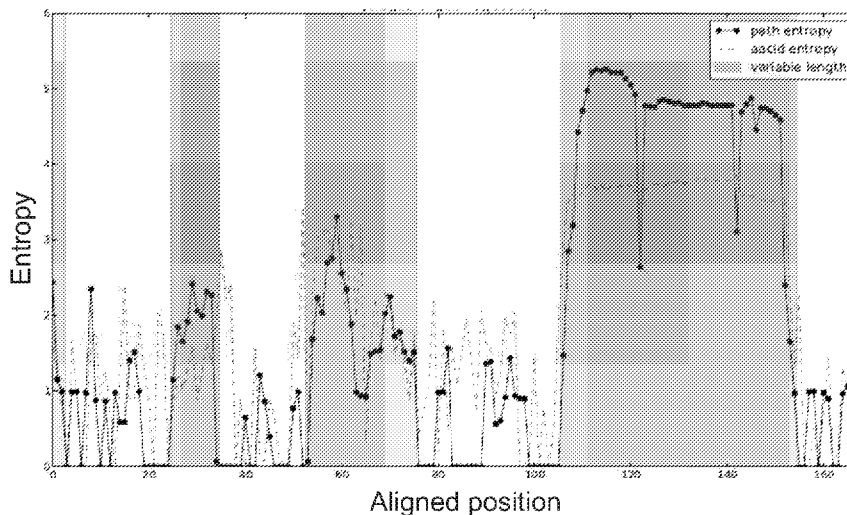




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(54) **Title:** DYNAMIC HUMAN HEAVY CHAIN ANTIBODY LIBRARIES

FIG. 1A



(57) **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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DYNAMIC HUMAN HEAVY CHAIN ANTIBODY LIBRARIES

FIELD OF THE INVENTION

[0001] 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

[0002] 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.

[0003] 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.

[0004] 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.

[0005] 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

[0006] 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_H regions), 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%).

[0007] 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.

[0008] 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): IGX1IYX2SGX3TX4YNPSLKSRV (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): V SX1ISGX2GX3X4TYYADSVKGRF (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): IGX1INPNX2GX3TX4YAQKFQGRV (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): VGRIX1SKX2X3GX4TTX5YAAX6VKGRF (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): IGX1IYX2SGX3TX4YNPSLKSRV (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): VGRIX1SKX2X3GX4TTEYAAX5VKGRF (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.

[0009] 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.

[0010] 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.

[0011] 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.

[0012] 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).

[0013] 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.

[0014] 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.

[0015] 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.

[0016] 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).

[0017] 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).

[0018] 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.

[0019] 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.

[0020] 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.

[0021] 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).

[0022] 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).

[0023] 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.

[0024] 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).

[0025] 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.

[0026] In some embodiments that may be combined with any of the preceding embodiments, the polynucleotides in the library contain less than about 6.5×10^4 (*e.g.*, less than about 6.5×10^4 , less than about 5.5×10^4 , less than about 2.5×10^4 , less than about 1×10^4 , 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.

[0027] 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.

[0028] 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.

[0029] 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 10^3 unique sequences, at least 10^4 unique sequences, at least 10^5 unique sequences, at least 10^6 unique sequences, at least 10^7 unique sequences, at least 10^8 unique sequences, or least about 10^9 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.

[0030] 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

[0031] 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 10^3 unique sequences, at least 10^4 unique sequences, at least 10^5 unique sequences, at least 10^6 unique sequences, at least 10^7 unique sequences, at least 10^8 unique sequences, or least about 10^9 unique sequences.

[0032] 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-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 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 10^3 unique sequences, at least 10^4 unique sequences, at least 10^5 unique sequences, at least 10^6 unique sequences, at least 10^7 unique sequences, at least 10^8 unique sequences, or least about 10^9 unique sequences.

[0033] 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 10^3 , at least 10^4 , at least 10^5 , at least 10^6 , at least 10^7 , at least 10^8 , at least 10^9 , *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).

[0034] 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).

[0035] 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.

[0036] 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.

[0037] 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.

[0038] 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).

[0039] 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).

[0040] 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.

[0041] 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.

[0042] 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.

[0043] 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).

[0044] 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).

[0045] 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, 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.

[0046] 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).

[0047] 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.

[0048] 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.

[0049] 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.

[0050] 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 6.5×10^4 (*e.g.*, less than about 6.5×10^4 , less than about 5.5×10^4 , less than about 2.5×10^4 , less than about 1×10^4 , 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.

[0051] 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 10^3 unique sequences, at least 10^4 unique sequences, at least 10^5 unique sequences, at least 10^6 unique sequences, at least 10^7 unique sequences, at least 10^8 unique sequences, or least about 10^9 unique sequences.

[0052] 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 10^3 unique sequences, at least 10^4 unique sequences, at least 10^5 unique sequences, at least 10^6 unique sequences, at least 10^7 unique sequences, at least 10^8 unique sequences, or least about 10^9 unique sequences.

[0053] 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 10^3 unique sequences, at least 10^4 unique sequences, at least 10^5 unique sequences, at least 10^6 unique sequences, at least 10^7 unique sequences, at least 10^8 unique sequences, or least about 10^9 unique sequences.

[0054] In some embodiments that may be combined with any of the preceding embodiments, the antibodies contain less than about 6.5×10^4 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 5.5×10^4 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.

[0055] 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^{-7} and about 10^{-11} M. In some embodiments, the antibody has a melting temperature (Tm) of between about 60°C and about 90°C.

[0056] 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.

[0057] 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.

[0058] 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).

[0059] 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.

[0060] In another aspect, provided herein are methods of screening for a polypeptide that binds to a target, comprising incubating any of the libraries comprising polypeptides 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.

[0061] 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.

[0062] 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.

[0063] 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.

[0064] 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 C_L domain (*e.g.*, a human kappa C_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 C_L domain (*e.g.*, a human lambda C_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 kappa C_L domain (*e.g.*, a human kappa C_L domain), and the second light chain comprises the second light chain variable region and a lambda C_L domain (*e.g.*, a human lambda C_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_L domain (*e.g.*, a human lambda C_L domain), and the second light chain comprises the second light chain variable region and a kappa C_L domain (*e.g.*, a human kappa C_L domain).

[0065] 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.

[0066] 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.

BRIEF DESCRIPTION OF THE DRAWINGS

[0067] FIG. 1A shows an entropy plot by residue number for the amino acids of a V_H domain. 113 V_H structures of human antibodies were used to calculate the entropy.

[0068] FIG. 1B 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.

[0069] FIG. 2A shows the affinity measurements for fabs with confirmed binding to the antigens TAGT-1 to TAGT-12.

[0070] FIG. 2B shows the melting temperature (T_m) measurements for fabs with confirmed binding to the antigens TAGT-1 to TAGT-12.

DETAILED DESCRIPTION

[0071] 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

[0072] 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

[0073] 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.

[0074] 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.

[0075] 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.

[0076] It is understood that aspects and embodiments of the present disclosure described herein include “comprising,” “consisting,” and “consisting essentially of” aspects and embodiments.

[0077] 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.

[0078] 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_H and V_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.

[0079] The L chain from any vertebrate species can be assigned to one of two clearly distinct types, called kappa (“ κ ”) and lambda (“ λ ”), 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 (“ α ”), delta (“ δ ”), epsilon (“ ϵ ”), gamma (“ γ ”) and mu (“ μ ”), respectively. The γ and α 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*, 4th ed. (W.B. Saunders Co., 2000).

[0080] 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 “ V_H .” The variable domain of the light chain may be referred to as

“V_L.” These domains are generally the most variable parts of an antibody and contain the antigen-binding sites.

[0081] 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.

[0082] 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.

[0083] 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_H1, C_H2 and C_H3 domains (collectively, CH) of the heavy chain and the CHL (or CL) domain of the light chain.

[0084] 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.

[0085] 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. Patent 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. Patent Nos.

5,545,807; 5,545,806; 5,569,825; 5,625,126; 5,633,425; and 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).

