8M 5.77E−09 5024 TAGT-8 4.52E−09 5024 TAGT-8M 3.48E−09 5030 TAGT-8 7.03E−10 5030 TAGT-8M 4.27E−09 5037 TAGT-8 1.06E−09 5037 TAGT-8M 4.36E−09 5039 TAGT-8 4.30E−10 5039 TAGT-8M 2.69E−09 5040 TAGT-8 4.37E−10 5040 TAGT-8M 3.13E−09 5041 TAGT-8 1.68E−09 5041 TAGT-8M 1.67E−09 5045 TAGT-8 1.00E−09 5045 TAGT-8M 3.91E−09 5048 TAGT-8 5.10E−10 5048 TAGT-8M 2.52E−09 5066 TAGT-8 5.23E−09 5066 TAGT-8M 9.99E−09 5070 TAGT-8 1.34E−09 5070 TAGT-8M 6.63E−09 5074 TAGT-8 4.31E−09 5074 TAGT-8M 2.98E−09 5082 TAGT-8 4.79E−09 5082 TAGT-8M 3.23E−09 5113 TAGT-12 6.80E−09 5114 TAGT-12 3.42E−08 5116 TAGT-12 1.46E−08 5119 TAGT-12 7.54E−09 5121 TAGT-12 9.29E−09 5123 TAGT-12 5.67E−09 5125 TAGT-12 2.42E−08 5128 TAGT-12 7.12E−09 5138 TAGT-12 8.55E−09 5273 TAGT-1 1.34E−08 5423 TAGT-9 4.90E−09 5720 TAGT-11 1.93E−08 5924 TAGT-12 5.95E−08 5934 TAGT-12 1.66E−08 6026 TAGT-2 2.95E−09 6526 TAGT-4 1.16E−08 7040 TAGT-8 2.72E−08 7228 TAGT-12 7.62E−09 7244 TAGT-12 1.05E−08 7254 TAGT-12 1.07E−08 7258 TAGT-12 9.72E−09 7358 TAGT-3 5.15E−08 7442 TAGT-9 6.83E−09 7443 TAGT-9 1.27E−08 HVR-H1_2 and 4052 TAGT-10 9.73E−09 HVR-H2_1 4059 TAGT-10 3.30E−07 5094 TAGT-10 4.34E−08 5095 TAGT-10 1.27E−08 5097 TAGT-10 1.27E−08 5099 TAGT-10 4.20E−08 5109 TAGT-10 2.59E−08 5215 TAGT-1 6.64E−09 5271 TAGT-1 1.24E−08 5274 TAGT-1 2.52E−08 5299 TAGT-6 1.37E−08 5432 TAGT-9 4.83E−09 5491 TAGT-11 1.43E−08 5744 TAGT-11 1.14E−08 5936 TAGT-10 1.75E−08 6475 TAGT-4 7.22E−09 7207 TAGT-5 4.99E−10 7272 TAGT-5 3.49E−09 7313 TAGT-5 5.69E−09 7388 TAGT-5 2.72E−09 7389 TAGT-5 4.50E−09 7395 TAGT-5 1.65E−08 7421 TAGT-9 2.47E−08 7440 TAGT-9 6.79E−09 7513 TAGT-9 8.43E−09 HVR-H1_2 and 4812 TAGT-12 2.89E−09 HVR-H2_2 4815 TAGT-12 5.91E−09 4817 TAGT-12 2.06E−09 4818 TAGT-12 1.02E−09 4836 TAGT-12 2.49E−09 4841 TAGT-12 4.50E−10 4846 TAGT-12 3.19E−09 4852 TAGT-12 2.26E−09 4860 TAGT-12 2.44E−09 4876 TAGT-12 7.75E−09 4880 TAGT-12 2.77E−09 4897 TAGT-12 6.83E−10 4901 TAGT-12 3.19E−09 4904 TAGT-12 5.39E−09 5115 TAGT-12 1.16E−08 5220 TAGT-1 5.03E−09 5404 TAGT-6 3.30E−09 5421 TAGT-9 1.05E−08 5422 TAGT-9 5.12E−09 5584 TAGT-2 1.76E−09 5658 TAGT-11 2.61E−10 7273 TAGT-5 6.01E−09 7316 TAGT-5 2.04E−08 7394 TAGT-5 8.75E−09 HVR-H1_2 and 4037 TAGT-8 5.53E−09 HVR-H2_3 4041 TAGT-8 1.54E−09 4180 TAGT-10 7.39E−08 4809 TAGT-12 3.69E−10 4820 TAGT-12 3.96E−09 4825 TAGT-12 6.05E−09 4837 TAGT-12 5.36E−09 4838 TAGT-12 2.52E−09 4839 TAGT-12 6.16E−09 4844 TAGT-12 6.95E−10 4847 TAGT-12 3.64E−10 4879 TAGT-12 3.13E−09 4911 TAGT-7 1.50E−08 5228 TAGT-1 3.06E−08 5292 TAGT-1 1.57E−08 5398 TAGT-9 1.97E−08 7248 TAGT-12 1.28E−08 7249 TAGT-12 5.36E−09 7380 TAGT-5 1.24E−08 7386 TAGT-5 1.32E−08 7444 TAGT-9 5.53E−09 7508 TAGT-9 1.36E−08 HVR-H1_1 and 4097 TAGT-8 6.24E−09 HVR-H2_1 5202 TAGT-1 1.50E−08 5203 TAGT-1 1.31E−08 5207 TAGT-1 7.44E−09 5221 TAGT-1 1.18E−08 5226 TAGT-1 8.36E−09 5230 TAGT-1 9.21E−09 5238 TAGT-1 5.04E−08 5280 TAGT-1 8.43E−09 5281 TAGT-1 4.70E−09 5285 TAGT-1 1.42E−08 5288 TAGT-1 1.08E−08 5425 TAGT-9 2.15E−08 7032 TAGT-8 2.08E−08 7268 TAGT-5 3.76E−09 7277 TAGT-5 2.56E−09 7278 TAGT-5 1.53E−08 7390 TAGT-5 1.44E−09 HVR-H1_2 and 4102 TAGT-8 2.54E−09 HVR-H2_5 4116 TAGT-10 <1.0E−12 4827 TAGT-12 1.51E−09 4834 TAGT-12 9.68E−10 4851 TAGT-12 3.84E−10 4863 TAGT-12 6.63E−10 4875 TAGT-12 1.03E−09 5217 TAGT-1 1.08E−08 5921 TAGT-12 8.01E−09 5930 TAGT-12 5.66E−09 5932 TAGT-12 1.12E−08 5968 TAGT-12 1.27E−08 5980 TAGT-12 1.14E−08 5990 TAGT-12 1.15E−08 6010 TAGT-12 2.83E−08 7310 TAGT-5 1.41E−08 7379 TAGT-5 5.43E−09 HVR-H1_1 and 4161 TAGT-8 2.98E−08 HVR-H2_3 4177 TAGT-8 1.48E−08 4823 TAGT-12 2.62E−09 5192 TAGT-1 2.16E−08 5193 TAGT-1 3.69E−08 5204 TAGT-1 1.48E−08 5234 TAGT-1 1.28E−08 5237 TAGT-1 3.28E−09 5615 TAGT-2 1.22E−08 5733 TAGT-11 7.15E−09 5741 TAGT-11 1.91E−08 7324 TAGT-5 5.68E−09 7367 TAGT-5 2.04E−08 7372 TAGT-5 7.27E−10 7506 TAGT-9 7.73E−09 HVR-H1_3 and 5208 TAGT-1 3.36E−09 HVR-H2_1 5283 TAGT-1 2.88E−08 5303 TAGT-6 5.12E−09 5310 TAGT-6 5.72E−09 5314 TAGT-6 8.39E−09 5318 TAGT-6 1.90E−08 5342 TAGT-6 3.89E−08 5359 TAGT-6 7.10E−10 5365 TAGT-6 2.56E−09 5370 TAGT-6 1.91E−09 5413 TAGT-6 9.93E−10 7275 TAGT-5 6.85E−09 HVR-H1_1 and 4840 TAGT-12 2.08E−09 HVR-H2_2 5195 TAGT-1 2.62E−08 5201 TAGT-1 5.33E−09 5211 TAGT-1 2.11E−09 5216 TAGT-1 3.08E−09

5286 TAGT-1 6.34E−09 5287 TAGT-1 1.02E−08 5290 TAGT-1 6.73E−09 5722 TAGT-11 3.08E−08 6030 TAGT-2 8.27E−08 7370 TAGT-5 1.07E−08 7385 TAGT-5 3.26E−09 HVR-H1_3 and 4036 TAGT-8 3.13E−09 HVR-H2_2 4096 TAGT-8 2.70E−09 5323 TAGT-6 1.04E−08 5387 TAGT-8 1.13E−09 5756 TAGT-11 3.00E−08 5985 TAGT-12 3.92E−08 5986 TAGT-12 4.65E−08 7163 TAGT-6 1.26E−08 7375 TAGT-5 6.03E−09 7391 TAGT-5 1.35E−08 HVR-H1_3 and 4026 TAGT-8 3.08E−09 HVR-H2_3 4858 TAGT-12 5.86E−09 6533 TAGT-3 2.62E−08 7159 TAGT-6 3.79E−08 7166 TAGT-6 1.24E−08 7239 TAGT-12 2.40E−08 7274 TAGT-5 1.63E−08 7433 TAGT-9 1.67E−08 HVR-H1_3 and 4857 TAGT-12 4.05E−09 HVR-H2_6 5227 TAGT-1 1.04E−08 7221 TAGT-12 5.58E−09 7229 TAGT-12 8.91E−09 HVR-H1_2 and 4220 TAGT-6 5.72E−08 HVR-H2_7 4861 TAGT-12 5.11E−09 5284 TAGT-1 1.84E−08 HVR-H1_1 and 4079 TAGT-6 3.15E−08 HVR-H2_7 7129 TAGT-6 1.90E−08 HVR-H1_3 and 4072 TAGT-6 6.95E−09 HVR-H2_5 HVR-H1_3 and 5333 TAGT-6 5.02E−09 HVR-H2_7

(143) Hits containing the same HVR-H1 and HVR-H2 sequences were discovered that could bind different target antigens when these HVR-H1 and 2 sequences were paired with different HVR-H3 and VL sequences. For example, Hit IDs 4029, 7097, and 5906 contained the same HVR-H1 and HVR-H2 combination (HVR-H1_2 and HVR-H2_4) but were paired with different HVR-H3 and VL sequences, and bound three different target antigens (TAGT-8, TAGT-6, and TAGT-12, respectively). Hits 7040 and 5924 contained the same HVR-H1 and HVR-H2 combination (HVR-H1_2 and HVR-H2_6) but were paired with different HVR-H3 and VL sequences, and bound two different target antigens (TAGT-8 and TAGT-12, respectively).

(144) Table 5 below shows sequence usage and number of targets bound for the HVR-H1 and HVR-H2s identified during the library analyses. Without wishing to be bound by theory, it is thought that a high number of antigens bound by an antibody comprising a given hypervariable region may be indicative of a high degree of flexibility of that particular hypervariable region, while a high segment usage of a given hypervariable region may be indicative of robust folding of the hypervariable region (and surrounding polypeptide sequence).

(145) TABLE-US-00006 TABLE 5 target binding capability of HVR-H1 and HVR-H2 designed variants Sequence Number of Antigens Variant ID Usage Percent hit out of 14 HVR-H1_1 45.0% 11 HVR-H1_2 33.8% 14 HVR-H1_3 19.1% 8 HVR-H2_1 7.9% 8 HVR-H2_2 6.6% 8 HVR-H2_3 6.8% 11 HVR-H2_4 36.4% 12 HVR-H2_5 16.8% 8 HVR-H2_6 21.8% 13 HVR-H2_7 0.9% 3

(146) Table 6 below shows sequence usage and number of antigens bound for the HVR-H1 and HVR-H2 combinations identified during the library analyses.

(147) TABLE-US-00007 TABLE 6 HVR-H1 and HVR-H2 designed variants combination usage Sequence Number of Preference HVR-H1 HVR-H2 Usage Antigens Ranking Variant ID Variant ID Percent hit out of 14 Tier 1 HVR-H1_2 HVR-H2_6 7.6% 11 Tier 1 HVR-H1_2 HVR-H2_4 11.6% 10 Tier 1 HVR-H1_1 HVR-H2_4 11.2% 9 Tier 1 HVR-H1_1 HVR-H2_6 13.5% 7 Tier 1 HVR-H1_2 HVR-H2_1 3.6% 7 Tier 1 HVR-H1_2 HVR-H2_2 3.4% 7 Tier 1 HVR-H1_2 HVR-H2_3 3.4% 7 Tier 1 HVR-H1_1 HVR-H2_3 2.2% 7 Tier 1 HVR-H1_3 HVR-H2_3 1.1% 6 Tier 1 HVR-H1_3 HVR-H2_4 13.1% 5 Tier 1 HVR-H1_2 HVR-H2_5 2.4% 5 Tier 1 HVR-H1_1 HVR-H2_2 1.7% 5 Tier 1 HVR-H1_3 HVR-H2_2 1.4% 5 Tier 1 HVR-H1_1 HVR-H2_5 13.4% 4 Tier 2 HVR-H1_1 HVR-H2_1 2.6% 4 Tier 2 HVR-H1_3 HVR-H2_1 1.7% 3 Tier 2 HVR-H1_2 HVR-H2_7 0.4% 3 Tier 2 HVR-H1_3 HVR-H2_6 0.6% 2 Tier 3 HVR-H1_1 HVR-H2_7 0.3% 1 Tier 3 HVR-H1_3 HVR-H2_5 0.1% 1 Tier 3 HVR-H1_3 HVR-H2_7 0.1% 1

(148) 74 HVR-H1 sequences (SEQ ID NOS: 1-52 and 137-158, Table 1) and 90 HVR-H2 sequences (SEQ ID NOS: 53-136 and 159-164, Table 1) were identified that appeared in >1 of the unique antibody hits described above. When combined with various HVR-H3s and variable light chain domains, these HVRs were capable of forming antibodies that bound to multiple antigens. An additional 65 novel HVR-H1 and HVR-H2 sequence combinations were identified that appeared in >1 of the unique antibody hits described. Table 7 below shows HVR-H1 and HVR-H2 usage and number of antigens bound during the library analysis using these new HVR sequences.

(149) TABLE-US-00008 TABLE 7 Usage of new HVR-H1 and HVR-H2 sequences Number of Antigens SEQ ID NO: Number of hits hit out of 14 1 12 8 5 10 7 16 9 6 8 37 5 22 12 5 21 7 5 31 14 4 12 12 4 4 11 4 7 11 4 26 7 4 19 6 4 23 6 4 47 6 4 18 5 4 24 5 4 28 5 4 9 5 4 38 4 4 49 4 4 25 16 3 50 13 3 51 8 3 27 5 3 11 5 3 40 4 3 43 4 3 20 3 3 33 3 3 42 3 3 45 3 3 13 27 2 34 7 2 35 5 2 41 5 2 3 4 2 15 3 2 30 3 2 44 3 2 46 3 2 32 2 2 37 2 2 39 2 2 2 2 2 14 2 2 48 6 1 29 3 1 6 3 1 17 2 1 36 2 1 52 2 1 10 2 1 63 40 7 93 12 5 66 8 5 122 7 5 65 6 5 105 5 5 124 14 4 123 7 4 70 4 4 110 46 3 129 26 3 121 15 3 89 9 3 134 9 3 128 7 3 60 4 3 67 4 3 95 3 3 117 14 2 82 11 2 130 11 2 132 10 2 53 9 2 131 7 2 109 6 2 72 5 2 118 5 2 100 4 2 103 4 2 106 4 2 61 3 2 71 3 2 75 3 2 77 3 2 79 3 2 108 3 2 112 3 2 113 3 2 55 2 2 56 2 2 59 2 2 62 2 2 64 2 2 68 2 2 69 2 2 73 2 2 74 2

2 76 2 2 78 2 2 81 2 2 83 2 2 86 2 2 90 2 2 91 2 2 99 2 2 107 2 2 135 2 2 136 2 2 126 29 1 116 10 1 87 5 1 84 4 1 85 4 1 92 4 1 104 4 1 57 3 1 80 3 1 94 3 1 96 3 1 101 3 1 111 3 1 114 3 1 120 3 1 133 3 1 54 2 1 58 2 1 88 2 1 97 2 1 98 2 1 102 2 1 115 2 1 119 2 1 125 2 1 127 2 1

(150) Table 8 below shows usage and number of antigens bound for the combination of new HVR-H1 and HVR-H2 sequences.

(151) TABLE-US-00009 TABLE 8 new HVR-H1 and HVR-H2 combination usage Number of Preference HVR-H1 HVR-H2 Number Antigens Ranking SEQ ID NO: SEQ ID NO: of hits hit out of 14 Tier 1 157 63 4 3 Tier 1 1 122 4 3 Tier 1 138 63 3 3 Tier 1 154 63 5 2 Tier 1 158 161 5 2 Tier 1 158 63 3 2 Tier 1 145 128 3 2 Tier 1 22 61 2 2 Tier 1 31 63 2 2 Tier 1 153 63 2 2 Tier 1 155 67 2 2 Tier 1 156 100 2 2 Tier 1 51 162 2 2 Tier 1 138 123 2 2 Tier 1 139 110 38 1 Tier 1 8 126 29 1 Tier 1 13 129 21 1 Tier 1 31 124 11 1 Tier 1 25 130 10 1 Tier 1 150 132 9 1 Tier 1 158 162 8 1 Tier 1 12 82 8 1 Tier 1 149 117 7 1 Tier 1 7 134 6 1 Tier 2 26 53 4 1 Tier 2 151 53 4 1 Tier 2 34 63 3 1 Tier 2 50 162 3 1 Tier 2 158 104 3 1 Tier 2 5 121 3 1 Tier 2 6 116 3 1 Tier 2 7 121 3 1 Tier 2 17 63 2 1 Tier 2 25 101 2 1 Tier 2 25 114 2 1 Tier 2 29 112 2 1 Tier 2 152 63 2 1 Tier 2 156 89 2 1 Tier 2 157 94 2 1 Tier 2 48 58 2 1 Tier 2 50 89 2 1 Tier 2 50 163 2 1 Tier 2 158 160 2 1 Tier 2 158 87 2 1 Tier 2 158 92 2 1 Tier 2 158 93 2 1 Tier 2 158 97 2 1 Tier 2 158 103 2 1 Tier 2 158 164 2 1 Tier 2 137 54 2 1 Tier 2 3 127 2 1 Tier 2 4 85 2 1 Tier 2 4 110 2 1 Tier 2 139 109 2 1 Tier 2 139 121 2 1 Tier 2 8 120 2 1 Tier 2 140 131 2 1 Tier 2 141 116 2 1 Tier 2 142 159 2 1 Tier 2 143 116 2 1 Tier 2 144 121 2 1 Tier 2 146 110 2 1 Tier 2 147 133 2 1 Tier 2 148 63 2 1 Tier 2 13 118 2 1

(152) Table 9 shows affinity data for unique hits using the indicated new HVR-H1 and HVR-H2 sequences.

(153) TABLE-US-00010 TABLE 9 Affinity data for confirmed hits using new HVR-H1 and HVR-H2 sequences HVR SEQ ID NO(S): Hit ID Antigen Kd (M) 8 4025 TAGT-8 2.89E−09 8 4033 TAGT-8 8.75E−10 8 4614 TAGT-8 3.53E−10 8 4615 TAGT-8 2.28E−10 8 4617 TAGT-8 2.88E−10 8 4622 TAGT-8 2.74E−10 8 4627 TAGT-8 1.82E−10 8 4631 TAGT-8 1.83E−10 8 4633 TAGT-8 3.22E−10 8 4634 TAGT-8 2.07E−10 8 4638 TAGT-8 3.14E−10 8 4642 TAGT-8 1.89E−10 8 4644 TAGT-8 2.48E−10 8 4645 TAGT-8 2.96E−10 8 4650 TAGT-8 3.57E−10 8 4651 TAGT-8 3.01E−10 8 4652 TAGT-8 2.94E−10 8 4654 TAGT-8 2.32E−10 8 4658 TAGT-8 1.42E−10 8 4665 TAGT-8 3.69E−10 8 4673 TAGT-8 3.23E−10 8 4674 TAGT-8 5.02E−10 8 4681 TAGT-8 5.43E−10 8 4689 TAGT-8 1.63E−10 8 4690 TAGT-8 4.67E−10 8 5532 TAGT-2 3.65E−09 8 5558 TAGT-2 2.43E−09 8 5970 TAGT-12 1.35E−08 8 6190 TAGT-10 2.55E−09 8 6203 TAGT-10 1.05E−08 8 7032 TAGT-8 2.08E−08 8 7043 TAGT-8 1.34E−08 8 7367 TAGT-5 2.04E−08 8 BH3002 TAGT-8 2.51E−10 8 BH3004 TAGT-8 3.00E−10 8 BH3005 TAGT-8 3.46E−10 8 BH3006 TAGT-8 1.94E−10 13 4043 TAGT-8 2.69E−09 13 4084 TAGT-8 2.94E−09 13 4618 TAGT-8 1.08E−09 13 4620 TAGT-8 3.48E−10 13 4623 TAGT-8 4.85E−10 13 4624 TAGT-8 1.00E−12 13 4625 TAGT-8 4.02E−10 13 4630 TAGT-8 2.67E−10 13 4653 TAGT-8 3.27E−10 13 4659 TAGT-8 2.12E−10 13 4662 TAGT-8 8.98E−10 13 4666 TAGT-8 1.17E−09 13 4668 TAGT-8 5.79E−10 13 4670 TAGT-8 8.21E−10 13 4675 TAGT-8 1.00E−12 13 4676 TAGT-8 1.62E−10 13 4678 TAGT-8 5.98E−10 13 4683 TAGT-8 8.97E−10 13 4684 TAGT-8 6.69E−10 13 4685 TAGT-8 4.78E−10 13 4686 TAGT-8 4.78E−10 13 4687 TAGT-8 4.08E−10 13 5739 TAGT-11 1.29E−08 13 7025 TAGT-8 4.87E−08 13 7035 TAGT-8 3.04E−09 13 7037 TAGT-8 2.10E−08 13 7038 TAGT-8 2.33E−08 25 4201 TAGT-6 1.41E−08 25 4217 TAGT-6 9.67E−08 25 4218 TAGT-6 2.85E−08 25 4813 TAGT-12 2.45E−10 25 5113 TAGT-12 6.80E−09 25 5114 TAGT-12 3.42E−08 25 5116 TAGT-12 1.46E−08 25 5119 TAGT-12 7.54E−09 25 5121 TAGT-12 9.29E−09 25 5123 TAGT-12 5.67E−09 25 5125 TAGT-12 2.42E−08 25 5128 TAGT-12 7.12E−09 25 5138 TAGT-12 8.55E−09 25 5968 TAGT-12 1.27E−08 25 5990 TAGT-12 1.15E−08 25 7442 TAGT-9 6.83E−09 31 4027 TAGT-8 1.55E−09 31 4027 TAGT-8M 3.81E−09 31 5020 TAGT-8 8.78E−10 31 5020 TAGT-8M 7.00E−09 31 5023 TAGT-8 9.46E−10 31 5023 TAGT-8M 5.77E−09 31 5030 TAGT-8 7.03E−10 31 5030 TAGT-8M 4.27E−09 31 5037 TAGT-8 1.06E−09 31 5037 TAGT-8M 4.36E−09 31 5039 TAGT-8 4.30E−10 31 5039 TAGT-8M 2.69E−09 31 5040 TAGT-8 4.37E−10 31 5040 TAGT-8M 3.13E−09 31 5045 TAGT-8 1.00E−09 31 5045 TAGT-8M 3.91E−09 31 5048 TAGT-8 5.10E−10 31 5048 TAGT-8M 2.52E−09 31 5066 TAGT-8 5.23E−09 31 5066 TAGT-8M 9.99E−09 31 5070 TAGT-8 1.34E−09 31 5070 TAGT-8M 6.63E−09 31 5658 TAGT-11 2.61E−10 31 5926 TAGT-12 3.23E−08 31 7394 TAGT-5 8.75E−09 50 5929 TAGT-12 3.20E−08 50 5978 TAGT-12 3.25E−08 50 5999 TAGT-12 6.29E−08 50 7077 TAGT-6 1.88E−08 50 7090 TAGT-6 5.55E−08 50 7128 TAGT-6 3.97E−08 50 7209 TAGT-12 9.36E−09 50 7219 TAGT-12 1.44E−08 50 7235 TAGT-12 2.18E−08 50 7240 TAGT-12 1.17E−08 50 7256 TAGT-12 7.08E−09 50 7257 TAGT-12 1.11E−08 50 7375 TAGT-5 6.03E−09 22 4116 TAGT-10 <1.0E−12 22 4129 TAGT-6 <1.0E−12 22 4140 TAGT-6 <1.0E−12 22 4842 TAGT-12 4.01E−10 22 5212 TAGT-1