[0086] 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. 1B**.

[0087] 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.

[0088] 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.

[0089] 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.

[0090] The terms “polypeptide,” “protein,” and “peptide” are used interchangeably herein and may refer to polymers of two or more amino acids.

[0091] “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, poly-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.

[0092] 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).

[0093] 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

[0094] Certain aspects of the present disclosure relate to libraries of polynucleotides, *e.g.*, that encode an antibody heavy chain variable region (V_H) or light chain variable region (V_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.

[0095] In some embodiments, a library of the present disclosure contains a smaller number of unique heavy chain HVR sequences and/or unique V_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.

[0096] 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).

[0097] 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) $X_1T F X_2 X_3 Y X_4 I H W V$, wherein X_1 is F or Y, X_2 is S or T, X_3 is D, G, N, or S, and X_4 is A, G, or W (SEQ ID NO:198); (Formula II) $Y S I X_1 S G X_2 X_3 W X_4 W I$, wherein X_1 is S or T, X_2 is H or Y, X_3 is H or Y, and X_4 is A, D, G, N, S, or T (SEQ ID NO:199); and (Formula III) $F S L S T X_1 G V X_2 V X_3 W I$, wherein X_1 is G or S, X_2 is A or G, and X_3 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) 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 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 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)

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). 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) 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).

[0098] 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) LAX1IX2WX3X4DKX5YSX6SLKSRV, 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); and/or less than about 6.5×10^4 (e.g., less than about 6.5×10^4 , less than about 5.5×10^4 , less than about 2.5×10^4 , less than about 1×10^4 , 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 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) 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) VSX₁ISGX₂GX₃X₄TYADSVKGRF, 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, one or more polynucleotides of the library are in a vector (*e.g.*, an expression vector or display vector).

[0099] 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 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); and/or less than about 6.5×10^4 (*e.g.*, less than about 6.5×10^4 , less than about 5.5×10^4 , less than about 2.5×10^4 , less than about 1×10^4 , 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 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).

[0100] 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 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).

[0101] 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 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).

[0102] 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: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).

[0103] 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).

[0104] 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) 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).

[0105] 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) 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).

[0106] 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.

[0107] 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.

[0108] 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.

[0109] 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.

[0110] 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.

[0111] 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).

[0112] 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.

[0113] 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.

[0114] 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 TISRDNKNTLYLQLNSLRAEDTAVYYC	(SEQ ID NO:167)
FW-H4 is WGQGTLVTVSS	(SEQ ID NO:168).

[0115] 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.

[0116] 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 10^3 , at least 10^4 , at least 10^5 , at least 10^6 , at least 10^7 , at least 10^8 , at least 10^9 , at least 10^{10} , at least 10^{11} , or at least 10^{12} unique sequences of antibody light chain variable regions. In some embodiments, a library contains a plurality of polynucleotides that

encodes at least 10^3 unique sequences of antibody light chain variable regions. In some embodiments, a library contains a plurality of polynucleotides that encodes at least 10^5 unique sequences of antibody light chain variable regions. In some embodiments, a library contains a plurality of polynucleotides that encodes at least 10^9 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 10^3 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 the patent application(s) filed under attorney docket number 69540-3000100, 69540-2000140, and/or 69540-2000100 (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 the patent application(s) filed under attorney docket number 69540-3000100, 69540-2000140, and/or 69540-2000100 (the disclosures of which are each incorporated herein by reference in their entireties).

[0117] 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).

[0118] 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 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). 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).

[0119] 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.

[0120] 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.*, X1 TFX2X3YX4IHWV, 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); V SX1ISGX2GX3X4TY YADSVKGRF, 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).

[0121] 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.

[0122] 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.

[0123] 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.

[0124] 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_H and V_L are each attached to the 3' end of a sequence encoding a signal sequence, such as the *ompA*, *phoA* or *pelB* 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.

[0125] 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.

[0126] 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.

[0127] 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_H and V_L fragments, Fab fragments, single domains, or as single chains (scFv).

[0128] 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.

[0129] 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™).

[0130] 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.

[0131] 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

[0132] 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).

[0133] 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) 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, 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 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) 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). 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).

[0134] 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 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).

[0135] 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 XIII) 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).

[0136] 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) 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).

[0137] 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 XIII) 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).

[0138] 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) 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) VVSX₁ISGX₂GX₃X₄TYADSVKGRF, 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).

[0139] 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).

[0140] 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.

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	IGEYHSGSTYYSPSLKSRV
64	IGEYYSGSTYYSPSLKSRV
65	IGSIYHSGNTNYPNPSLKSRV
66	IGEYHSGNTYYNPSLKSRV
67	IGEYHSGSTYYNPSLKSRV
68	IGEYYSGSTYYNPSLKSRV
69	IGDIYHSGNTYYNPSLKSRV
70	IGDIYHSGSTYYNPSLKSRV
71	VSAISGYGDTTYADSVKGRF
72	VSAISGYGGSTYYADSVKGRF
73	VSAISGYGGTTYADSVKGRF
74	VSGISGAGDTTYADSVKGRF
75	VSGISGDGDTTYADSVKGRF
76	VSGISGDGGSTYYADSVKGRF
77	VSGISGYGDTTYADSVKGRF
78	VSGISGYGGTTYADSVKGRF
79	VSVISGDGDTTYADSVKGRF
80	VSVISGYGGSTYYADSVKGRF
81	VSGISGDGSTTYADSVKGRF
82	VSGISGYGSTTYADSVKGRF
83	VSVISGSGSTTYADSVKGRF
84	VSVISGYGSSTYYADSVKGRF

85	VSVISGYGSTTTYADSVKGRF
86	VSAISGYGSTTTYADSVKGRF
87	VSSISGYGDTTYADSVKGRF
88	VSSISGYGGSTTYADSVKGRF
89	VSSISGYGGTTYADSVKGRF
90	VSYISGAGDTTYADSVKGRF
91	VSSISGAGDTTYADSVKGRF
92	VSYISGAGGTTYADSVKGRF
93	VSYISGDGDTTYADSVKGRF
94	VSYISGDGGSTTYADSVKGRF
95	VSYISGDGGTTYADSVKGRF
96	VSYISGSGDTTYADSVKGRF
97	VSSISGAGGSTTYADSVKGRF
98	VSYISGYGDTTYADSVKGRF
99	VSYISGYGGTTYADSVKGRF
100	VSSISGAGGTTYADSVKGRF
101	VSSISGDGDTTYADSVKGRF
102	VSSISGDGGTTYADSVKGRF
103	VSSISGAGSSTTYADSVKGRF
104	VSSISGAGSTTYADSVKGRF
105	VSSISGDGSSTTYADSVKGRF
106	VSSISGDGSTTYADSVKGRF
107	VSSISGYGSSTTYADSVKGRF
108	VSSISGYGSTTYADSVKGRF
109	IGWINPNRGDTKYAQKFQGRV
110	IGWINPNRGDTNYAQKFQGRV
111	IGWINPNRGGTKYAQKFQGRV
112	IGWINPNRGGTNYAQKFQGRV
113	IGWINPNRGSTKYAQKFQGRV
114	IGWINPNRGSTNYAQKFQGRV
115	IGWINPNFGDTNYAQKFQGRV
116	IGWINPNFGDTNYAQKFQGRV
117	IGWINPNFGSTKYAQKFQGRV
118	IGWINPNFGSTNYAQKFQGRV
119	IGIINPNRGDTKYAQKFQGRV
120	IGIINPNRGDTNYAQKFQGRV
121	IGIINPNFGDTNYAQKFQGRV
122	IGWISPSGGGTKYAQKFQGRV
123	IGWISPSGGTNYAQKFQGRV
124	IGWISPSSGGTKYAQKFQGRV
125	IGWISPSSGGTNYAQKFQGRV

126	IGWIYPSGGGTKYAQKFQGRV
127	IGWIYPSGGGTNYAQKFQGRV
128	IGWISPSGGSTNYAQKFQGRV
129	IGWISPSSGGSTKYAQKFQGRV
130	IGWISPSSGGSTNYAQKFQGRV
131	IGWISPSGGSTKYAQKFQGRV
132	IGIIYPSGGGTNYAQKFQGRV
133	IGIISPSGGGTKYAQKFQGRV
134	IGIISPSGGGTNYAQKFQGRV
135	IGIIYPSGGSTNYAQKFQGRV
136	VGRIKSKTDGYTTEYAAPVKGRF
159	VSAISGSGSTTTYADSVKGRF
160	VSSISGSGDTTYADSVKGRF
161	VSSISGSGGSTTYADSVKGRF
162	VSSISGSGGTTYADSVKGRF
163	VSSISGDGGSTTYADSVKGRF
164	VSSISGSGSTTTYADSVKGRF

[0141] 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.