9.19E−09 22 5218 TAGT-1 6.04E−09 22 5271 TAGT-1 1.24E−08 22 5284 TAGT-1 1.84E−08 22 5301 TAGT-6 2.61E−07 22 5336 TAGT-6 6.04E−07 22 5906 TAGT-12 1.50E−08 22 7207 TAGT-5 4.99E−10 1 3757 TAGT-6 1.84E−08 1 3869 TAGT-11 2.35E−08 1 5103 TAGT-10 2.67E−09 1 5163 TAGT-11 1.71E−08 1 5201 TAGT-1 5.33E−09 1 5287 TAGT-1 1.02E−08 1 5315 TAGT-6 2.10E−06 1 5612 TAGT-2 7.85E−09 1 7129 TAGT-6 1.90E−08 1 7317 TAGT-5 2.02E−08 1 7411 TAGT-4 3.82E−08 1 7419 TAGT-9 1.72E−08 12 4048 TAGT-10 3.24E−09 12 4163 TAGT-8 1.37E−08 12 4723 TAGT-10 9.11E−10 12 4733 TAGT-10 3.05E−10 12 4734 TAGT-10 5.72E−10 12 4767 TAGT-10 2.77E−10 12 4771 TAGT-10 7.23E−10 12 4797 TAGT-10 5.63E−10 12 4807 TAGT-10 1.17E−09 12 5200 TAGT-1 1.53E−08 12 7030 TAGT-8 3.47E−08 12 7324 TAGT-5 5.68E−09 4 4054 TAGT-10 1.58E−08 4 5203 TAGT-1 1.31E−08 4 5354 TAGT-6 4.96E−09 4 6179 TAGT-10 1.99E−09 4 6183 TAGT-10 2.70E−09 4 6206 TAGT-10 3.44E−09 4 6217 TAGT-10 4.99E−09 4 7260 TAGT-5 2.30E−09 4 7278 TAGT-5 1.53E−08 4 7371 TAGT-5 2.31E−08 4 7374 TAGT-5 1.97E−08 7 3898 TAGT-11 1.83E−08 7 4065 TAGT-10 4.31E−08 7 4182 TAGT-10 4.24E−09 7 4741 TAGT-10 1.66E−09 7 5149 TAGT-11 2.91E−09 7 5159 TAGT-11 4.09E−09 7 5160 TAGT-11 8.07E−09 7 5162 TAGT-11 9.87E−09 7 5165 TAGT-11 4.06E−09 7 5510 TAGT-2 2.62E−09 7 7370 TAGT-5 1.07E−08 5 4060 TAGT-10 1.10E−08 5 4130 TAGT-6 1.00E−09 5 4798 TAGT-10 4.35E−09 5 5204 TAGT-1 1.48E−08 5 5526 TAGT-2 1.54E−09 5 5600 TAGT-2 5.33E−09 5 5733 TAGT-11 7.15E−09 5 6219 TAGT-10 3.15E−09 5 6531 TAGT-3 1.08E−08 5 6539 TAGT-4 3.45E−09 16 4034 TAGT-8 4.27E−09 16 4102 TAGT-8 2.54E−09 16 4903 TAGT-12 1.91E−09 16 5220 TAGT-1 5.03E−09 16 5321 TAGT-6 7.16E−07 16 5720 TAGT-11 1.93E−08 16 6010 TAGT-12 2.83E−08 16 7183 TAGT-6 1.48E−08 51 4074 TAGT-6 1.95E−08 51 5347 TAGT-6 1.21E−08 51 7190 TAGT-6 1.03E−08 51 7237 TAGT-12 2.13E−08 51 7242 TAGT-12 1.71E−08 51 7251 TAGT-12 2.69E−08 51 7253 TAGT-12 1.62E−08 51 7433 TAGT-9 1.67E−08 21 4038 TAGT-8 2.98E−09 21 4127 TAGT-6 <1.0E−12 21 4844 TAGT-12 6.95E−10 21 5235 TAGT-1 1.41E−08 21 5328 TAGT-6 3.42E−07 21 5924 TAGT-12 5.95E−08 21 7395 TAGT-5 1.65E−08 26 4052 TAGT-10 9.73E−09 26 5094 TAGT-10 4.34E−08 26 5097 TAGT-10 1.27E−08 26 5109 TAGT-10 2.59E−08 26 5275 TAGT-1 9.65E−09 26 5399 TAGT-9 3.62E−08 26 7040 TAGT-8 2.72E−08 34 4836 TAGT-12 2.49E−09 34 4839 TAGT-12 6.16E−09 34 4852 TAGT-12 2.26E−09 34 4876 TAGT-12 7.75E−09 34 5349 TAGT-6 6.20E−09 34 5351 TAGT-6 7.29E−09 34 5369 TAGT-6 2.05E−08 19 5282 TAGT-1 1.07E−08 19 5298 TAGT-6 3.41E−07 19 5316 TAGT-6 1.14E−08 19 5404 TAGT-6 3.30E−09 19 7386 TAGT-5 1.32E−08 19 7426 TAGT-9 1.12E−08 23 5215 TAGT-1 6.64E−09 23 5272 TAGT-1 2.49E−08 23 5491 TAGT-11 1.43E−08 23 5744 TAGT-11 1.14E−08 23 5933 TAGT-12 3.13E−08 47 4072 TAGT-6 6.95E−09 47 4132 TAGT-6 <1.0E−12 47 4200 TAGT-6 5.68E−08 47 7229 TAGT-12 8.91E−09 47 7275 TAGT-5 6.85E−09 48 5314 TAGT-6 8.39E−09 48 5326 TAGT-6 7.84E−07 48 5342 TAGT-6 3.89E−08 48 5348 TAGT-6 1.02E−08 48 5364 TAGT-6 7.26E−09 48 5413 TAGT-6 9.93E−10 18 4809 TAGT-12 3.69E−10 18 4861 TAGT-12 5.11E−09 18 5363 TAGT-6 9.87E−09 18 6555 TAGT-3 4.18E−08 18 7513 TAGT-9 8.43E−09 24 7097 TAGT-6 2.43E−08 24 7228 TAGT-12 7.62E−09 24 7244 TAGT-12 1.05E−08 24 7388 TAGT-5 2.72E−09 24 7421 TAGT-9 2.47E−08 27 3761 TAGT-6 9.65E−08 27 4135 TAGT-6 <1.0E−12 27 4846 TAGT-12 3.19E−09 27 4874 TAGT-12 4.19E−09 27 5236 TAGT-1 1.49E−08 28 4925 TAGT-7 1.32E−08 28 5317 TAGT-6 3.34E−07 28 5341 TAGT-6 2.93E−08 28 5584 TAGT-2 1.76E−09 28 7315 TAGT-5 5.15E−09 35 4849 TAGT-12 8.40E−10 35 4850 TAGT-12 1.23E−09 35 4851 TAGT-12 3.84E−10 35 5694 TAGT-11 9.45E−09 35 5980 TAGT-12 1.14E−08 41 5934 TAGT-12 1.66E−08 41 5983 TAGT-12 2.09E−08 41 5993 TAGT-12 1.13E−08 41 5995 TAGT-12 1.42E−08 41 6475 TAGT-4 7.22E−09 9 5297 TAGT-6 1.77E−06 9 5561 TAGT-2 1.64E−08 9 5568 TAGT-2 1.14E−09 9 7268 TAGT-5 3.76E−09 9 7431 TAGT-9 3.53E−08 11 4051 TAGT-10 1.80E−08 11 4067 TAGT-10 1.97E−08 11 4103 TAGT-8 3.59E−10 11 5300 TAGT-6 1.53E−08 11 7047 TAGT-8 2.15E−08 38 4204 TAGT-10 6.83E−09 38 4204 TAGT-10M 6.89E−09 38 4847 TAGT-12 3.64E−10 38 5398 TAGT-9 1.97E−08 40 4029 TAGT-8 1.89E−09 40 4076 TAGT-6 7.44E−09 40 4126 TAGT-6 7.27E−09 40 7444 TAGT-9 5.53E−09 43 5408 TAGT-6 2.36E−08 43 5992 TAGT-12 1.70E−08 43 7249 TAGT-12 5.36E−09 43 7264 TAGT-5 3.17E−09 49 5756 TAGT-11 3.00E−08 49 6543 TAGT-3 6.78E−08 49 7420 TAGT-9 1.38E−08 3 5614 TAGT-2 5.29E−09 3 5642 TAGT-2 3.84E−09 3 7044 TAGT-8 1.12E−09 3 7045 TAGT-8 1.11E−09 15 4077 TAGT-6 <1.0E−12 15 5409 TAGT-6 1.70E−08 15 7380 TAGT-5 1.24E−08 20 4037 TAGT-8 5.53E−09 20 5732 TAGT-11 5.24E−09 20 7258 TAGT-12 9.72E−09 29 5930 TAGT-12 5.66E−09 29 5932 TAGT-12 1.12E−08 29 7254 TAGT-12 1.07E−08 30 5411 TAGT-6 1.25E−08 30 5420 TAGT-6 1.41E−08 30 7272 TAGT-5 3.49E−09 33 4180 TAGT-10 7.39E−08 33 5228 TAGT-1 3.06E−08 42 4141 TAGT-6 <1.0E−12 42 4816 TAGT-12

5.32E−09 42 5274 TAGT-1 2.52E−08 44 4045 TAGT-8 1.10E−09 44 4875 TAGT-12 1.03E−09 44 5921 TAGT-12 8.01E−09 45 5403 TAGT-6 8.26E−09 45 6526 TAGT-4 1.16E−08 45 7379 TAGT-5 5.43E−09 46 4828 TAGT-12 1.10E−09 46 4863 TAGT-12 6.63E−10 46 7427 TAGT-9 5.58E−09 6 4752 TAGT-10 3.34E−09 6 6210 TAGT-10 5.17E−10 6 6212 TAGT-10 2.25E−09 17 4818 TAGT-12 1.02E−09 17 4841 TAGT-12 4.50E−10 32 7248 TAGT-12 1.28E−08 32 7310 TAGT-5 1.41E−08 36 4815 TAGT-12 5.91E−09 36 4825 TAGT-12 6.05E−09 37 5360 TAGT-6 2.41E−08 39 7358 TAGT-3 5.15E−08 39 7389 TAGT-5 4.50E−09 52 5370 TAGT-6 1.91E−09 52 7166 TAGT-6 1.24E−08 2 5438 TAGT-9 9.30E−09 2 7373 TAGT-5 5.13E−09 10 7055 TAGT-8 7.57E−10 10 7067 TAGT-8 3.41E−08 14 4062 TAGT-10 2.11E−08 14 5237 TAGT-1 3.28E−09 110 4055 TAGT-10 1.07E−08 110 4061 TAGT-10 3.42E−08 110 4066 TAGT-10 4.76E−08 110 4181 TAGT-10 4.27E−08 110 4693 TAGT-10 4.87E−10 110 4696 TAGT-10 4.58E−10 110 4697 TAGT-10 6.21E−10 110 4698 TAGT-10 5.70E−10 110 4700 TAGT-10 2.62E−10 110 4701 TAGT-10 5.60E−10 110 4702 TAGT-10 5.02E−10 110 4703 TAGT-10 2.85E−10 110 4704 TAGT-10 6.65E−10 110 4705 TAGT-10 3.02E−10 110 4706 TAGT-10 2.50E−10 110 4707 TAGT-10 4.29E−10 110 4708 TAGT-10 5.29E−10 110 4710 TAGT-10 6.26E−10 110 4714 TAGT-10 4.46E−10 110 4717 TAGT-10 4.61E−10 110 4718 TAGT-10 5.32E−10 110 4722 TAGT-10 7.46E−10 110 4725 TAGT-10 4.84E−10 110 4729 TAGT-10 8.80E−10 110 4731 TAGT-10 4.67E−10 110 4732 TAGT-10 3.33E−10 110 4738 TAGT-10 5.34E−10 110 4743 TAGT-10 7.40E−09 110 4744 TAGT-10 3.73E−10 110 4748 TAGT-10 3.92E−10 110 4749 TAGT-10 2.55E−10 110 4750 TAGT-10 7.86E−10 110 4753 TAGT-10 3.43E−10 110 4759 TAGT-10 6.59E−10 110 4766 TAGT-10 4.09E−10 110 4788 TAGT-10 2.88E−10 110 4794 TAGT-10 5.56E−10 110 4803 TAGT-10 1.88E−10 110 4805 TAGT-10 4.26E−10 110 4808 TAGT-10 8.28E−10 110 4909 TAGT-10 2.90E−10 110 6010 TAGT-12 2.83E−08 110 6183 TAGT-10 2.70E−09 110 6191 TAGT-10 6.58E−11 110 6206 TAGT-10 3.44E−09 110 7066 TAGT-8 1.80E−08 63 4036 TAGT-8 3.13E−09 63 4096 TAGT-8 2.70E−09 63 4812 TAGT-12 2.89E−09 63 4815 TAGT-12 5.91E−09 63 4817 TAGT-12 2.06E−09 63 4818 TAGT-12 1.02E−09 63 4836 TAGT-12 2.49E−09 63 4840 TAGT-12 2.08E−09 63 4841 TAGT-12 4.50E−10 63 4846 TAGT-12 3.19E−09 63 4852 TAGT-12 2.26E−09 63 4860 TAGT-12 2.44E−09 63 4876 TAGT-12 7.75E−09 63 4880 TAGT-12 2.77E−09 63 4897 TAGT-12 6.83E−10 63 4901 TAGT-12 3.19E−09 63 4904 TAGT-12 5.39E−09 63 5115 TAGT-12 1.16E−08 63 5195 TAGT-1 2.62E−08 63 5216 TAGT-1 3.08E−09 63 5286 TAGT-1 6.34E−09 63 5287 TAGT-1 1.02E−08 63 5290 TAGT-1 6.73E−09 63 5323 TAGT-6 1.04E−08 63 5387 TAGT-8 1.13E−09 63 5404 TAGT-6 3.30E−09 63 5421 TAGT-9 1.05E−08 63 5422 TAGT-9 5.12E−09 63 5658 TAGT-11 2.61E−10 63 5722 TAGT-11 3.08E−08 63 5756 TAGT-11 3.00E−08 63 5985 TAGT-12 3.92E−08 63 5986 TAGT-12 4.65E−08 63 7273 TAGT-5 6.01E−09 63 7316 TAGT-5 2.04E−08 63 7370 TAGT-5 1.07E−08 63 7375 TAGT-5 6.03E−09 63 7385 TAGT-5 3.26E−09 63 7391 TAGT-5 1.35E−08 63 7394 TAGT-5 8.75E−09 126 4033 TAGT-8 8.75E−10 126 4614 TAGT-8 3.53E−10 126 4615 TAGT-8 2.28E−10 126 4617 TAGT-8 2.88E−10 126 4622 TAGT-8 2.74E−10 126 4627 TAGT-8 1.82E−10 126 4631 TAGT-8 1.83E−10 126 4633 TAGT-8 3.22E−10 126 4634 TAGT-8 2.07E−10 126 4638 TAGT-8 3.14E−10 126 4642 TAGT-8 1.89E−10 126 4644 TAGT-8 2.48E−10 126 4645 TAGT-8 2.96E−10 126 4650 TAGT-8 3.57E−10 126 4651 TAGT-8 3.01E−10 126 4652 TAGT-8 2.94E−10 126 4654 TAGT-8 2.32E−10 126 4658 TAGT-8 1.42E−10 126 4665 TAGT-8 3.69E−10 126 4673 TAGT-8 3.23E−10 126 4674 TAGT-8 5.02E−10 126 4681 TAGT-8 5.43E−10 126 4689 TAGT-8 1.63E−10 126 4690 TAGT-8 4.67E−10 126 7043 TAGT-8 1.34E−08 126 BH3002 TAGT-8 2.51E−10 126 BH3004 TAGT-8 3.00E−10 126 BH3005 TAGT-8 3.46E−10 126 BH3006 TAGT-8 1.94E−10 129 4038 TAGT-8 2.98E−09 129 4084 TAGT-8 2.94E−09 129 4618 TAGT-8 1.08E−09 129 4620 TAGT-8 3.48E−10 129 4623 TAGT-8 4.85E−10 129 4624 TAGT-8 1.00E−12 129 4625 TAGT-8 4.02E−10 129 4630 TAGT-8 2.67E−10 129 4653 TAGT-8 3.27E−10 129 4659 TAGT-8 2.12E−10 129 4662 TAGT-8 8.98E−10 129 4666 TAGT-8 1.17E−09 129 4668 TAGT-8 5.79E−10 129 4670 TAGT-8 8.21E−10 129 4675 TAGT-8 1.00E−12 129 4676 TAGT-8 1.62E−10 129 4678 TAGT-8 5.98E−10 129 4683 TAGT-8 8.97E−10 129 4684 TAGT-8 6.69E−10 129 4685 TAGT-8 4.78E−10 129 4686 TAGT-8 4.78E−10 129 4687 TAGT-8 4.08E−10 129 5970 TAGT-12 1.35E−08 129 7213 TAGT-12 8.87E−09 129 7232 TAGT-12 8.06E−09 129 7357 TAGT-3 6.14E−08 121 4054 TAGT-10 1.58E−08 121 4060 TAGT-10 1.10E−08 121 4065 TAGT-10 4.31E−08 121 4072 TAGT-6 6.95E−09 121 4182 TAGT-10 4.24E−09 121 4741 TAGT-10 1.66E−09 121 4798 TAGT-10 4.35E−09 121 5295 TAGT-9 2.21E−09 121 6185 TAGT-10 1.57E−09 121 6187 TAGT-10 2.74E−08 121 6195 TAGT-10 4.30E−09 121 6197 TAGT-10 8.56E−09 121 6198 TAGT-10 2.85E−09 121 6209 TAGT-10 3.35E−09 121 6219 TAGT-10 3.15E−09 117 4031 TAGT-8 1.06E−09 117 5126 TAGT-8 9.54E−09 117 5129 TAGT-8 1.12E−09 117 5132 TAGT-8 3.06E−09 117 5145 TAGT-8 7.00E−09 117 7067 TAGT-8 3.41E−08 117 7068 TAGT-8 1.11E−08 117 7073 TAGT-8 3.19E−09 124 4027 TAGT-8 1.55E−09 124 4027 TAGT-8M