[0142] 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);

VSX1ISGX2GX3X4TYADSVKGRF, 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).

[0143] 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.

[0144] 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.

[0145] 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.

[0146] 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.

[0147] 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).

[0148] 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.

[0149] 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.

[0150] 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.

[0151] 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 TISRDNKNTLYLQLNSLRAEDTAVYYC (SEQ ID NO:167)

FW-H4 is WGQGTLVTVSS (SEQ ID NO:168).

[0152] 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.

[0153] 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 the patent application(s) filed under attorney docket number 69540-3000100, 69540-2000140, and/or 69540-2000100 (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 the patent application(s) filed under attorney docket number 69540-3000100, 69540-2000140, and/or 69540-2000100 (the disclosures of which are each incorporated herein by reference in their entireties).

[0154] 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.

[0155] 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); 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); V SX1ISGX2GX3X4TYYADSVKGRF, 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). 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).

[0156] 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.

[0157] 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.

[0158] 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^{-7} M or less, 10^{-8} M or less, 10^{-9} M or less, 10^{-10} M or less, or 10^{-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^{-7} and about 10^{-11} M. Exemplary assays for determining binding affinity are described and exemplified *infra* (See e.g., the ForteBio assay of Example 4 below).

[0159] 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).

[0160] Antibodies of the present disclosure may be produced using recombinant methods and compositions, e.g., as described in U.S. Patent 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_L and/or an amino acid sequence comprising the V_H 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_L of the antibody and an amino acid sequence comprising the V_H of the antibody, or (2) a first vector comprising a nucleic acid that encodes an amino acid sequence comprising the V_L of the antibody and a second vector comprising a nucleic acid that encodes an amino acid sequence comprising the V_H 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).

[0161] 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).

[0162] 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. Patent 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.

[0163] 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* Gemgross, *Nat. Biotech.* 22:1409-1414 (2004), and Li et al., *Nat. Biotech.* 24:210-215 (2006).

[0164] 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.

[0165] Plant cell cultures can also be utilized as hosts. *See, e.g.*, US Patent Nos. 5,959,177, 6,040,498, 6,420,548, 7,125,978, and 6,417,429 (describing PLANTIBODIESTM technology for producing antibodies in transgenic plants).

[0166] 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).

Bispecific Antibodies with identical/common/single heavy chains

[0167] 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_L domain (*e.g.*, a human kappa C_L domain), and the second light chain comprises a lambda C_L domain (*e.g.*, a human lambda C_L domain). Methods of making and/or purifying bispecific antibodies comprising a kappa C_L domain and a lambda C_L 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_L domain, and c) a second light chain comprising a second light chain variable region and a lambda C_L domain (*e.g.*, the constant region of a second light chain comprising a kappa C_L domain is switched with a lambda C_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_L domain) may be purified using the following steps: first, total IgGs are recovered from the culture supernatant using protein A or IgG-CH1 Capture Select affinity chromatography, resulting in the elimination of free light chains and other contaminants; next, IgGs containing a kappa C_L domain are captured using KappaSelect affinity resin, and monospecific IgGs with light chains containing only lambda C_L 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_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_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.*).

[0168] 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.

[0169] 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.

[0170] 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.

[0171] 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

[0172] 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

[0173] 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

[0174] 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 Jul;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. 1A**; 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. 1B**).

[0175] 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 10^6 , 10^{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

Construction of the heavy chain libraries

[0176] 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 μL of 0.2 μM template oligos were mixed with 10 μL 5x 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 (CGTTTGTCTGTGCAGCTTCCGG) (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).

[0177] 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 5x 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

Table 2: formulas for HVR-H1 and HVR-H2 designed variant sequences

Variant Group	Amino Acid Sequence Formula	X ₁ Residue Identity	X ₂ Residue Identity	X ₃ Residue Identity	X ₄ Residue Identity	X ₅ Residue Identity	X ₆ Residue Identity
HVR-H1_A (SEQ ID NO:198)	X1TFX2X3YX4IHWV	F, Y	S, T	D, G, N, S	A, G, W	n/a	n/a
HVR-H1_B (SEQ ID NO:199)	YSIX1SGX2X3WX4WI	S, T	H, Y	H, Y	A, D, G, N, S, T	n/a	n/a
HVR-H1_C (SEQ ID NO:200)	FSLSTX1GVX2VX3WI	G, S	A, G	A, G, S, T	n/a	n/a	n/a
HVR-H2_A (SEQ ID NO:201)	LAX1IX2WX3X4DKX5Y SX6SLKSRL	L, R	D, Y	A, D, S, Y	D, G	R, S, Y	P, T
HVR-H2_B (SEQ ID NO:202)	IGX1IX2X3SGSTYYSPS LKSRV	A, D, E, S, Y	S, Y	H, Y	n/a	n/a	n/a
HVR-H2_C (SEQ ID NO:203)	IGX1IYX2SGX3TX4YNP SLKSRV	D, E, R, S, Y	H, Y	N, S	N, Y	n/a	n/a
HVR-H2_D (SEQ ID NO:204)	VSX1ISGX2GX3X4TYY ADSVKGRF	A, G, S, V, Y	A, D, S, Y	D, G, S	S, T	n/a	n/a
HVR-H2_E (SEQ ID NO:205)	IGX1INPNX2GX3TX4YA QKFQGRV	I, R, W	F, R	D, G, S	K, N	n/a	n/a
HVR-H2_F (SEQ ID NO:206)	IGX1IX2PSX3GX4TX5Y AQKFQGRV	I, R, W	S, Y	G, S	D, G, S	K, N	n/a
HVR-H2_G (SEQ ID NO:207)	VGRIX1SKX2X3GX4TT X5YAAAX6VKGRF	K, R	A, T	D, Y	G, Y	D, E	P, S

n/a, not applicable.

[0178] Hundreds of degenerate oligos encoding the VH_vr3 with sequence diversity approaching 10^5 were designed and synthesized, and converted into double strand DNA through the following protocol: 0.75 μ L of 0.2 μ M template oligos were mixed with 10 μ L 5x PrimeSTAR buffer, 4 μ L dNTP mixture, 1 μ L of 100 μ M forward primer, 1 μ L of 100 μ M reverse primer, 0.5 μ L of PrimeSTAR HS DNA Polymerase (2.5 U/ μ L), and 33 μ L 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 (ACAACCTGAACAGCTTAAGAGCTGAGGACACTGCCGTCTATTATTG) (SEQ ID NO:215) and the reverse primer was S1090 (GAGGAGACGGTGACTAGTGTTCCCTTGACCCCA) (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.

[0179] 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 10x 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 x 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).

[0180] 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.

Construction of the VL library

[0181] 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 5x 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).

[0182] 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 μ L 5x PrimeSTAR buffer, 4 μ L dNTP mixture, 1 μ L of 100 μ M F_2898 primer, 1 μ L of 100 μ M R_2013 primer, 0.5 μ L of PrimeSTAR HS DNA Polymerase (2.5 U/ μ L), and water (up to 50 μ L), 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.

[0183] 22 groups of degenerate oligos encoding VL_vr3 were designed, synthesized, and converted into double stranded DNA through the following protocol: 0.75 μ L of 0.2 μ M template oligos were mixed with 10 μ L 5x PrimeSTAR buffer, 4 μ L dNTP mixture, 1 μ L of 100 μ M forward primer F2929 (ACCATCAGCAGTCTGCAGCCGGAAGACTTCGCAAC) (SEQ ID NO:221), 1 μ L of 100 μ M reverse primer R2929 (GATCTCCACCTTGGTACCCTGTCCGAA) (SEQ ID NO:222), 0.5 μ L of PrimeSTAR HS DNA Polymerase (2.5 U/ μ L), and 33 μ L 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 FTV013 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.

[0184] 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-vr12 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 4×10^7 .

Construction of the complete dynamic library

[0185] 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 μ L 10x NEBuffer 4, 50 μ L of 100 μ M pd(N)8, and water (up to 88.5 μ L), 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 μ L of 10 mM dNTP mix, 1 μ L of 100 x BSA, and 0.5 μ L 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^{10} colonies were collected from plates (2xYT, 1% glucose, 100 μ g/mL ampicillin) to make the DPL6 library.

Example 3: Screening the common heavy chain libraries to isolate antibodies of interest*Preparation of dynamic library phagemid particles*

[0186] 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 2xYT, 2% glucose, 100 µg/mL ampicillin and 12.5 µg/mL tetracycline at a starting OD₆₀₀ of 0.1. The cultures were grown at 37°C, shaking at 250 rpm, until they reached OD₆₀₀ 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 2xYT, 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 OD₂₆₈ measurement (assuming 1 unit at OD₂₆₈ is approximately 1*10¹³ phage particles/mL) and confirmed by plaque assay. Library phagemid particles were stocked in 20% glycerol at -80°C.

Phage library panning

[0187] 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*10¹² 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)

[0188] 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 μ L 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^{12} to 1×10^{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 μ L of 0.2 M glycine-HCl for 10 minutes at room temperature. The eluted phages were immediately neutralized with 18 μ L 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.

[0189] For some of the antigens tested, 2 mL of antigens (10 - 30 μ g/mL) were used to coat immune-tubes overnight at 4°C. The volume of blocking, washing, and elution solutions were increased accordingly.

Amplification of enriched phage

[0190] 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 2xYT agar plates with 2% glucose, 100 μ g/mL ampicillin and 12.5 μ g/mL tetracycline. The colonies were harvested from plates, grown in 100 ml of 2% glucose, 100 μ g/mL ampicillin and 12.5 μ 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.

Supernatant sandwich Elisa assay

[0191] 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 I5260) 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 A₄₅₀ 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).

[0192] 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**).

Table 3: formulas for HVR-H1 and HVR-H2 designed variant sequences from positive hits

Variant Group	Amino Acid Sequence Formula	X ₁ Residue Identity	X ₂ Residue Identity	X ₃ Residue Identity	X ₄ Residue Identity	X ₅ Residue Identity	X ₆ Residue Identity
HVR-H1_1 (SEQ ID NO:198)	X1TFX2X3YX4IHWV	F, Y	S, T	D, G, N, S	A, G, W	n/a	n/a
HVR-H1_2 (SEQ ID NO:199)	YSIX1SGX2X3WX4WI	S, T	H, Y	H, Y	A, D, G, N, S, T	n/a	n/a
HVR-H1_3 (SEQ ID NO:200)	FSLSTX1GVX2VX3WI	G, S	A, G	A, G, S, T	n/a	n/a	n/a
HVR-H2_1 (SEQ ID NO:201)	LAX1IX2WX3X4DKX5Y SX6SLKSRL	L, R	D, Y	A, D, S, Y	D, G	R, S, Y	P, T
HVR-H2_2 (SEQ ID NO:208)	IGX1IX2X3SGSTYYSPS LKSRV	A, D, E	S, Y	H, Y	n/a	n/a	n/a
HVR-H2_3 (SEQ ID NO:209)	IGX1IYX2SGX3TX4YNP SLKSRL	D, E, S	H, Y	N, S	N, Y	n/a	n/a
HVR-H2_4 (SEQ ID NO:204)	VSX1ISGX2GX3X4TYY ADSVKGRF	A, G, S, V, Y	A, D, S, Y	D, G, S	S, T	n/a	n/a
HVR-H2_5 (SEQ ID NO:205)	IGX1INPNX2GX3TX4YA QKFQGRV	I, R, W	F, R	D, G, S	K, N	n/a	n/a
HVR-H2_6 (SEQ ID NO:206)	IGX1IX2PSX3GX4TX5Y AQKFQGRV	I, R, W	S, Y	G, S	D, G, S	K, N	n/a
HVR-H2_7 (SEQ ID NO:210)	VGRIX1SKX2X3GX4TT EYAAAX5VKGRF	K, R	A, T	D, Y	G, Y	P, S	n/a

n/a, not applicable.

Example 4: Characterization of antibodies *in vitro*

[0193] 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 $\mu\text{g/mL}$ 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 5000x stock 50 fold to 100x 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 100x 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, T_m , 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).

[0194] 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. 2A**). In addition, the confirmed binders demonstrated good stability, with T_m ranges shown in **FIG. 2B**.

Example 5: Application of the dynamic heavy chain libraries

[0195] 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 10^7 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 10^7 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 rationale 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 10^7 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.

Table 4: Affinity data for confirmed hits

HVR-H1 and H2 Usage	Hit ID	Target ID	Kd (M)
HVR-H1_1 and HVR-H2_6	3757	TAGT-6	1.84E-08
	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 HVR-H2_5	4025	TAGT-8	2.89E-09
	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 HVR-H2_4	4074	TAGT-6	1.95E-08
	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 HVR-H2_4	3761	TAGT-6	9.65E-08
	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 HVR-H2_4	3760	TAGT-6	1.26E-08
	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	1.07E-09
5526	TAGT-2	1.54E-09
5528	TAGT-2	4.55E-09
5532	TAGT-2	3.65E-09
5553	TAGT-2	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 HVR-H2_6	4027	TAGT-8	1.55E-09
	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 HVR-H2_1	4052	TAGT-10	9.73E-09
	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 HVR-H2_2	4812	TAGT-12	2.89E-09
	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 HVR-H2_3	4037	TAGT-8	5.53E-09
	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 HVR-H2_1	4097	TAGT-8	6.24E-09
	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 HVR-H2_5	4102	TAGT-8	2.54E-09
	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 HVR-H2_3	4161	TAGT-8	2.98E-08
	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 HVR-H2_1	5208	TAGT-1	3.36E-09
	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 HVR-H2_2	4840	TAGT-12	2.08E-09
	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 HVR-H2_2	4036	TAGT-8	3.13E-09
	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 HVR-H2_3	4026	TAGT-8	3.08E-09
	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 HVR-H2_6	4857	TAGT-12	4.05E-09
	5227	TAGT-1	1.04E-08
	7221	TAGT-12	5.58E-09
	7229	TAGT-12	8.91E-09
HVR-H1_2 and HVR-H2_7	4220	TAGT-6	5.72E-08
	4861	TAGT-12	5.11E-09
	5284	TAGT-1	1.84E-08
HVR-H1_1 and HVR-H2_7	4079	TAGT-6	3.15E-08
	7129	TAGT-6	1.90E-08
HVR-H1_3 and HVR-H2_5	4072	TAGT-6	6.95E-09
HVR-H1_3 and HVR-H2_7	5333	TAGT-6	5.02E-09

[0196] 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).

[0197] **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).

Table 5: target binding capability of HVR-H1 and HVR-H2 designed variants

Variant ID	Sequence Usage Percent	Number of Antigens 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

[0198] **Table 6** below shows sequence usage and number of antigens bound for the HVR-H1 and HVR-H2 combinations identified during the library analyses.

Table 6: HVR-H1 and HVR-H2 designed variants combination usage

Preference Ranking	HVR-H1 Variant ID	HVR-H2 Variant ID	Sequence Usage Percent	Number of Antigens hit out of 14
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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

[0199] 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.