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84 7373 TAGT-5 5.13E−09 84 7378 TAGT-5 5.66E−09 85 7260 TAGT-5 2.30E−09 85 7365 TAGT-5 1.82E−09 85 7369 TAGT-5 2.46E−09 85 7374 TAGT-5 1.97E−08 92 4073 TAGT-6 <1.0E−12 92 5355 TAGT-6 8.71E−10 92 7080 TAGT-6 2.44E−08 92 7081 TAGT-6 4.31E−08 100 5328 TAGT-6 3.42E−07 100 5417 TAGT-6 4.04E−08 100 5974 TAGT-12 5.02E−08 100 5977 TAGT-12 2.70E−08 103 4075 TAGT-6 <1.0E−12 103 5961 TAGT-12 2.41E−08 103 5993 TAGT-12 1.13E−08 103 7255 TAGT-12 1.20E−08 104 5912 TAGT-12 1.68E−08 104 5923 TAGT-12 1.60E−08 104 5978 TAGT-12 3.25E−08 104 7226 TAGT-12 7.57E−09 106 4141 TAGT-6 <1.0E−12 106 4222 TAGT-6 5.55E−08 106 5321 TAGT-6 7.16E−07 106 7317 TAGT-5 2.02E−08 57 5303 TAGT-6 5.12E−09 57 5359 TAGT-6 7.10E−10 57 5365 TAGT-6 2.56E−09 61 5230 TAGT-1 9.21E−09 61 5271 TAGT-1 1.24E−08 61 7207 TAGT-5 4.99E−10 71 5336 TAGT-6 6.04E−07 71 5418 TAGT-6 2.02E−08 71 5438 TAGT-9 9.30E−09 75 5194 TAGT-1 1.29E−08 75 5235 TAGT-1 1.41E−08 75 5403 TAGT-6 8.26E−09 77 4063 TAGT-10 1.90E−08 77 4067 TAGT-10 1.97E−08 77 7429 TAGT-9 2.12E−08 79 5353 TAGT-6 1.61E−08 79 7419 TAGT-9 1.72E−08 79 7431 TAGT-9 3.53E−08 80 7276 TAGT-5 1.02E−08 80 7311 TAGT-5 9.20E−09 80 7371 TAGT-5 2.31E−08 94 5371 TAGT-6 3.97E−09 94 7088 TAGT-6 4.36E−08 94 7100 TAGT-6 3.50E−08 95 5236 TAGT-1 1.49E−08 95 5983 TAGT-12 2.09E−08 95 7128 TAGT-6 3.97E−08 96 7077 TAGT-6 1.88E−08 96 7107 TAGT-6 1.22E−07 96 7109 TAGT-6 3.20E−08 10 3761 TAGT-6 9.65E−08 10 4217 TAGT-6 9.67E−08 10 4218 TAGT-6 2.85E−08 108 4034 TAGT-8 4.27E−09 108 5351 TAGT-6 7.29E−09 108 5357 TAGT-6 7.14E−09 111 4827 TAGT-12 1.51E−09 111 4834 TAGT-12 9.68E−10 111 4875 TAGT-12 1.03E−09 112 4025 TAGT-8 2.89E−09 112 5930 TAGT-12 5.66E−09 112 5932 TAGT-12 1.12E−08 113 4116 TAGT-10 <1.0E−12 113 4863 TAGT-12 6.63E−10 113 5980 TAGT-12 1.14E−08 114 5921 TAGT-12 8.01E−09 114 5968 TAGT-12 1.27E−08 114 5990 TAGT-12 1.15E−08 120 6180 TAGT-10 6.11E−09 120 6190 TAGT-10 2.55E−09 120 6203 TAGT-10 1.05E−08 133 5935 TAGT-12 8.78E−09 133 6008 TAGT-12 5.10E−08 133 7222 TAGT-12 1.26E−09 54 7277 TAGT-5 2.56E−09 54 7390 TAGT-5 1.44E−09 55 5238 TAGT-1 5.04E−08 55 5370 TAGT-6 1.91E−09 56 5285 TAGT-1 1.42E−08 56 5310 TAGT-6 5.72E−09 58 5314 TAGT-6 8.39E−09 58 5342 TAGT-6 3.89E−08 59 5202 TAGT-1 1.50E−08 59 7032 TAGT-8 2.08E−08 62 5220 TAGT-1 5.03E−09 62 7163 TAGT-6 1.26E−08 64 5211 TAGT-1 2.11E−09 64 5584 TAGT-2 1.76E−09 68 4177 TAGT-8 1.48E−08 68 5234 TAGT-1 1.28E−08 69 4838 TAGT-12 2.52E−09 69 7166 TAGT-6 1.24E−08 73 4878 TAGT-12 4.07E−09 73 5315 TAGT-6 2.10E−06 74 3760 TAGT-6 1.26E−08 76 5297 TAGT-6 1.77E−06 76 5745 TAGT-11 1.06E−08 78 4058 TAGT-10 1.13E−08 78 5291 TAGT-1 6.57E−09 81 5212 TAGT-1 9.19E−09 81 5568 TAGT-2 1.14E−09 83 5411 TAGT-6 1.25E−08 83 5565 TAGT-2 3.02E−09 86 4129 TAGT-6 <1.0E−12 86 6473 TAGT-4 2.30E−08 88 5905 TAGT-12 3.83E−08 88 5919 TAGT-12 2.38E−08 90 4029 TAGT-8 1.89E−09 90 7097 TAGT-6 2.43E−08 91 5272 TAGT-1 2.49E−08 91 7242 TAGT-12 1.71E−08 97 5915 TAGT-12 1.82E−08 97 5964 TAGT-12 1.40E−08 98 4131 TAGT-6 <1.0E−12 98 5347 TAGT-6 1.21E−08 99 7090 TAGT-6 5.55E−08 102 6004 TAGT-12 5.50E−08 102 7251 TAGT-12 2.69E−08 107 4133 TAGT-6 3.90E−10 107 7262 TAGT-5 2.63E−09 115 7310 TAGT-5 1.41E−08 115 7379 TAGT-5 5.43E−09 119 6193 TAGT-10 3.18E−09 119 6220 TAGT-10 3.45E−09 125 4030 TAGT-8 4.90E−09 125 7038 TAGT-8 2.33E−08 127 7044 TAGT-8 1.12E−09 127 7045 TAGT-8 1.11E−09 135 4204 TAGT-10 6.83E−09 135 4204 TAGT-10M 6.89E−09 135 5423 TAGT-9 4.90E−09 136 4861 TAGT-12 5.11E−09 136 7129 TAGT-6 1.90E−08 139 and 110 4181 TAGT-10 4.27E−08 139 and 110 4693 TAGT-10 4.87E−10 139 and 110 4696 TAGT-10 4.58E−10 139 and 110 4697 TAGT-10 6.21E−10 139 and 110 4698 TAGT-10 5.70E−10 139 and 110 4700 TAGT-10 2.62E−10 139 and 110 4701 TAGT-10 5.60E−10 139 and 110 4702 TAGT-10 5.02E−10 139 and 110 4703 TAGT-10 2.85E−10 139 and 110 4704 TAGT-10 6.65E−10 139 and 110 4705 TAGT-10 3.02E−10 139 and 110 4706 TAGT-10 2.50E−10 139 and 110 4707 TAGT-10 4.29E−10 139 and 110 4708 TAGT-10 5.29E−10 139 and 110 4710 TAGT-10 6.26E−10 139 and 110 4714 TAGT-10 4.46E−10 139 and 110 4717 TAGT-10 4.61E−10 139 and 110 4718 TAGT-10 5.32E−10 139 and 110 4722 TAGT-10 7.46E−10 139 and 110 4725 TAGT-10 4.84E−10 139 and 110 4729 TAGT-10 8.80E−10 139 and 110 4731 TAGT-10 4.67E−10 139 and 110 4732 TAGT-10 3.33E−10 139 and 110 4738 TAGT-10 5.34E−10 139 and 110 4744 TAGT-10 3.73E−10 139 and 110 4748 TAGT-10 3.92E−10 139 and 110 4749 TAGT-10 2.55E−10 139 and 110 4750 TAGT-10 7.86E−10 139 and 110 4753 TAGT-10 3.43E−10 139 and 110 4759 TAGT-10 6.59E−10 139 and 110 4766 TAGT-10 4.09E−10 139 and 110 4788 TAGT-10 2.88E−10 139 and 110 4794 TAGT-10 5.56E−10 139 and 110 4803 TAGT-10 1.88E−10 139 and 110 4805 TAGT-10 4.26E−10 139 and 110 4808 TAGT-10 8.28E−10 139 and 110 4909 TAGT-10 2.90E−10 139 and 110 6191 TAGT-10 6.58E−11 8 and 126 4033 TAGT-8 8.75E−10 8 and 126 4614 TAGT-8 3.53E−10 8 and 126 4615 TAGT-8 2.28E−10 8 and 126 4617 TAGT-8 2.88E−10 8 and 126 4622 TAGT-8 2.74E−10 8 and 126 4627 TAGT-8 1.82E−10 8 and 126 4631 TAGT-8 1.83E−10 8 and 126

4633 TAGT-8 3.22E−10 8 and 126 4634 TAGT-8 2.07E−10 8 and 126 4638 TAGT-8 3.14E−10 8 and 126 4642 TAGT-8 1.89E−10 8 and 126 4644 TAGT-8 2.48E−10 8 and 126 4645 TAGT-8 2.96E−10 8 and 126 4650 TAGT-8 3.57E−10 8 and 126 4651 TAGT-8 3.01E−10 8 and 126 4652 TAGT-8 2.94E−10 8 and 126 4654 TAGT-8 2.32E−10 8 and 126 4658 TAGT-8 1.42E−10 8 and 126 4665 TAGT-8 3.69E−10 8 and 126 4673 TAGT-8 3.23E−10 8 and 126 4674 TAGT-8 5.02E−10 8 and 126 4681 TAGT-8 5.43E−10 8 and 126 4689 TAGT-8 1.63E−10 8 and 126 4690 TAGT-8 4.67E−10 8 and 126 7043 TAGT-8 1.34E−08 8 and 126 BH3002 TAGT-8 2.51E−10 8 and 126 BH3004 TAGT-8 3.00E−10 8 and 126 BH3005 TAGT-8 3.46E−10 8 and 126 BH3006 TAGT-8 1.94E−10 13 and 129 4084 TAGT-8 2.94E−09 13 and 129 4618 TAGT-8 1.08E−09 13 and 129 4620 TAGT-8 3.48E−10 13 and 129 4623 TAGT-8 4.85E−10 13 and 129 4624 TAGT-8 1.00E−12 13 and 129 4625 TAGT-8 4.02E−10 13 and 129 4630 TAGT-8 2.67E−10 13 and 129 4653 TAGT-8 3.27E−10 13 and 129 4659 TAGT-8 2.12E−10 13 and 129 4662 TAGT-8 8.98E−10 13 and 129 4666 TAGT-8 1.17E−09 13 and 129 4668 TAGT-8 5.79E−10 13 and 129 4670 TAGT-8 8.21E−10 13 and 129 4675 TAGT-8 1.00E−12 13 and 129 4676 TAGT-8 1.62E−10 13 and 129 4678 TAGT-8 5.98E−10 13 and 129 4683 TAGT-8 8.97E−10 13 and 129 4684 TAGT-8 6.69E−10 13 and 129 4685 TAGT-8 4.78E−10 13 and 129 4686 TAGT-8 4.78E−10 13 and 129 4687 TAGT-8 4.08E−10 31 and 124 4027 TAGT-8 1.55E−09 31 and 124 4027 TAGT-8M 3.81E−09 31 and 124 5020 TAGT-8 8.78E−10 31 and 124 5020 TAGT-8M 7.00E−09 31 and 124 5023 TAGT-8 9.46E−10 31 and 124 5023 TAGT-8M 5.77E−09 31 and 124 5030 TAGT-8 7.03E−10 31 and 124 5030 TAGT-8M 4.27E−09 31 and 124 5037 TAGT-8 1.06E−09 31 and 124 5037 TAGT-8M 4.36E−09 31 and 124 5039 TAGT-8 4.30E−10 31 and 124 5039 TAGT-8M 2.69E−09 31 and 124 5040 TAGT-8 4.37E−10 31 and 124 5040 TAGT-8M 3.13E−09 31 and 124 5045 TAGT-8 1.00E−09 31 and 124 5045 TAGT-8M 3.91E−09 31 and 124 5048 TAGT-8 5.10E−10 31 and 124 5048 TAGT-8M 2.52E−09 31 and 124 5066 TAGT-8 5.23E−09 31 and 124 5066 TAGT-8M 9.99E−09 31 and 124 5070 TAGT-8 1.34E−09 31 and 124 5070 TAGT-8M 6.63E−09 25 and 130 4813 TAGT-12 2.45E−10 25 and 130 5113 TAGT-12 6.80E−09 25 and 130 5114 TAGT-12 3.42E−08 25 and 130 5116 TAGT-12 1.46E−08 25 and 130 5119 TAGT-12 7.54E−09 25 and 130 5121 TAGT-12 9.29E−09 25 and 130 5123 TAGT-12 5.67E−09 25 and 130 5125 TAGT-12 2.42E−08 25 and 130 5128 TAGT-12 7.12E−09 25 and 130 5138 TAGT-12 8.55E−09 150 and 132 4032 TAGT-8 5.11E−09 150 and 132 4032 TAGT-8M 4.84E−09 150 and 132 5012 TAGT-8 1.76E−09 150 and 132 5012 TAGT-8M 2.03E−09 150 and 132 5014 TAGT-8 2.43E−09 150 and 132 5014 TAGT-8M 3.87E−09 150 and 132 5016 TAGT-8 3.56E−09 150 and 132 5016 TAGT-8M 2.84E−09 150 and 132 5022 TAGT-8 3.68E−09 150 and 132 5022 TAGT-8M 3.03E−09 150 and 132 5024 TAGT-8 4.52E−09 150 and 132 5024 TAGT-8M 3.48E−09 150 and 132 5041 TAGT-8 1.68E−09 150 and 132 5041 TAGT-8M 1.67E−09 150 and 132 5074 TAGT-8 4.31E−09 150 and 132 5074 TAGT-8M 2.98E−09 150 and 132 5082 TAGT-8 4.79E−09 150 and 132 5082 TAGT-8M 3.23E−09 158 and 162 5962 TAGT-12 8.06E−08 158 and 162 5996 TAGT-12 2.21E−08 158 and 162 6000 TAGT-12 7.86E−08 158 and 162 7210 TAGT-12 9.85E−09 158 and 162 7218 TAGT-12 1.49E−08 158 and 162 7225 TAGT-12 9.53E−09 158 and 162 7241 TAGT-12 6.43E−09 158 and 162 7247 TAGT-12 8.93E−09 12 and 82 4048 TAGT-10 3.24E−09 12 and 82 4723 TAGT-10 9.11E−10 12 and 82 4733 TAGT-10 3.05E−10 12 and 82 4734 TAGT-10 5.72E−10 12 and 82 4767 TAGT-10 2.77E−10 12 and 82 4771 TAGT-10 7.23E−10 12 and 82 4797 TAGT-10 5.63E−10 12 and 82 4807 TAGT-10 1.17E−09 149 and 117 4031 TAGT-8 1.06E−09 149 and 117 5126 TAGT-8 9.54E−09 149 and 117 5129 TAGT-8 1.12E−09 149 and 117 5132 TAGT-8 3.06E−09 149 and 117 5145 TAGT-8 7.00E−09 149 and 117 7068 TAGT-8 1.11E−08 149 and 117 7073 TAGT-8 3.19E−09 7 and 134 3898 TAGT-11 1.83E−08 7 and 134 5149 TAGT-11 2.91E−09 7 and 134 5159 TAGT-11 4.09E−09 7 and 134 5160 TAGT-11 8.07E−09 7 and 134 5162 TAGT-11 9.87E−09 7 and 134 5165 TAGT-11 4.06E−09 154 and 63 4812 TAGT-12 2.89E−09 154 and 63 4904 TAGT-12 5.39E−09 154 and 63 5115 TAGT-12 1.16E−08 154 and 63 5421 TAGT-9 1.05E−08 154 and 63 5422 TAGT-9 5.12E−09 158 and 161 5922 TAGT-12 1.95E−08 158 and 161 7135 TAGT-6 3.17E−08 158 and 161 7245 TAGT-12 1.38E−08 158 and 161 7246 TAGT-12 6.22E−09 158 and 161 7252 TAGT-12 9.56E−09 26 and 53 4052 TAGT-10 9.73E−09 26 and 53 5094 TAGT-10 4.34E−08 26 and 53 5097 TAGT-10 1.27E−08 26 and 53 5109 TAGT-10 2.59E−08 151 and 53 4059 TAGT-10 3.30E−07 151 and 53 5095 TAGT-10 1.27E−08 151 and 53 5099 TAGT-10 4.20E−08 151 and 53 5936 TAGT-10 1.75E−08 157 and 63 4036 TAGT-8 3.13E−09 157 and 63 4096 TAGT-8 2.70E−09 157 and 63 5323 TAGT-6 1.04E−08 157 and 63 7391 TAGT-5 1.35E−08 1 and 122 3757 TAGT-6 1.84E−08 1 and 122 3869 TAGT-11 2.35E−08 1 and 122 5103 TAGT-10 2.67E−09 1 and 122 5163 TAGT-11 1.71E−08 34 and 63 4836 TAGT-12 2.49E−09 34 and 63 4852 TAGT-12 2.26E−09 34 and 63 4876 TAGT-12 7.75E−09 50 and 162 7240 TAGT-12 1.17E−08 50 and 162 7256 TAGT-12 7.08E−09 50 and

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(154) An HVR-H1 comprising SEQ ID NO:16 was used in 8 unique hits. Using this same HVR-H1 sequence, but different sequences of the other HVRs, those 8 hits were capable of binding to 5 different target antigens. Exemplary hit IDs 4034, 6010, and 7183, which bound to TAGT-8, TAGT-12, and TAGT-6, respectively, contained an HVR-H1 comprising SEQ ID NO:16.

(155) An HVR-H2 comprising SEQ ID NO:63 was used in 40 unique hits. Using this same HVR-H2 sequence, but different sequences of the other HVRs, those 40 hits were capable of binding to 7 different target antigens. Exemplary hit IDs 4036, 5115, and 5404, which bound to TAGT-8, TAGT-12, and TAGT-6, respectively, contained an HVR-H2 comprising SEQ ID NO:63.

(156) Exemplary hit IDs 3757 and 5103 contained the same heavy chain variable region, including the same HVR-H1 and HVR-H2 sequences (SEQ ID NOS: 1 and 122), but when combined with different variable light chain domains, they bound to two different target antigens (TAGT-6 and TAGT-10, respectively). Two additional hits with these same HVR-H1 and HVR-H2 sequences could bind to another target antigen, TAGT-11.

(157) Exemplary hit ID 4027, containing the HVR-H1 and HVR-H2 sequences of SEQ ID NOS:31 and 124, was capable of binding the same antigen from two different species (TAGT-8H and TAGT-8M). Several other hits with these same HVR-H1 and HVR-H2 sequences demonstrated species cross-reactivity.

(158) The novel methodology employed to identify the dynamic motif of the redefined hyper-variable regions of antibodies based upon structural and sequence variability has led to the design of a limited number

of V.sub.H components that can bind to the same or multiple different targets depending upon the V.sub.L segment with which the V.sub.H components are paired. The data and antibodies described herein reveals that the heavy chain library, either used as a whole set or a subset, is robust enough to serve as the V.sub.H component for antibody discovery.

SEQUENCES

(159) All polypeptide sequences are presented N-terminal to C-terminal unless otherwise noted.

(160) All polynucleotide sequences are presented 5′ to 3′ unless otherwise noted. Designed HVR-H1 sequence 1: FTFTDYGIHWV (SEQ ID NO:1) Designed HVR-H1 sequence 2: FTFTGYAIHWV (SEQ ID NO:2) Designed HVR-H1 sequence 3: FTFTNYGIHWV (SEQ ID NO:3) Designed HVR-H1 sequence 4: YTFSDYAIHWV (SEQ ID NO:4) Designed HVR-H1 sequence 5: YTFSDYGIHWV (SEQ ID NO:5) Designed HVR-H1 sequence 6: YTFSGYAIHWV (SEQ ID NO:6) Designed HVR-H1 sequence 7: YTFSGYGIHWV (SEQ ID NO:7) Designed HVR-H1 sequence 8: YTFSNYGIHWV (SEQ ID NO:8) Designed HVR-H1 sequence 9: YTFSSYGIHWV (SEQ ID NO:9) Designed HVR-H1 sequence 10: YTFSGYWIHWV (SEQ ID NO:10) Designed HVR-H1 sequence 11: YTFSNYWIHWV (SEQ ID NO:11) Designed HVR-H1 sequence 12: FTFSGYWIHWV (SEQ ID NO: 12) Designed HVR-H1 sequence 13: FTFSNYWIHWV (SEQ ID NO:13) Designed HVR-H1 sequence 14: YTFSDYWIHWV (SEQ ID NO: 14) Designed HVR-H1 sequence 15: YSISSGHHWAWI (SEQ ID NO:15) Designed HVR-H1 sequence 16: YSISSGHYWNWI (SEQ ID NO:16) Designed HVR-H1 sequence 17: YSISSGHYWSWI (SEQ ID NO:17) Designed HVR-H1 sequence 18: YSISSGHYWTWI (SEQ ID NO:18) Designed HVR-H1 sequence 19: YSISSGYHWAWI (SEQ ID NO:19) Designed HVR-H1 sequence 20: YSISSGYHWDWI (SEQ ID NO:20) Designed HVR-H1 sequence 21: YSISSGYHWGWI (SEQ ID NO:21) Designed HVR-H1 sequence 22: YSISSGYHWNWI (SEQ ID NO:22) Designed HVR-H1 sequence 23: YSISSGYHWSWI (SEQ ID NO:23) Designed HVR-H1 sequence 24: YSISSGHHWDWI (SEQ ID NO:24) Designed HVR-H1 sequence 25: YSISSGYYWDWI (SEQ ID NO:25) Designed HVR-H1 sequence 26: YSISSGYYWNWI (SEQ ID NO:26) Designed HVR-H1 sequence 27: YSISSGYYWTWI (SEQ ID NO:27) Designed HVR-H1 sequence 28: YSITSGHHWAWI (SEQ ID NO:28) Designed HVR-H1 sequence 29: YSITSGHHWDWI (SEQ ID NO:29) Designed HVR-H1 sequence 30: YSITSGHHWGWI (SEQ ID NO:30) Designed HVR-H1 sequence 31: YSITSGHHWNWI (SEQ ID NO:31) Designed HVR-H1 sequence 32: YSITSGHHWSWI (SEQ ID NO:32) Designed HVR-H1 sequence 33: YSISSGHHWGWI (SEQ ID NO:33) Designed HVR-H1 sequence 34: YSITSGHYWAWI (SEQ ID NO:34) Designed HVR-H1 sequence 35: YSITSGHYWDWI (SEQ ID NO:35) Designed HVR-H1 sequence 36: YSITSGHYWGWI (SEQ ID NO:36) Designed HVR-H1 sequence 37: YSITSGHYWNWI (SEQ ID NO:37) Designed HVR-H1 sequence 38: YSITSGHYWSWI (SEQ ID NO:38) Designed HVR-H1 sequence 39: YSITSGYHWAWI (SEQ ID NO:39) Designed HVR-H1 sequence 40: YSITSGYHWGWI (SEQ ID NO:40) Designed HVR-H1 sequence 41: YSISSGHHWNWI (SEQ ID NO:41) Designed HVR-H1 sequence 42: YSITSGYHWNWI (SEQ ID NO:42) Designed HVR-H1 sequence 43: YSITSGYHWSWI (SEQ ID NO:43) Designed HVR-H1 sequence 44: YSITSGYYWDWI (SEQ ID NO:44) Designed HVR-H1 sequence 45: YSISSGHHWTWI (SEQ ID NO:45) Designed HVR-H1 sequence 46: YSISSGHYWDWI (SEQ ID NO:46) Designed HVR-H1 sequence 47: FSLSTSGVAVSWI (SEQ ID NO:47) Designed HVR-H1 sequence 48: FSLSTGGVAVGWI (SEQ ID NO:48) Designed HVR-H1 sequence 49: FSLSTGGVAVSWI (SEQ ID NO:49) Designed HVR-H1 sequence 50: FSLSTGGVGVAWI (SEQ ID NO:50) Designed HVR-H1 sequence 51: FSLSTGGVGVSWI (SEQ ID NO:51) Designed HVR-H1 sequence 52: FSLSTSGVAVAWI (SEQ ID NO:52) Designed HVR-H1 sequence 53: FTFSDYAIHWV (SEQ ID NO: 137) Designed HVR-H1 sequence 54: FTFSDYGIHWV (SEQ ID NO:138) Designed HVR-H1 sequence 55: YTFSNYAIHWV (SEQ ID NO: 139) Designed HVR-H1 sequence 56: YTFSSYAIHWV (SEQ ID NO:140) Designed HVR-H1 sequence 57: YTFTDYAIHWV (SEQ ID NO:141) Designed HVR-H1 sequence 58: YTFTDYGIHWV (SEQ ID NO:142) Designed HVR-H1 sequence 59: YTFTNYAIHWV (SEQ ID NO:143) Designed HVR-H1 sequence 60: YTFTNYGIHWV (SEQ ID NO: 144) Designed HVR-H1 sequence 61: FTFSGYGIHWV (SEQ ID NO:145) Designed HVR-H1 sequence 62: FTFSNYAIHWV (SEQ ID NO:146) Designed HVR-H1 sequence 63: FTFSSYGIHWV (SEQ ID NO:147) Designed HVR-H1 sequence 64: FTFSDYWIHWV (SEQ ID NO:148) Designed HVR-H1 sequence 65: FTFTSYWIHWV (SEQ ID NO: 149) Designed HVR-H1 sequence 66: YSISSGYYWGWI (SEQ ID NO:150) Designed HVR-H1 sequence 67: YSITSGYYWNWI (SEQ ID NO:151) Designed HVR-H1 sequence 68: YSITSGYYWSWI (SEQ ID NO:152) Designed HVR-H1 sequence 69: YSISSGHYWAWI (SEQ ID NO:153) Designed HVR-H1 sequence 70: YSISSGHYWGWI (SEQ ID NO:154) Designed HVR-H1 sequence 71: FSLSTSGVAVGWI (SEQ ID NO:155) Designed HVR-H1 sequence 72: FSLSTSGVGVAWI (SEQ ID