Table 7: Usage of new HVR-H1 and HVR-H2 sequences

SEQ ID NO:	Number of hits	Number of Antigens 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

[0200] Table 8 below shows usage and number of antigens bound for the combination of new HVR-H1 and HVR-H2 sequences.

Table 8: new HVR-H1 and HVR-H2 combination usage

Preference Ranking	HVR-H1 SEQ ID NO:	HVR-H2 SEQ ID NO:	Number of hits	Number of Antigens 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

[0201] Table 9 shows affinity data for unique hits using the indicated new HVR-H1 and HVR-H2 sequences.

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	3.81E-09
124	4043	TAGT-8	2.69E-09
124	5020	TAGT-8	8.78E-10
124	5020	TAGT-8M	7.00E-09
124	5023	TAGT-8	9.46E-10
124	5023	TAGT-8M	5.77E-09

124	5030	TAGT-8	7.03E-10
124	5030	TAGT-8M	4.27E-09
124	5037	TAGT-8	1.06E-09
124	5037	TAGT-8M	4.36E-09
124	5039	TAGT-8	4.30E-10
124	5039	TAGT-8M	2.69E-09
124	5040	TAGT-8	4.37E-10
124	5040	TAGT-8M	3.13E-09
124	5045	TAGT-8	1.00E-09
124	5045	TAGT-8M	3.91E-09
124	5048	TAGT-8	5.10E-10
124	5048	TAGT-8M	2.52E-09
124	5066	TAGT-8	5.23E-09
124	5066	TAGT-8M	9.99E-09
124	5070	TAGT-8	1.34E-09
124	5070	TAGT-8M	6.63E-09
124	5994	TAGT-12	1.58E-08
124	7442	TAGT-9	6.83E-09
93	4062	TAGT-10	2.11E-08
93	4132	TAGT-6	<1.0E-12
93	4201	TAGT-6	1.41E-08
93	5300	TAGT-6	1.53E-08
93	5694	TAGT-11	9.45E-09
93	5906	TAGT-12	1.50E-08
93	5926	TAGT-12	3.23E-08
93	7078	TAGT-6	2.52E-08
93	7087	TAGT-6	6.96E-08
93	7120	TAGT-6	3.45E-08
93	7190	TAGT-6	1.03E-08
93	7271	TAGT-5	3.13E-08
82	4048	TAGT-10	3.24E-09
82	4051	TAGT-10	1.80E-08
82	4723	TAGT-10	9.11E-10
82	4733	TAGT-10	3.05E-10
82	4734	TAGT-10	5.72E-10
82	4767	TAGT-10	2.77E-10
82	4771	TAGT-10	7.23E-10
82	4797	TAGT-10	5.63E-10
82	4807	TAGT-10	1.17E-09
82	5346	TAGT-6	1.61E-08
82	6221	TAGT-10	6.92E-10

130	4813	TAGT-12	2.45E-10
130	5113	TAGT-12	6.80E-09
130	5114	TAGT-12	3.42E-08
130	5116	TAGT-12	1.46E-08
130	5119	TAGT-12	7.54E-09
130	5121	TAGT-12	9.29E-09
130	5123	TAGT-12	5.67E-09
130	5125	TAGT-12	2.42E-08
130	5128	TAGT-12	7.12E-09
130	5138	TAGT-12	8.55E-09
116	4752	TAGT-10	3.34E-09
116	6194	TAGT-10	2.49E-10
116	6196	TAGT-10	<1.0E-12
116	6202	TAGT-10	1.03E-09
116	6204	TAGT-10	6.46E-09
116	6208	TAGT-10	3.50E-09
116	6210	TAGT-10	5.17E-10
116	6212	TAGT-10	2.25E-09
116	6214	TAGT-10	1.51E-09
116	6217	TAGT-10	4.99E-09
132	4032	TAGT-8	5.11E-09
132	4032	TAGT-8M	4.84E-09
132	4050	TAGT-10	1.65E-08
132	5012	TAGT-8	1.76E-09
132	5012	TAGT-8M	2.03E-09
132	5014	TAGT-8	2.43E-09
132	5014	TAGT-8M	3.87E-09
132	5016	TAGT-8	3.56E-09
132	5016	TAGT-8M	2.84E-09
132	5022	TAGT-8	3.68E-09
132	5022	TAGT-8M	3.03E-09
132	5024	TAGT-8	4.52E-09
132	5024	TAGT-8M	3.48E-09
132	5041	TAGT-8	1.68E-09
132	5041	TAGT-8M	1.67E-09
132	5074	TAGT-8	4.31E-09
132	5074	TAGT-8M	2.98E-09
132	5082	TAGT-8	4.79E-09
132	5082	TAGT-8M	3.23E-09
53	4052	TAGT-10	9.73E-09
53	4059	TAGT-10	3.30E-07

53	5094	TAGT-10	4.34E-08
53	5095	TAGT-10	1.27E-08
53	5097	TAGT-10	1.27E-08
53	5099	TAGT-10	4.20E-08
53	5109	TAGT-10	2.59E-08
53	5280	TAGT-1	8.43E-09
53	5936	TAGT-10	1.75E-08
89	4045	TAGT-8	1.10E-09
89	4123	TAGT-6	5.98E-09
89	4125	TAGT-6	<1.0E-12
89	5910	TAGT-12	3.30E-08
89	5920	TAGT-12	1.88E-08
89	5929	TAGT-12	3.20E-08
89	7079	TAGT-6	2.99E-08
89	7133	TAGT-6	4.03E-08
89	7219	TAGT-12	1.44E-08
134	3898	TAGT-11	1.83E-08
134	4925	TAGT-7	1.32E-08
134	5149	TAGT-11	2.91E-09
134	5159	TAGT-11	4.09E-09
134	5160	TAGT-11	8.07E-09
134	5162	TAGT-11	9.87E-09
134	5165	TAGT-11	4.06E-09
134	5752	TAGT-11	6.33E-09
134	7231	TAGT-12	3.38E-09
66	4161	TAGT-8	2.98E-08
66	4180	TAGT-10	7.39E-08
66	4809	TAGT-12	3.69E-10
66	4847	TAGT-12	3.64E-10
66	4879	TAGT-12	3.13E-09
66	6533	TAGT-3	2.62E-08
66	7372	TAGT-5	7.27E-10
66	7386	TAGT-5	1.32E-08
122	3757	TAGT-6	1.84E-08
122	3869	TAGT-11	2.35E-08
122	4163	TAGT-8	1.37E-08
122	4828	TAGT-12	1.10E-09
122	5103	TAGT-10	2.67E-09
122	5163	TAGT-11	1.71E-08
122	5740	TAGT-11	7.26E-09
123	3762	TAGT-6	3.04E-08

123	3780	TAGT-8	1.47E-09
123	3865	TAGT-11	9.48E-09
123	7030	TAGT-8	3.47E-08
123	7035	TAGT-8	3.04E-09
123	7055	TAGT-8	7.57E-10
123	7358	TAGT-3	5.15E-08
128	4101	TAGT-8	2.12E-09
128	4661	TAGT-8	1.62E-09
128	4792	TAGT-10	7.39E-09
128	5997	TAGT-12	8.51E-09
128	7040	TAGT-8	2.72E-08
128	7221	TAGT-12	5.58E-09
128	7228	TAGT-12	7.62E-09
131	4103	TAGT-8	3.59E-10
131	7215	TAGT-12	1.61E-08
131	7229	TAGT-12	8.91E-09
131	7243	TAGT-12	4.95E-09
131	7244	TAGT-12	1.05E-08
131	7254	TAGT-12	1.07E-08
131	7258	TAGT-12	9.72E-09
65	4037	TAGT-8	5.53E-09
65	4823	TAGT-12	2.62E-09
65	5292	TAGT-1	1.57E-08
65	5741	TAGT-11	1.91E-08
65	7239	TAGT-12	2.40E-08
65	7433	TAGT-9	1.67E-08
109	6179	TAGT-10	1.99E-09
109	6184	TAGT-10	<1.0E-12
109	6188	TAGT-10	8.76E-09
109	6189	TAGT-10	2.38E-10
109	6216	TAGT-10	6.58E-10
109	6539	TAGT-4	3.45E-09
72	5301	TAGT-6	2.61E-07
72	5326	TAGT-6	7.84E-07
72	5420	TAGT-6	1.41E-08
72	5710	TAGT-11	1.01E-08
72	5746	TAGT-11	5.00E-09
87	4216	TAGT-6	2.59E-08
87	5320	TAGT-6	6.13E-07
87	5408	TAGT-6	2.36E-08
87	7183	TAGT-6	1.48E-08