NO:156) Designed HVR-H1 sequence 73: FSLSTSGVGVGWI (SEQ ID NO:157) Designed HVR-H1 sequence 74: FSLSTGGVGVGWI (SEQ ID NO:158) Designed HVR-H2 sequence 1: LARIDWDDDKRYSPSLKSRL (SEQ ID NO:53) Designed HVR-H2 sequence 2: LALIDWDDDKRYSPSLKSRL (SEQ ID NO:54) Designed HVR-H2 sequence 3: LALIDWDDDKRYSTSLKSRL (SEQ ID NO:55) Designed HVR-H2 sequence 4: LALIDWDDDKYYSPSLKSRL (SEQ ID NO:56) Designed HVR-H2 sequence 5: LALIDWADDKYYSPSLKSRL (SEQ ID NO:57) Designed HVR-H2 sequence 6: LALIDWAGDKSYSTSLKSRL (SEQ ID NO:58) Designed HVR-H2 sequence 7: LARIDWDDDKYYSPSLKSRL (SEQ ID NO:59) Designed HVR-H2 sequence 8: LARIDWDDDKYYSTSLKSRL (SEQ ID NO:60) Designed HVR-H2 sequence 9: LARIDWDGDKYYSTSLKSRL (SEQ ID NO:61) Designed HVR-H2 sequence 10: IGDIYHSGSTYYSPSLKSRV (SEQ ID NO:62) Designed HVR-H2 sequence 11: IGEIYHSGSTYYSPSLKSRV (SEQ ID NO:63) Designed HVR-H2 sequence 12: IGEIYYSGSTYYSPSLKSRV (SEQ ID NO:64) Designed HVR-H2 sequence 13: IGSIYHSGNTNYNPSLKSRV (SEQ ID NO:65) Designed HVR-H2 sequence 14: IGEIYHSGNTYYNPSLKSRV (SEQ ID NO:66) Designed HVR-H2 sequence 15: IGEIYHSGSTYYNPSLKSRV (SEQ ID NO:67) Designed HVR-H2 sequence 16: IGEIYYSGSTYYNPSLKSRV (SEQ ID NO:68) Designed HVR-H2 sequence 17: IGDIYHSGNTYYNPSLKSRV (SEQ ID NO:69) Designed HVR-H2 sequence 18: IGDIYHSGSTYYNPSLKSRV (SEQ ID NO:70) Designed HVR-H2 sequence 19: VSAISGYGDTTYYADSVKGRF (SEQ ID NO:71) Designed HVR-H2 sequence 20: VSAISGYGGSTYYADSVKGRF (SEQ ID NO:72) Designed HVR-H2 sequence 21: VSAISGYGGTTYYADSVKGRF (SEQ ID NO:73) Designed HVR-H2 sequence 22: VSGISGAGDTTYYADSVKGRF (SEQ ID NO:74) Designed HVR-H2 sequence 23: VSGISGDGDTTYYADSVKGRF (SEQ ID NO:75) Designed HVR-H2 sequence 24: VSGISGDGGSTYYADSVKGRF (SEQ ID NO:76) Designed HVR-H2 sequence 25: VSGISGYGDTTYYADSVKGRF (SEQ ID NO:77) Designed HVR-H2 sequence 26: VSGISGYGGTTYYADSVKGRF (SEQ ID NO:78) Designed HVR-H2 sequence 27: VSVISGDGDTTYYADSVKGRF (SEQ ID NO:79) Designed HVR-H2 sequence 28: VSVISGYGGSTYYADSVKGRF (SEQ ID NO:80) Designed HVR-H2 sequence 29: VSGISGDGSTTYYADSVKGRF (SEQ ID NO:81) Designed HVR-H2 sequence 30: VSGISGYGSTTYYADSVKGRF (SEQ ID NO:82) Designed HVR-H2 sequence 31: VSVISGSGSTTYYADSVKGRF (SEQ ID NO:83) Designed HVR-H2 sequence 32: VSVISGYGSSTYYADSVKGRF (SEQ ID NO:84) Designed HVR-H2 sequence 33: VSVISGYGSTTYYADSVKGRF (SEQ ID NO:85) Designed HVR-H2 sequence 34: VSAISGYGSTTYYADSVKGRF (SEQ ID NO:86) Designed HVR-H2 sequence 35: VSSISGYGDTTYYADSVKGRF (SEQ ID NO:87) Designed HVR-H2 sequence 36: VSSISGYGGSTYYADSVKGRF (SEQ ID NO:88) Designed HVR-H2 sequence 37: VSSISGYGGTTYYADSVKGRF (SEQ ID NO:89) Designed HVR-H2 sequence 38: VSYISGAGDTTYYADSVKGRF (SEQ ID NO:90) Designed HVR-H2 sequence 39: VSSISGAGDTTYYADSVKGRF (SEQ ID NO:91) Designed HVR-H2 sequence 40: VSYISGAGGTTYYADSVKGRF (SEQ ID NO:92) Designed HVR-H2 sequence 41: VSYISGDGDTTYYADSVKGRF (SEQ ID NO:93) Designed HVR-H2 sequence 42: VSYISGDGGSTYYADSVKGRF (SEQ ID NO:94) Designed HVR-H2 sequence 43: VSYISGDGGTTYYADSVKGRF (SEQ ID NO:95) Designed HVR-H2 sequence 44: VSYISGSGDTTYYADSVKGRF (SEQ ID NO:96) Designed HVR-H2 sequence 45: VSSISGAGGSTYYADSVKGRF (SEQ ID NO:97) Designed HVR-H2 sequence 46: VSYISGYGDTTYYADSVKGRF (SEQ ID NO:98) Designed HVR-H2 sequence 47: VSYISGYGGTTYYADSVKGRF (SEQ ID NO:99) Designed HVR-H2 sequence 48: VSSISGAGGTTYYADSVKGRF (SEQ ID NO:100) Designed HVR-H2 sequence 49: VSSISGDGDTTYYADSVKGRF (SEQ ID NO:101) Designed HVR-H2 sequence 50: VSSISGDGGTTYYADSVKGRF (SEQ ID NO:102) Designed HVR-H2 sequence 51: VSSISGAGSSTYYADSVKGRF (SEQ ID NO:103) Designed HVR-H2 sequence 52: VSSISGAGSTTYYADSVKGRF (SEQ ID NO:104) Designed HVR-H2 sequence 53: VSSISGDGSSTYYADSVKGRF (SEQ ID NO:105) Designed HVR-H2 sequence 54:

VSSISGDGSTTYYADSVKGRF (SEQ ID NO:106) Designed HVR-H2 sequence 55:
VSSISGYGSSTYYADSVKGRF (SEQ ID NO:107) Designed HVR-H2 sequence 56:
VSSISGYGSTTYYADSVKGRF (SEQ ID NO:108) Designed HVR-H2 sequence 57:
IGWINPNRGDTKYAQKFQGRV (SEQ ID NO:109) Designed HVR-H2 sequence 58:
IGWINPNRGDTNYAQKFQGRV (SEQ ID NO:110) Designed HVR-H2 sequence 59:
IGWINPNRGGTKYAQKFQGRV (SEQ ID NO:111) Designed HVR-H2 sequence 60:
IGWINPNRGGTNYAQKFQGRV (SEQ ID NO: 112) Designed HVR-H2 sequence 61:
IGWINPNRGSTKYAQKFQGRV (SEQ ID NO:113) Designed HVR-H2 sequence 62:
IGWINPNRGSTNYAQKFQGRV (SEQ ID NO:114) Designed HVR-H2 sequence 63:
IGRINPNFGDTNYAQKFQGRV (SEQ ID NO: 115) Designed HVR-H2 sequence 64:
IGWINPNFGDTNYAQKFQGRV (SEQ ID NO:116) Designed HVR-H2 sequence 65:
IGWINPNFGSTKYAQKFQGRV (SEQ ID NO: 117) Designed HVR-H2 sequence 66:
IGWINPNFGSTNYAQKFQGRV (SEQ ID NO: 118) Designed HVR-H2 sequence 67:
IGIINPNRGDTKYAQKFQGRV (SEQ ID NO: 119) Designed HVR-H2 sequence 68:
IGIINPNRGDTNYAQKFQGRV (SEQ ID NO:120) Designed HVR-H2 sequence 69:
IGIINPNFGDTNYAQKFQGRV (SEQ ID NO:121) Designed HVR-H2 sequence 70:
IGWISPSGGGTKYAQKFQGRV (SEQ ID NO:122) Designed HVR-H2 sequence 71:
IGWISPSGGGTNYAQKFQGRV (SEQ ID NO:123) Designed HVR-H2 sequence 72:
IGWISPSSGGTKYAQKFQGRV (SEQ ID NO:124) Designed HVR-H2 sequence 73:
IGWISPSSGGTNYAQKFQGRV (SEQ ID NO:125) Designed HVR-H2 sequence 74:
IGWIYPSGGGTKYAQKFQGRV (SEQ ID NO:126) Designed HVR-H2 sequence 75:
IGWIYPSGGGTNYAQKFQGRV (SEQ ID NO:127) Designed HVR-H2 sequence 76:
IGWISPSGGSTNYAQKFQGRV (SEQ ID NO:128) Designed HVR-H2 sequence 77:
IGWISPSSGSTKYAQKFQGRV (SEQ ID NO:129) Designed HVR-H2 sequence 78:
IGWISPSSGSTNYAQKFQGRV (SEQ ID NO:130) Designed HVR-H2 sequence 79:
IGWISPSGGSTKYAQKFQGRV (SEQ ID NO:131) Designed HVR-H2 sequence 80:
IGIIYPSGGGTNYAQKFQGRV (SEQ ID NO:132) Designed HVR-H2 sequence 81:
IGIISPSGGGTKYAQKFQGRV (SEQ ID NO:133) Designed HVR-H2 sequence 82:
IGIISPSGGGTNYAQKFQGRV (SEQ ID NO134) Designed HVR-H2 sequence 83:
IGIIYPSGGSTNYAQKFQGRV (SEQ ID NO:135) Designed HVR-H2 sequence 84:
VGRIKSKTDGYTTEYAAPVKGRF (SEQ ID NO:136) Designed HVR-H2 sequence 85:
VSAISGSGSTTYYADSVKGRF (SEQ ID NO:159) Designed HVR-H2 sequence 86:
VSSISGSGDTTYYADSVKGRF (SEQ ID NO:160) Designed HVR-H2 sequence 87:
VSSISGSGGSTYYADSVKGRF (SEQ ID NO:161) Designed HVR-H2 sequence 88:
VSSISGSGGTTYYADSVKGRF (SEQ ID NO:162) Designed HVR-H2 sequence 89:
VSSISGDGGSTYYADSVKGRF (SEQ ID NO:163) Designed HVR-H2 sequence 90:
VSSISGSGSTTYYADSVKGRF (SEQ ID NO:164) Framework FW-H1 sequence:
EVQLVESGGGLVQPGGSLRLSCAASG (SEQ ID NO:165) Framework FW-H2 sequence:
RQAPGKGLEW (SEQ ID NO:166) Framework FW-H3 sequence:
TISSRDNSKNTLYLQLNSLRAEDTAVYYC (SEQ ID NO:167) Framework FW-H4 sequence:
WGQGTLVTVSS (SEQ ID NO: 168) Hit ID 4029—VH
EVQLVESGGGLVQPGGSLRLSCAASGYSITSGYHWGWIRQAPGKGLEWVSYISGAGDTTYYADSVKGRFT
ISRDNSKNTLYLQLNSLRAEDTAVYYCARDYGDYYGFDYWGQGTLVTVSS (SEQ ID NO: 169) HIT
ID 4029—VL
DIQLTQSPSSLSASVGDRVTITCRASQSVDFYGISFLAWYQQKPGKAPKLLIYDASNLETGVPSRFSGSGSGT
DFTLTISSLQPEDFATYYCQQSYRTPFTFGQGTKVEIKR (SEQ ID NO: 170) Hit ID 7097—VH
EVQLVESGGGLVQPGGSLRLSCAASGYSISSGHHWDWIRQAPGKGLEWVSYISGAGDTTYYADSVKGRFT
SRDNSKNTLYLQLNSLRAEDTAVYYCAREGSDAVLGDWFAYWGQGTLVTVSS (SEQ ID NO: 171)
HIT ID 7097—VL
DIQLTQSPSSLSASVGDRVTITCRASQGISSYLAWYQQKPGKAPKLLIYDASNLETGVPSRFSGSGSGTDFTL
TISSLQPEDFATYYCQQYYSTPLTFGQGTKVEIKR (SEQ ID NO: 172) Hit ID 5906—VH
EVQLVESGGGLVQPGGSLRLSCAASGYSISSGYHWNWIRQAPGKGLEWVSYISGDGDTTYYADSVKGRFT
SRDNSKNTLYLQLNSLRAEDTAVYYCARDLGGYYGWGRYFDYWGQGTLVTVSS (SEQ ID NO: 173)
HIT ID 5906—VL
DIQLTQSPSSLSASVGDRVTITCRASQSVSSYLAWYQQKPGKAPKLLIYDASNLETGVPSRFSGSGSGTDFTL