87	7201	TAGT-6	3.26E-08
105	5218	TAGT-1	6.04E-09
105	5316	TAGT-6	1.14E-08
105	5513	TAGT-2	1.07E-09
105	6543	TAGT-3	6.78E-08
105	7427	TAGT-9	5.58E-09
118	4851	TAGT-12	3.84E-10
118	7025	TAGT-8	4.87E-08
118	7036	TAGT-8	1.59E-08
118	7037	TAGT-8	2.10E-08
118	7047	TAGT-8	2.15E-08
60	5226	TAGT-1	8.36E-09
60	5281	TAGT-1	4.70E-09
60	5425	TAGT-9	2.15E-08
60	5744	TAGT-11	1.14E-08
67	4026	TAGT-8	3.08E-09
67	4820	TAGT-12	3.96E-09
67	4839	TAGT-12	6.16E-09
67	7274	TAGT-5	1.63E-08
70	4041	TAGT-8	1.54E-09
70	4844	TAGT-12	6.95E-10
70	7159	TAGT-6	3.79E-08
70	7380	TAGT-5	1.24E-08
84	7204	TAGT-5	2.33E-09
84	7323	TAGT-5	3.23E-09
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 162	7257	TAGT-12	1.11E-08
158 and 63	5387	TAGT-8	1.13E-09
158 and 63	5985	TAGT-12	3.92E-08
158 and 63	5986	TAGT-12	4.65E-08
158 and 104	5912	TAGT-12	1.68E-08
158 and 104	5923	TAGT-12	1.60E-08
158 and 104	7226	TAGT-12	7.57E-09

5 and 121	4060	TAGT-10	1.10E-08
5 and 121	4798	TAGT-10	4.35E-09
5 and 121	6219	TAGT-10	3.15E-09
6 and 116	4752	TAGT-10	3.34E-09
6 and 116	6210	TAGT-10	5.17E-10
6 and 116	6212	TAGT-10	2.25E-09
138 and 63	4840	TAGT-12	2.08E-09
138 and 63	5722	TAGT-11	3.08E-08
138 and 63	7385	TAGT-5	3.26E-09
7 and 121	4065	TAGT-10	4.31E-08
7 and 121	4182	TAGT-10	4.24E-09
7 and 121	4741	TAGT-10	1.66E-09
145 and 128	4101	TAGT-8	2.12E-09
145 and 128	4661	TAGT-8	1.62E-09
145 and 128	4792	TAGT-10	7.39E-09
17 and 63	4818	TAGT-12	1.02E-09
17 and 63	4841	TAGT-12	4.50E-10
22 and 61	5271	TAGT-1	1.24E-08
22 and 61	7207	TAGT-5	4.99E-10
25 and 101	4217	TAGT-6	9.67E-08
25 and 101	4218	TAGT-6	2.85E-08
25 and 114	5968	TAGT-12	1.27E-08
25 and 114	5990	TAGT-12	1.15E-08
29 and 112	5930	TAGT-12	5.66E-09
29 and 112	5932	TAGT-12	1.12E-08
31 and 63	5658	TAGT-11	2.61E-10
31 and 63	7394	TAGT-5	8.75E-09
152 and 63	4897	TAGT-12	6.83E-10
152 and 63	4901	TAGT-12	3.19E-09
153 and 63	4817	TAGT-12	2.06E-09
153 and 63	7316	TAGT-5	2.04E-08
155 and 67	4026	TAGT-8	3.08E-09
155 and 67	7274	TAGT-5	1.63E-08
156 and 89	7079	TAGT-6	2.99E-08
156 and 89	7133	TAGT-6	4.03E-08
156 and 100	5417	TAGT-6	4.04E-08
156 and 100	5974	TAGT-12	5.02E-08
157 and 94	7088	TAGT-6	4.36E-08
157 and 94	7100	TAGT-6	3.50E-08
48 and 58	5314	TAGT-6	8.39E-09
48 and 58	5342	TAGT-6	3.89E-08

50 and 89	5929	TAGT-12	3.20E-08
50 and 89	7219	TAGT-12	1.44E-08
50 and 163	5999	TAGT-12	6.29E-08
50 and 163	7235	TAGT-12	2.18E-08
158 and 160	5911	TAGT-12	3.35E-08
158 and 160	7216	TAGT-12	1.88E-08
158 and 87	4216	TAGT-6	2.59E-08
158 and 87	7201	TAGT-6	3.26E-08
158 and 92	7080	TAGT-6	2.44E-08
158 and 92	7081	TAGT-6	4.31E-08
158 and 93	7078	TAGT-6	2.52E-08
158 and 93	7087	TAGT-6	6.96E-08
158 and 97	5915	TAGT-12	1.82E-08
158 and 97	5964	TAGT-12	1.40E-08
158 and 103	5961	TAGT-12	2.41E-08
158 and 103	7255	TAGT-12	1.20E-08
158 and 164	7211	TAGT-12	1.26E-08
158 and 164	7220	TAGT-12	9.12E-09
51 and 162	4074	TAGT-6	1.95E-08
51 and 162	7237	TAGT-12	2.13E-08
137 and 54	7277	TAGT-5	2.56E-09
137 and 54	7390	TAGT-5	1.44E-09
3 and 127	7044	TAGT-8	1.12E-09
3 and 127	7045	TAGT-8	1.11E-09
4 and 85	7260	TAGT-5	2.30E-09
4 and 85	7374	TAGT-5	1.97E-08
4 and 110	6183	TAGT-10	2.70E-09
4 and 110	6206	TAGT-10	3.44E-09
138 and 123	3762	TAGT-6	3.04E-08
138 and 123	3865	TAGT-11	9.48E-09
139 and 109	6184	TAGT-10	<1.0E-12
139 and 109	6216	TAGT-10	6.58E-10
139 and 121	6187	TAGT-10	2.74E-08
139 and 121	6197	TAGT-10	8.56E-09
8 and 120	6190	TAGT-10	2.55E-09
8 and 120	6203	TAGT-10	1.05E-08
140 and 131	7215	TAGT-12	1.61E-08
140 and 131	7243	TAGT-12	4.95E-09
141 and 116	6204	TAGT-10	6.46E-09
141 and 116	6214	TAGT-10	1.51E-09
142 and 159	5554	TAGT-2	2.88E-09

142 and 159	5622	TAGT-2	3.06E-09
143 and 116	6194	TAGT-10	2.49E-10
143 and 116	6196	TAGT-10	<1.0E-12
144 and 121	6185	TAGT-10	1.57E-09
144 and 121	6209	TAGT-10	3.35E-09
146 and 110	4055	TAGT-10	1.07E-08
146 and 110	4743	TAGT-10	7.40E-09
147 and 133	5935	TAGT-12	8.78E-09
147 and 133	6008	TAGT-12	5.10E-08
148 and 63	5195	TAGT-1	2.62E-08
148 and 63	5290	TAGT-1	6.73E-09
13 and 118	7025	TAGT-8	4.87E-08
13 and 118	7037	TAGT-8	2.10E-08

[0202] 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.

[0203] 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.

[0204] 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.

[0205] 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.

[0206] 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_H components that can bind to the same or multiple different targets depending upon the V_L segment with which the V_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_H component for antibody discovery.