TISSLQPEDFATYYCQQSYSTPLTFGQGTKVEIKR (SEQ ID NO: 174) Hit ID 7040—VH
EVQLVESGGGLVQPGGSLRLSCAASGYSISSGYYWNWIRQAPGKGLEWIGWISPSGGSTNYAQKFQGRVTI
SRDNSKNTLYLQLNSLRAEDTAVYYCARDLTAGGFDYWGQGTLVTVSS (SEQ ID NO: 175) HIT ID
7040—VL
DIQLTQSPSSLSASVGDRVTITCRASQGISSYLAWYQQKPGKAPKLLIYDASNLETGVPSRFSGSGSGTDFTL
TISSLQPEDFATYYCQQYYSTPLTFGQGTKVEIKR (SEQ ID NO: 176) Hit ID 5924—VH
EVQLVESGGGLVQPGGSLRLSCAASGYSISSGYHWGWIRQAPGKGLEWIGIISPSSGSTKYAQKFQGRVTIS
RDNSKNTLYLQLNSLRAEDTAVYYCARGAGVHYALDYWGQGTLVTVSS (SEQ ID NO: 177) HIT ID
5924—VL
DIQLTQSPSSLSASVGDRVTITCRASQSVSSYLAWYQQKPGKAPKLLIYDASNLETGVPSRFSGSGSGTDFTL
TISSLQPEDFATYYCQQSYSTPLTFGQGTKVEIKR (SEQ ID NO: 178) Hit ID 4034—VH
EVQLVESGGGLVQPGGSLRLSCAASGYSISSGHYWNWIRQAPGKGLEWVSSISGYGSTTYYADSVKGRFTI
SRDNSKNTLYLQLNSLRAEDTAVYYCARERYYGSTDYAFDYWGQGTLVTVSS (SEQ ID NO: 179)
HIT ID 4034—VL
DIQLTQSPSSLSASVGDRVTITCSASSRVSHVFWYQQKPGKAPKLLIYAASTLQSGVPSRFSGSGSGTDFTLTI
SSLQPEDFATYFCLQGTHFPWTFGQGTKVEIKR (SEQ ID NO: 180) Hit ID 6010—VH
EVQLVESGGGLVQPGGSLRLSCAASGYSISSGHYWNWIRQAPGKGLEWIGWINPNRGDTNYAQKFQGRVT
ISRDNSKNTLYLQLNSLRAEDTAVYYCARDYYGDFDYWGQGTLVTVSS (SEQ ID NO: 181) HIT ID
6010—VL
DIQLTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYDASNLETGVPSRFSGSGSGTDFTL
TISSLQPEDFATYYCQHHYGTPLTFGQGTKVEIKR (SEQ ID NO: 182) Hit ID 7183—VH
EVQLVESGGGLVQPGGSLRLSCAASGYSISSGHYWNWIRQAPGKGLEWVSSISGYGDTTYYADSVKGRFTI
SRDNSKNTLYLQLNSLRAEDTAVYYCAREGSDTVLGDWFAYWGQGTLVTVSS (SEQ ID NO: 183)
HIT ID 7183—VL
DIQLTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYDASNRATGIPSRFSGSGSGTDFTLT
ISSLQPEDFATYYCQQSYSTPPTFGQGTKVEIKR (SEQ ID NO: 184) Hit ID 4036—VH
EVQLVESGGGLVQPGGSLRLSCAASGFSLSTSGVGVGWIRQAPGKGLEWIGEIYHSGSTYYSPSLKSRVTIS
RDNSKNTLYLQLNSLRAEDTAVYYCARERYGSYYFDYWGQGTLVTVSS (SEQ ID NO: 185) HIT ID
4036—VL
DIQLTQSPSSLSASVGDRVTITCRASQSVDFYGKSFLDWYQQKPGKAPKLLIYDASSLESGVPSRFSGSGSGT
DFTLTISSLQPEDFATYYCQQYYRIPPTFGQGTKVEIKR (SEQ ID NO: 186) Hit ID 5115—VH
EVQLVESGGGLVQPGGSLRLSCAASGYSISSGHYWGWIRQAPGKGLEWIGEIYHSGSTYYSPSLKSRVTISR
DNSKNTLYLQLNSLRAEDTAVYYCARESYYAFDYWGQGTLVTVSS (SEQ ID NO: 187) HIT ID 5115
—VL
DIQLTQSPSSLSASVGDRVTITCRASQSVSSYLAWYQQKPGKAPKLLIYAASTLQSGVPSRFSGSGSGTDFTL
TISSLQPEDFATYYCQQYYTTPLTFGQGTKVEIKR (SEQ ID NO: 188) Hit ID 5404—VH
EVQLVESGGGLVQPGGSLRLSCAASGYSISSGYHWAWIRQAPGKGLEWIGEIYHSGSTYYSPSLKSRVTISR
DNSKNTLYLQLNSLRAEDTAVYYCARSPYYYGVFDYWGQGTLVTVSS (SEQ ID NO: 189) HIT ID
5404—VL
DIQLTQSPSSLSASVGDRVTITCSASSRVGSVYWYQQKPGKAPKLLIYDASNLETGVPSRFSGSGSGTDFTLT
ISSLQPEDFATYYCQQYTHDPVTFGQGTKVEIKR (SEQ ID NO: 190) Hit ID 3757—VH
EVQLVESGGGLVQPGGSLRLSCAASGFTFTDYGIHWVRQAPGKGLEWIGWISPSGGGTKYAQKFQGRVTIS
RDNSKNTLYLQLNSLRAEDTAVYYCARHSYYGVGDFDYWGQGTLVTVSS (SEQ ID NO: 191) HIT
ID 3757—VL
DIQLTQSPSSLSASVGDRVTITCRASQSVSSYLAWYQQKPGKAPKLLIYDASNLETGVPSRFSGSGSGTDFTL
TISSLQPEDFATYYCQQSYSTPLTFGQGTKVEIKR (SEQ ID NO: 192) Hit ID 5103—VH
EVQLVESGGGLVQPGGSLRLSCAASGFTFTDYGIHWVRQAPGKGLEWIGWISPSGGGTKYAQKFQGRVTIS
RDNSKNTLYLQLNSLRAEDTAVYYCARHSYYGVGDFDYWGQGTLVTVSS (SEQ ID NO: 193) HIT
ID 5103—VL
DIQLTQSPSSLSASVGDRVTITCRASQSVSSYLAWYQQKPGKAPKLLIYDASNLETGVPSRFSGSGSGTDFTL
TISSLQPEDFATYYCQQSYSTPLTFGQGTKVEIKR (SEQ ID NO: 194) Hit ID 4027—VH
EVQLVESGGGLVQPGGSLRLSCAASGYSITSGHHWNWIRQAPGKGLEWIGWISPSSGGTKYAQKFQGRVTI
SRDNSKNTLYLQLNSLRAEDTAVYYCARGFDGFHYWGQGTLVTVSS (SEQ ID NO: 195) HIT ID 4027
—VL
DIQLTQSPSSLSASVGDRVTITCRASESVDFYGISFLPWYQQKPGKAPKLLIYDASNRATGIPSRFSGSGSGTD

FTLTISSLQPEDFATYYCQQSYSWPWTFGQGTKVEIKR (SEQ ID NO: 196) VH in FIG. **1**B
EVQLVESGGGLVQPGGSLRLSCAASGFTFTSYGIHWVRQAPGKGLEWVSGISGAGDTTYYADSVKGRFTIS
RDNSKNTLYLQLNSLRAEDTAVYYCARERDYDFDYWGQGTLVTVSS (SEQ ID NO:197)
Formula (I) X.sub.1TFX.sub.2X.sub.3YX.sub.4IHWV, wherein X.sub.1 is F or Y, X.sub.2 is S or T, X.sub.3 is D, G, N, or S, and X.sub.4 is A, G, or W (SEQ ID NO:198)
Formula (II) YSIX.sub.1SGX.sub.2X.sub.3WX.sub.4WI, wherein X.sub.1 is S or T, X.sub.2 is H or Y, X.sub.3 is H or Y, and X.sub.4 is A, D, G, N, S, or T (SEQ ID NO:199)
Formula (III) FSLSTX.sub.1GVX.sub.2VX.sub.3WI, wherein X.sub.1 is G or S, X.sub.2 is A or G, and X.sub.3 is A, G, S, or T (SEQ ID NO:200)
Formula (IV) LAX.sub.1X.sub.2WX.sub.3X.sub.4DKX.sub.5YSX.sub.6SLKSRL, wherein X.sub.1 is L or R, X.sub.2 is D or Y, X.sub.3 is A, D, S, or Y, X.sub.4 is D or G, X.sub.5 is R, S, or Y, and X.sub.6 is P or T (SEQ ID NO:201)
Formula (V) IGX.sub.1IX.sub.2X.sub.3SGSTYYSPSLKSRV, wherein X.sub.1 is A, D, E, S, or Y, X.sub.2 is S or Y, and X.sub.3 is H or Y (SEQ ID NO:202)
Formula (VI) IGX.sub.1IYX.sub.2SGX.sub.3TX.sub.4YNPSLKSRV, wherein X.sub.1 is D, E, R, S, or Y, X.sub.2 is H or Y, X.sub.3 is N or S, and X.sub.4 is N or Y (SEQ ID NO:203)
Formula (VII) VSX.sub.1ISGX.sub.2GX.sub.3X.sub.4TYYADSVKGRF, wherein X.sub.1 is A, G, S, V, or Y, X.sub.2 is A, D, S, or Y, X.sub.3 is D, G, or S, and X.sub.4 is S or T (SEQ ID NO:204)
Formula (VIII) IGX.sub.1INPNX.sub.2GX.sub.3TX.sub.4YAQKFQGRV, wherein X.sub.1 is I, R, or W, X.sub.2 is F or R, X.sub.3 is D, G, or S, and X.sub.4 is K or N (SEQ ID NO:205)
Formula (IX) IGX.sub.1IX.sub.2PSX.sub.3GX.sub.4TX.sub.5YAQKFQGRV, wherein X.sub.1 is I, R, or W, X.sub.2 is S or Y, X.sub.3 is G or S, X.sub.4 is D, G, or S, and X.sub.5 is K or N (SEQ ID NO:206)
Formula (X) VGRIX.sub.1SKX.sub.2X.sub.3GX.sub.4TTX.sub.5YAAX.sub.6VKGRF, wherein X.sub.1 is K or R, X.sub.2 is A or T, X.sub.3 is D or Y, X.sub.4 is G or Y, X.sub.5 is D or E, and X.sub.6 is P or S (SEQ ID NO:207)
Formula (XI) IGX.sub.1IX.sub.2X.sub.3SGSTYYSPSLKSRV, wherein X.sub.1 is A, D, or E, X.sub.2 is S or Y, and X.sub.3 is H or Y (SEQ ID NO:208)
Formula (XII) IGX.sub.1IYX.sub.2SGX.sub.3TX.sub.4YNPSLKSRV, wherein X.sub.1 is D, E, or S, X.sub.2 is H or Y, X.sub.3 is N or S, and X.sub.4 is N or Y (SEQ ID NO:209)
Formula (XIII) VGRIX.sub.1SKX.sub.2X.sub.3GX.sub.4TTEYAAX.sub.5VKGRF, wherein X.sub.1 is K or R, X.sub.2 is A or T, X.sub.3 is D or Y, X.sub.4 is G or Y, X.sub.5 is P or S (SEQ ID NO:210) Primer F_1999
CGTTTGTCCTGTGCAGCTTCCGG (SEQ ID NO:211) Primer R_1999
CGAGGCCCTTACCCGGGGCCTGACG (SEQ ID NO:212) Primer F_2003
CCGGGTAAGGGCCTCGAGTGG (SEQ ID NO:213) Primer R_2003
GAGCACGTCCGTTCGAATTGTCGCGACTTATAG (SEQ ID NO:214) Primer S1089
ACAACTGAACAGCTTAAGAGCTGAGGACACTGCCGTCTATTATTG (SEQ ID NO:215) Primer S1090
GAGGAGACGGTGACTAGTGTTCCTTGACCCCA (SEQ ID NO:216) Primer F_2898
TACTTATGTAGGCGATCGGGTCACCATCACCTGC (SEQ ID NO:217) Primer R_2898
CGGAGCTTTTCCTGGTTTCTGTTGATAC (SEQ ID NO:218) Primer F_2013
GAAACCAGGAAAAGCTCCGAAG (SEQ ID NO:219) Primer R_2013
CGTCCCGGAACCGGATCCAGAGAAGCGAG (SEQ ID NO:220) Primer F2929
ACCATCAGCAGTCTGCAGCCGGAAGACTTCGCAAC (SEQ ID NO:221) Primer R2929
GATCTCCACCTTGGTACCCTGTCCGAA (SEQ ID NO:222) HVR-H3 sequence 1:
ARDLGGYYGWGRYFDY (SEQ ID NO:223) HVR-H3 sequence 2: ARDLTAGGFDY (SEQ ID NO:224) HVR-H3 sequence 3: ARDPGVGGFDV (SEQ ID NO:225) HVR-H3 sequence 4: ARDPGYTWYFDV (SEQ ID NO:226) HVR-H3 sequence 5: ARDYGDYYGFDY (SEQ ID NO:227) HVR-H3 sequence 6: ARDYGYTWYFDV (SEQ ID NO:228) HVR-H3 sequence 7: ARDYYGDFDY (SEQ ID NO:229) HVR-H3 sequence 8: AREGSDAVLGDWFAY (SEQ ID NO:230) HVR-H3 sequence 9: AREGSDTVLGDWFAY (SEQ ID NO:231) HVR-H3 sequence 10: ARERYGSYYFDY (SEQ ID NO:232) HVR-H3 sequence 11: ARERYYGSTDYAFDY (SEQ ID NO:233) HVR-H3 sequence 12: ARESYYAFDY (SEQ ID NO:234) HVR-H3 sequence 13: ARGAGVHYALDY (SEQ ID NO:235) HVR-H3 sequence 14: ARGFDGFHY (SEQ ID NO:236) HVR-H3 sequence 15: ARGFYGGALDV (SEQ ID NO:237) HVR-H3 sequence 16: ARGGGGYYFDV (SEQ ID NO:238) HVR-H3 sequence 17: ARGGGLGFDY (SEQ ID NO:239) HVR-H3 sequence 18: ARGGLGPFDI (SEQ ID NO:240) HVR-H3 sequence 19: ARGGSDTVIGDWFAY (SEQ ID NO:241) HVR-H3 sequence 20: ARGGVGPFDI (SEQ ID NO:242) HVR-H3 sequence 21:

ARGGYGGYLDV (SEQ ID NO:243) HVR-H3 sequence 22: ARGLSSGYFDY (SEQ ID NO:244) HVR-H3 sequence 23: ARGSWYFDV (SEQ ID NO:245) HVR-H3 sequence 24: ARGTRGLDY (SEQ ID NO:246) HVR-H3 sequence 25: ARGYSDYFDY (SEQ ID NO:247) HVR-H3 sequence 26: ARGYYYGRAFDY (SEQ ID NO:248) HVR-H3 sequence 27: ARHSYYGVGDFDY (SEQ ID NO:249) HVR-H3 sequence 28: ARLFEGFPY (SEQ ID NO:250) HVR-H3 sequence 29: ARLYDYFAY (SEQ ID NO:251) HVR-H3 sequence 30: ARSGYYALDY (SEQ ID NO: 252) HVR-H3 sequence 31: ARSPYYYGVFDY (SEQ ID NO:253) HVR-H3 sequence 32: ARSYVYFDY (SEQ ID NO:254) HVR-H3 sequence 33: ARDGLGLRGVYYYYYGLDV (SEQ ID NO:255) HVR-H3 sequence 34: ARVGESGGIESPYYYYGLDV (SEQ ID NO:256) HVR-L1 sequence 1: RASESVDFYGISFLP (SEQ ID NO: 257) HVR-L1 sequence 2: RASQSVDFYGISFLA (SEQ ID NO:258) HVR-L1 sequence 3: RASQSVDFYGKSFLD (SEQ ID NO:259) HVR-L1 sequence 4: SASSRVGSVY (SEQ ID NO:260) HVR-L1 sequence 5: SASSRVSHVF (SEQ ID NO:261) HVR-L1 sequence 6: RASQGISSYLA (SEQ ID NO:262) HVR-L1 sequence 7: RASQSVSSYLA (SEQ ID NO:263) HVR-L1 sequence 8: RASQSISSYLN (SEQ ID NO:264) HVR-L3 sequence 1: FCLQGTHFPWT (SEQ ID NO:265) HVR-L3 sequence 2: YCQQSYRTPFT (SEQ ID NO:266) HVR-L3 sequence 3: YCQQSYSWPWT (SEQ ID NO:267) HVR-L3 sequence 4: YCQQYTHDPVT (SEQ ID NO:268) HVR-L3 sequence 5: YCQQYYRIPPT (SEQ ID NO:269) HVR-L3 sequence 6: YCQHHYGTPLT (SEQ ID NO:270) HVR-L3 sequence 7: YCQQSYSTPLT (SEQ ID NO:271) HVR-L3 sequence 8: YCQQSYSTPPT (SEQ ID NO:272) HVR-L3 sequence 9: YCQQYYSTPLT (SEQ ID NO:273) HVR-L3 sequence 10: YCQQYYTTPLT (SEQ ID NO:274)

Claims

1. A non-human animal comprising polynucleotides that encode antibody heavy chain variable domains (V.sub.Hs), wherein each of the V.sub.Hs comprises a HVR-H1, a HVR-H2 and a HVR-H3, and wherein at least one V.sub.H comprises an HVR-H1 that comprises an amino acid sequence according to a formula selected from the group consisting of: TABLE-US-00011 (Formula I) (SEQ ID NO: 198) X.sub.1TFX.sub.2X.sub.3YX.sub.4IHWV, wherein X.sub.1 is F or Y, X.sub.2 is S or T, X.sub.3 is D, G, N, or S, and X.sub.4 is A, G, or W; (Formula II) (SEQ ID NO: 199) YSIX.sub.1SGX.sub.2X.sub.3WX.sub.4WI, wherein X.sub.1 is S or T, X.sub.2 is H or Y, X.sub.3 is H or Y, and X.sub.4 is A, D, G, N, S, or T; and (Formula III) (SEQ ID NO: 200) FSLSTX.sub.1GVX.sub.2VX.sub.3WI, wherein X.sub.1 is G or S, X.sub.2 is A or G, and X.sub.3 is A, G, S, or T; and an HVR-H2 that comprises an amino acid sequence according to a formula selected from the group consisting of: TABLE-US-00012 (Formula IV) (SEQ ID NO: 201) LAX.sub.1IX.sub.2WX.sub.3X.sub.4DKX.sub.5YSX.sub.6SLKSRL, wherein X.sub.1 is L or R, X.sub.2 is D or Y, X.sub.3 is A, D, S, or Y, X.sub.4 is D or G, X.sub.5 is R, S, or Y, and X.sub.6 is P or T; (Formula V) (SEQ ID NO: 202) IGX.sub.1IX.sub.2X.sub.3SGSTYYSPSLKSRV, wherein X.sub.1 is A, D, E, S, or Y, X.sub.2 is S or Y, and X.sub.3 is H or Y; (Formula VI) (SEQ ID NO: 203) IGX.sub.1IYX.sub.2SGX.sub.3TX.sub.4YNPSLKSRV, wherein X.sub.1 is D, E, R, S, or Y, X.sub.2 is Hor Y, X.sub.3 is N or S, and X.sub.4 is N or Y; (Formula VII) (SEQ ID NO: 204) VSXIISGX.sub.2GX.sub.3X.sub.4TYYADSVKGRF, wherein X.sub.1 is A, G, S, V, or Y, X.sub.2 is A, D, S, or Y, X.sub.3 is D, G, or S, and X.sub.4 is S or T; (Formula VIII) (SEQ ID NO: 205) IGX.sub.1INPNX.sub.2GX.sub.3TX.sub.4YAQKFQGRV, wherein X.sub.1 is I, R, or W, X.sub.2 is For R, X.sub.3 is D, G, or S, and X.sub.4 is K or N; (Formula IX) (SEQ ID NO: 206) IGX.sub.1IX.sub.2PSX.sub.3GX.sub.4TXYAQKFQGRV, wherein X.sub.1 is I, R, or W, X.sub.2 is S or Y, X.sub.3 is G or S, X.sub.4 is D, G, or S, and X.sub.5 is K or N; and (Formula X) (SEQ ID NO: 207) VGRIX.sub.1SKX.sub.2X.sub.3GX.sub.4TTX.sub.5YAAX.sub.6VKGRF, wherein X.sub.1 is K or R, X.sub.2 is A or T, X.sub.3 is D or Y, X.sub.4 is G or Y, X.sub.5 is D or E, and X.sub.6 is P or S.

2. The non-human animal of claim 1, wherein at least two, at least three, at least four, at least five or at least ten of the V.sub.Hs comprise, an HVR-H1 that comprises an amino acid sequence according to a formula

selected from the group consisting of: TABLE-US-00013 (Formula I) (SEQ ID NO: 198) X.sub.1TFX.sub.2X.sub.3YX.sub.4IHWV, wherein X.sub.1 is F or Y, X.sub.2 is S or T, X.sub.3 is D, G, N, or S, and X.sub.4 is A, G, or W; (Formula II) (SEQ ID NO: 199) YSIX.sub.1SGX.sub.2X.sub.3WX.sub.4WI, wherein X.sub.1 is S or T, X.sub.2 is H or Y, X.sub.3 is Hor Y, and X.sub.4 is A, D, G, N, S, or T; and (Formula III) (SEQ ID NO: 200) FSLSTX.sub.1GVX.sub.2VX.sub.3WI, wherein X.sub.1 is G or S, X.sub.2 is A or G, and X.sub.3 is A, G, S, or T; and an HVR-H2 that comprises an amino acid sequence according to a formula selected from the group consisting of: TABLE-US-00014 (Formula IV) (SEQ ID NO: 201) LAX.sub.1IX.sub.2WX.sub.3X.sub.4DKX.sub.5YSX.sub.6SLKSRL, wherein X.sub.1 is L or R, X.sub.2 is D or Y, X.sub.3 is A, D, S, or Y, X.sub.4 is D or G, X.sub.5 is R, S, or Y, and X.sub.6 is P or T; (Formula V) (SEQ ID NO: 202) IGX.sub.1IX.sub.2X.sub.3SGSTYYSPSLKSRV, wherein X.sub.1 is A, D, E, S, or Y, X.sub.2 is S or Y, and X.sub.3 is H or Y; (Formula VI) (SEQ ID NO: 203) IGX.sub.1IYX.sub.2SGX.sub.3TX.sub.4YNPSLKSRV, wherein X.sub.1 is D, E, R, S, or Y, X.sub.2 is H or Y, X.sub.3 is N or S, and X.sub.4 is N or Y; (Formula VII) (SEQ ID NO: 204) VSX.sub.1ISGX.sub.2GX.sub.3X.sub.4TYYADSVKGRF, wherein X.sub.1 is A, G, S, V, or Y, X.sub.2 is A, D, S, or Y, X.sub.3 is D, G, or S, and X.sub.4 is S or T; (Formula VIII) (SEQ ID NO: 205) IGX.sub.1INPNX.sub.2GX.sub.3TX.sub.4YAQKFQGRV, wherein X.sub.1 is I, R, or W, X.sub.2 is F or R, X.sub.3 is D, G, or S, and X.sub.4 is K or N; (Formula IX) (SEQ ID NO: 206) IGX.sub.1IX.sub.2PSX.sub.3GX.sub.4TXsYAQKFQGRV, wherein X.sub.1 is I, R, or W, X.sub.2 is S or Y, X.sub.3 is G or S, X.sub.4 is D, G, or S, and X.sub.5 is K or N; and (Formula X) (SEQ ID NO: 207) VGRIX.sub.1SKX.sub.2X.sub.3GX.sub.4TTX.sub.5YAAX.sub.6VKGRF, wherein X.sub.1 is K or R, X.sub.2 is A or T, X.sub.3 is D or Y, X.sub.4 is G or Y, X.sub.5 is D or E, and X.sub.6 is P or S.

3. The non-human animal of claim 1, wherein the HVR-H2 comprises an amino acid sequence according to a formula selected from the group consisting of: TABLE-US-00015 (Formula XI) (SEQ ID NO: 208) IGX.sub.1IX.sub.2X.sub.3SGSTYYSPSLKSRV, wherein X.sub.1 is A, D, or E, X.sub.2 is S or Y, and X.sub.3 is H or Y; (Formula XII) (SEQ ID NO: 209) IGXIIYX.sub.2SGX.sub.3TX.sub.4YNPSLKSRV, wherein X.sub.1 is D, E, or S, X.sub.2 is H or Y, X.sub.3 is N or S, and X.sub.4 is N or Y; and (Formula XIII) (SEQ ID NO: 210) VGRIX1SKX.sub.2X.sub.3GX.sub.4TTEYAAX.sub.5VKGRF, wherein X.sub.1 is K or R, X.sub.2 is A or T, X.sub.3 is D or Y, X.sub.4 is G or Y, X.sub.5 is P or S.

4. The non-human animal of claim 1, wherein each of the V.sub.Hs comprises an HVR-H1 that comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:1-52 and 137-158.

5. The non-human animal of claim 1, wherein at least one of the V.sub.Hs comprises an HVR-H1 that comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:1-52.

6. The non-human animal of claim 1, wherein each of the V.sub.Hs comprises an HVR-H2 that comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:53-136 and 159-164.

7. The non-human animal of claim 1, wherein at least one of the V.sub.Hs comprises an HVR-H2 that comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:53-136.

8. The non-human animal of claim 1, wherein the V.sub.Hs contain fewer than about 6.5*10.sup.4unique combinations of HVR-H1 and HVR-H2 sequences.

9. The non-human animal of claim 8, wherein the V.sub.Hs contain fewer than about 6700 unique combinations of HVR-H1 and HVR-H2 sequences.

10. The non-human animal of claim 9, wherein the V.sub.Hs contain about 6660 or contain fewer unique combinations of HVR-H1 and HVR-H2 sequences.

11. The non-human animal of claim 1, wherein each of the V.sub.Hs comprises a HVR-H1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOS:1-52 and 137-158, and a HVR-H2 of the antibody comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:53-136 and 159-164.

12. The non-human animal of claim 1, wherein at least one of the V.sub.Hs comprises a HVR-H1 comprising

an amino acid sequence selected from the group consisting of SEQ ID NOS:1-52, and a HVR-H2 of the antibody comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:53-136.

13. The non-human animal of claim 1, wherein the HVR-H1 and HVR-H2 of the at least one V.sub.H are selected from the group consisting of: a HVR-H1 comprising the amino acid sequence of Formula (II) and a HVR-H2 comprising the amino acid sequence of Formula (IX); a HVR-H1 comprising the amino acid sequence of Formula (II) and a HVR-H2 comprising the amino acid sequence of Formula (VII); a HVR-H1 comprising the amino acid sequence of Formula (I) and a HVR-H2 comprising the amino acid sequence of Formula (VII); a HVR-H1 comprising the amino acid sequence of Formula (I) and a HVR-H2 comprising the amino acid sequence of Formula (IX); a HVR-H1 comprising the amino acid sequence of Formula (II) and a HVR-H2 comprising the amino acid sequence of Formula (IV); a HVR-H1 comprising the amino acid sequence of Formula (II) and a HVR-H2 comprising the amino acid sequence of Formula (V); a HVR-H1 comprising the amino acid sequence of Formula (II) and a HVR-H2 comprising the amino acid sequence of Formula (VI); a HVR-H1 comprising the amino acid sequence of Formula (I) and a HVR-H2 comprising the amino acid sequence of Formula (VI); a HVR-H1 comprising the amino acid sequence of Formula (III) and a HVR-H2 comprising the amino acid sequence of Formula (VI); a HVR-H1 comprising the amino acid sequence of Formula (III) and a HVR-H2 comprising the amino acid sequence of Formula (VII); a HVR-H1 comprising the amino acid sequence of Formula (II) and a HVR-H2 comprising the amino acid sequence of Formula (VIII); a HVR-H1 comprising the amino acid sequence of Formula (I) and a HVR-H2 comprising the amino acid sequence of Formula (V); a HVR-H1 comprising the amino acid sequence of Formula (III) and a HVR-H2 comprising the amino acid sequence of Formula (V); and a HVR-H1 comprising the amino acid sequence of Formula (I) and a HVR-H2 comprising the amino acid sequence of Formula (VIII).

14. The non-human animal of claim 1, wherein the HVR-H1 and HVR-H2 of the at least one V.sub.H are selected from the group consisting of: a HVR-H1 comprising the amino acid sequence of SEQ ID NO:157, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:63; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:1, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:122; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:138, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:63; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:154, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:63; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:158, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:161; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:158, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:63; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:145, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:128; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:22, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:61; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:31, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:63; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:153, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:63; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:155, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:67; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:156, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:100; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:51, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:162; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:138, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:123; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:139, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:110; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:8, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:126; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:13, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:129; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:31, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:124; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:25, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:130; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:150, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:132; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:158, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:162; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:12, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:82; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:149, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:117; and a HVR-H1 comprising the amino acid sequence of SEQ ID NO:7, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:134.

15. The non-human animal of claim 1, wherein the at least one V.sub.Hcomprises a HVR-H3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 223-256.
16. The non-human animal of claim 1, wherein the at least one V.sub.Hcomprises a FW-H1 comprising the amino acid sequence of SEQ ID NO:165, a FW-H2 comprising the amino acid sequence of SEQ ID NO:166, a FW-H3 comprising the amino acid sequence of SEQ ID NO:167, and/or a FW-H4 comprising the amino acid sequence of SEQ ID NO:168.
17. The non-human animal of claim 1, wherein the at least one V.sub.H comprises a sequence selected from the group consisting of SEQ ID NOs: 169, 171, 173, 175, 177, 179, 181, 183, 185, 187, 189, 191, 193, and 195.
18. The non-human animal of claim 1, wherein the polynucleotides that encode V.sub.Hs encode full-length antibody heavy chains.
19. The non-human animal of claim 1, further comprising polynucleotides that encode antibody light chain variable regions.
20. The non-human animal of claim 19, wherein at least one light chain variable region comprises a HVR-L1, a HVR-L2 and a HVR-L3, wherein the HVR-L1 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 257-264 and/or the HVR-L3 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 265-274.
21. The non-human animal of claim 19, wherein the polynucleotides that encode the light chain variable regions include at least one unique light chain variable region sequence.
22. The non-human animal of claim 19, wherein the the polynucleotides that encode the light chain variable regions include at least about 280 unique light chain variable region sequences.
23. The non-human animal of claim 19, wherein the polynucleotides that encode the light chain variable regions include at least about 10.sup.5 unique light chain variable region sequences.
24. The non-human animal of claim 19, wherein the polynucleotides that encode V.sub.Hs and the polynucleotides that encode the light chain variable regions together encode a plurality of unique antibodies, wherein the V.sub.Hs of each antibody of the plurality comprise an identical sequence.
25. The non-human animal of claim 1, wherein at least one of the HVR-H1 and HVR-H2 of the at least one V.sub.H adopts multiple conformations, as assayed by structural determination and/or computational modeling.
26. The non-human animal of claim 1, wherein at least one of the polynucleotides encoding the V.sub.Hs is in a vector.
27. The non-human animal of claim 26, wherein the vector is an expression vector.
28. The non-human animal of claim 26, wherein the vector is a display vector.
29. The non-human animal of claim 1, wherein at least one of the polynucleotides encoding the V.sub.Hs is in a cell.
30. The non-human animal of claim 16, wherein all of the VHs comprise a FW-H1 comprising the amino acid sequence of SEQ ID NO:165, a FW-H2 comprising the amino acid sequence of SEQ ID NO:166, a FW-H3 comprising the amino acid sequence of SEQ ID NO:167, and/or a FW-H4 comprising the amino acid sequence of SEQ ID NO:168.
31. The non-human animal of claim 26, wherein each of the polynucleotides encoding the V.sub.Hs is in a vector.
32. The non-human animal of claim 1, wherein the non-human animal is a mammal.