SEQUENCES

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

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: YTFSSNYGIHWV (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: YTFSSNYWIHWV (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: YSISGHHWAWI (SEQ ID NO:15)

Designed HVR-H1 sequence 16: YSISGHHYWNWI (SEQ ID NO:16)

Designed HVR-H1 sequence 17: YSISGHHYWSWI (SEQ ID NO:17)

Designed HVR-H1 sequence 18: YSISGHHYWTWI (SEQ ID NO:18)

Designed HVR-H1 sequence 19: YSISGHHYHAWI (SEQ ID NO:19)

Designed HVR-H1 sequence 20: YSISGHHYHWDWI (SEQ ID NO:20)

Designed HVR-H1 sequence 21: YSISGHHYHWGWI (SEQ ID NO:21)

Designed HVR-H1 sequence 22: YSISGHHYHWNWI (SEQ ID NO:22)

Designed HVR-H1 sequence 23: YSISGHHYHWSWI (SEQ ID NO:23)

Designed HVR-H1 sequence 24: YSISGHHYHWDWI (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: FTFSYAIHWV (SEQ ID NO:137)
Designed HVR-H1 sequence 54: FTFSYGIHWV (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: YTFDYAIHWV (SEQ ID NO:141)
Designed HVR-H1 sequence 58: YTFDYGIHWV (SEQ ID NO:142)
Designed HVR-H1 sequence 59: YFTNYAIHWV (SEQ ID NO:143)
Designed HVR-H1 sequence 60: YFTNYGIHWV (SEQ ID NO:144)
Designed HVR-H1 sequence 61: FTFSYGIHWV (SEQ ID NO:145)
Designed HVR-H1 sequence 62: YTFSNYAIHWV (SEQ ID NO:146)
Designed HVR-H1 sequence 63: YTFSSYGIHWV (SEQ ID NO:147)
Designed HVR-H1 sequence 64: FTFSYWIHWV (SEQ ID NO:148)
Designed HVR-H1 sequence 65: YFTSYWIHWV (SEQ ID NO:149)
Designed HVR-H1 sequence 66: YSISGGYYWGW (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: YSISGGHYWAWI (SEQ ID NO:153)
Designed HVR-H1 sequence 70: YSISGGHYWGW (SEQ ID NO:154)
Designed HVR-H1 sequence 71: FSLSTSGVAVGW (SEQ ID NO:155)
Designed HVR-H1 sequence 72: FSLSTSGVGVAWI (SEQ ID NO:156)
Designed HVR-H1 sequence 73: FSLSTSGVGVGW (SEQ ID NO:157)
Designed HVR-H1 sequence 74: FSLSTGGVGVGW (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: IGDYHSGSTYYSPSLKSRV (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: IGSYHSGNTNYPNPSLKSRV (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: IGDYHSGNTYYNPSLKSRV (SEQ ID NO:69)
Designed HVR-H2 sequence 18: IGDYHSGSTYYNPSLKSRV (SEQ ID NO:70)
Designed HVR-H2 sequence 19: VSAISGYGDTTYADSVKGRF (SEQ ID NO:71)
Designed HVR-H2 sequence 20: VSAISGYGGSTYYADSVKGRF (SEQ ID NO:72)
Designed HVR-H2 sequence 21: VSAISGYGGTTYADSVKGRF (SEQ ID NO:73)
Designed HVR-H2 sequence 22: VSGISGAGDTTYADSVKGRF (SEQ ID NO:74)
Designed HVR-H2 sequence 23: VSGISGDGDTTYADSVKGRF (SEQ ID NO:75)
Designed HVR-H2 sequence 24: VSGISGDGGSTYYADSVKGRF (SEQ ID NO:76)
Designed HVR-H2 sequence 25: VSGISGYGDTTYADSVKGRF (SEQ ID NO:77)
Designed HVR-H2 sequence 26: VSGISGYGGTTYADSVKGRF (SEQ ID NO:78)
Designed HVR-H2 sequence 27: VSVISGDGDTTYADSVKGRF (SEQ ID NO:79)
Designed HVR-H2 sequence 28: VSVISGYGGSTYYADSVKGRF (SEQ ID NO:80)
Designed HVR-H2 sequence 29: VSGISGDGSTTYADSVKGRF (SEQ ID NO:81)
Designed HVR-H2 sequence 30: VSGISGYGSTTYADSVKGRF (SEQ ID NO:82)
Designed HVR-H2 sequence 31: VSVISGSGSTTYADSVKGRF (SEQ ID NO:83)
Designed HVR-H2 sequence 32: VSVISGYGSSTYYADSVKGRF (SEQ ID NO:84)
Designed HVR-H2 sequence 33: VSVISGYGSTTYADSVKGRF (SEQ ID NO:85)
Designed HVR-H2 sequence 34: VSAISGYGSTTYADSVKGRF (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: VSSISGYGGTYYADSVKGRF (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: VSYISGDGGTYYADSVKGRF (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: VSYISGYGGTYYADSVKGRF (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: VSSISGDGGTYYADSVKGRF (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: IGWINPNRGGTKY AQKFQGRV (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: IGWISPSGGGTKY AQKFQGRV (SEQ ID NO:122)
Designed HVR-H2 sequence 71: IGWISPSGGGTNYAQKFQGRV (SEQ ID NO:123)
Designed HVR-H2 sequence 72: IGWISPSGGTKY AQKFQGRV (SEQ ID NO:124)
Designed HVR-H2 sequence 73: IGWISPSGGTNYAQKFQGRV (SEQ ID NO:125)
Designed HVR-H2 sequence 74: IGWIYPSGGGTKY AQKFQGRV (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: IGWISPSGGSTKY AQKFQGRV (SEQ ID NO:129)
Designed HVR-H2 sequence 78: IGWISPSGGSTNYAQKFQGRV (SEQ ID NO:130)
Designed HVR-H2 sequence 79: IGWISPSGGSTKY AQKFQGRV (SEQ ID NO:131)
Designed HVR-H2 sequence 80: IGIYPSGGGTNYAQKFQGRV (SEQ ID NO:132)
Designed HVR-H2 sequence 81: IGIISPSGGGTKY AQKFQGRV (SEQ ID NO:133)
Designed HVR-H2 sequence 82: IGIISPSGGGTNYAQKFQGRV (SEQ ID NO:134)
Designed HVR-H2 sequence 83: IGIYPSGGSTNYAQKFQGRV (SEQ ID NO:135)
Designed HVR-H2 sequence 84: VGRIKSKTDGYTTEYAAPVKGRF (SEQ ID NO:136)
Designed HVR-H2 sequence 85: VSAISGSGSTTYADSVKGRF (SEQ ID NO:159)
Designed HVR-H2 sequence 86: VSSISGSGDTTYADSVKGRF (SEQ ID NO:160)
Designed HVR-H2 sequence 87: VSSISGSGGSTTYADSVKGRF (SEQ ID NO:161)
Designed HVR-H2 sequence 88: VSSISGSGGTTYADSVKGRF (SEQ ID NO:162)
Designed HVR-H2 sequence 89: VSSISGDGGSTTYADSVKGRF (SEQ ID NO:163)
Designed HVR-H2 sequence 90: VSSISGSGSTTYADSVKGRF (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

EVQLVESGGGLVQPGGSLRLSCAASGYSITSGYHWGWIRQAPGKGLEWVSYISGAGDTTYYADSVKGRFTISRDNKNTLYLQLNSLRAEDTAVYYCARDYGDYYGFDYWGQGTLVTVSS (SEQ ID NO: 169)

HIT ID 4029 – VL

DIQLTQSPSSLASVGDRVTITCRASQSVDFYGISFLAWYQQKPKAPKLLIYDASNLETGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYRTPFTFGQGTKVEIKR (SEQ ID NO: 170)

Hit ID 7097 – VH

EVQLVESGGGLVQPGGSLRLSCAASGYSISSGHHWDWIRQAPGKGLEWVSYISGAGDTTYYADSVKGRFTISRDNKNTLYLQLNSLRAEDTAVYYCAREGSDAVLGDWFAYWGQGTLVTVSS (SEQ ID NO: 171)

HIT ID 7097 – VL

DIQLTQSPSSLASVGDRVTITCRASQGISSYLAWYQQKPKAPKLLIYDASNLETGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQYYSTPLTFGQGTKVEIKR (SEQ ID NO: 172)

Hit ID 5906 – VH

EVQLVESGGGLVQPGGSLRLSCAASGYSISSGYHWNWIRQAPGKGLEWVSYISGDGDTTYYADSVKGRFTISRDNKNTLYLQLNSLRAEDTAVYYCARDLGGYYGWGRYFDYWGQGTLVTVSS (SEQ ID NO: 173)

HIT ID 5906 – VL

DIQLTQSPSSLASVGDRVTITCRASQSVSSYLAWYQQKPKAPKLLIYDASNLETGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPLTFGQGTKVEIKR (SEQ ID NO: 174)

Hit ID 7040 – VH

EVQLVESGGGLVQPGGSLRLSCAASGYSISSGYWYWNWIRQAPGKGLEWIGWISPSGGSTNYAQKFQGRVTISRDNKNTLYLQLNSLRAEDTAVYYCARDLTAGGFDYWGQGTLVTVSS (SEQ ID NO: 175)

HIT ID 7040 – VL

DIQLTQSPSSLASVGDRVTITCRASQGISSYLAWYQQKPKAPKLLIYDASNLETGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQYYSTPLTFGQGTKVEIKR (SEQ ID NO: 176)

Hit ID 5924 – VH

EVQLVESGGGLVQPGGSLRLSCAASGYSISSGYHWGWIRQAPGKGLEWIGIIPSSGSKYAQKFQGRVTISRDNKNTLYLQLNSLRAEDTAVYYCARGAGVHYALDYWGQGTLVTVSS (SEQ ID NO: 177)

HIT ID 5924 – VL

DIQLTQSPSSLASVGDRVTITCRASQSVSSYLAWYQQKPGKAPKLLIYDASNLETGVPSRFSGSGSGTDFTL
TISSLQPEDFATYYCQQSYSTPLTFGQGTKVEIKR (SEQ ID NO: 178)

Hit ID 4034 – VH

EVQLVESGGGLVQPGGSLRLSCAASGYSISSGHYWNWIRQAPGKGLEWVSSISGYGSTTTYADSVKGRFTI
SRDNSKNTLYLQLNSLRAEDTAVYYCARERYYGSTDYAFDYWGQGTLLTVSS (SEQ ID NO: 179)

HIT ID 4034 – VL

DIQLTQSPSSLASVGDRVTITCSASSRVSHVFWYQQKPGKAPKLLIYAASLQSGVPSRFSGSGSGTDFTLTI
SSLQPEDFATYFCLQGFHPWTFGQGTKVEIKR (SEQ ID NO: 180)

Hit ID 6010 – VH

EVQLVESGGGLVQPGGSLRLSCAASGYSISSGHYWNWIRQAPGKGLEWIGWINPNRGTNYAQKFQGRVT
ISRDNSKNTLYLQLNSLRAEDTAVYYCARDYYGDFDYWGQGTLLTVSS (SEQ ID NO: 181)

HIT ID 6010 – VL

DIQLTQSPSSLASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYDASNLETGVPSRFSGSGSGTDFTL
TISSLQPEDFATYYCQHGYGTPLTFGQGTKVEIKR (SEQ ID NO: 182)

Hit ID 7183 – VH

EVQLVESGGGLVQPGGSLRLSCAASGYSISSGHYWNWIRQAPGKGLEWVSSISGYGDTTYADSVKGRFTI
SRDNSKNTLYLQLNSLRAEDTAVYYCAREGSDTVLGDWFAYWGQGTLLTVSS (SEQ ID NO: 183)

HIT ID 7183 – VL

DIQLTQSPSSLASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYDASN RATGIPSRFSGSGSGTDFTLT
ISSLQPEDFATYYCQQSYSTPPTFGQGTKVEIKR (SEQ ID NO: 184)

Hit ID 4036 – VH

EVQLVESGGGLVQPGGSLRLSCAASGFSLSTSGVGVGWRQAPGKGLEWIGEIYHSGSTYYSPSLKSRVTIS
RDNSKNTLYLQLNSLRAEDTAVYYCARERYGSYYFDYWGQGTLLTVSS (SEQ ID NO: 185)

HIT ID 4036 – VL

DIQLTQSPSSLASVGDRVTITCRASQSVDFYGKSFLDWYQQKPGKAPKLLIYDASSLESGVPSRFSGSGSGT
DFTLTISSLQPEDFATYYCQQYYRIPPTFGQGTKVEIKR (SEQ ID NO: 186)

Hit ID 5115 – VH

EVQLVESGGGLVQPGGSLRLSCAASGYSISSGHYWGWRQAPGKGLEWIGEIYHSGSTYYSPSLKSRVTISR
DNSKNTLYLQLNSLRAEDTAVYYCARESYAFDYWGQGTLLTVSS (SEQ ID NO: 187)

HIT ID 5115 – VL

DIQLTQSPSSLASVGDRVTITCRASQSVSSYLAWYQQKPGKAPKLLIYAASLQSGVPSRFSGSGSGTDFTL
TISSLQPEDFATYYCQQYYTTPLTFGQGTKVEIKR (SEQ ID NO: 188)

Hit ID 5404 – VH

EVQLVESGGGLVQPGGSLRLSCAASGYSISSGYHWA WIRQAPGKGLEWIGEIYHSGSTYYSPSLKSRVTISR

DNSKNLTYLQLNSLRAEDTAVYYCARSPYVYGVFDYWGQGLVTVSS (SEQ ID NO: 189)

HIT ID 5404 – VL

DIQLTQSPSSLASVGDRTITCSASSRVGSVYWYQQKPKAPKLLIYDASNLETGVPSRFSGSGSGTDFTLT
 ISSLQPEDFATYYCQQYTHDPVTFGQGTKVEIKR (SEQ ID NO: 190)

Hit ID 3757 – VH

EVQLVESGGGLVQPGGSLRLSCAASGFTFTDYGHWVRQAPGKGLEWIGWISPSGGGTKYAQKFQGRVTIS
 RDNSKNLTYLQLNSLRAEDTAVYYCARHSYVGVDFDYWGQGLVTVSS (SEQ ID NO: 191)

HIT ID 3757 – VL

DIQLTQSPSSLASVGDRTITCRASQSVSSYLAWYQQKPKAPKLLIYDASNLETGVPSRFSGSGSGTDFTL
 TISSLQPEDFATYYCQQSYSTPLTFGQGTKVEIKR (SEQ ID NO: 192)

Hit ID 5103 – VH

EVQLVESGGGLVQPGGSLRLSCAASGFTFTDYGHWVRQAPGKGLEWIGWISPSGGGTKYAQKFQGRVTIS
 RDNSKNLTYLQLNSLRAEDTAVYYCARHSYVGVDFDYWGQGLVTVSS (SEQ ID NO: 193)

HIT ID 5103 – VL

DIQLTQSPSSLASVGDRTITCRASQSVSSYLAWYQQKPKAPKLLIYDASNLETGVPSRFSGSGSGTDFTL
 TISSLQPEDFATYYCQQSYSTPLTFGQGTKVEIKR (SEQ ID NO: 194)

Hit ID 4027 – VH

EVQLVESGGGLVQPGGSLRLSCAASGYSITSGHHWNWIRQAPGKGLEWIGWISPSGGGTKYAQKFQGRVTI
 SRDNSKNLTYLQLNSLRAEDTAVYYCARGFDGFHYWGQGLVTVSS (SEQ ID NO: 195)

HIT ID 4027 – VL

DIQLTQSPSSLASVGDRTITCRASESVDFYGISFLPWYQQKPKAPKLLIYDASNRTGIPSRFSGSGSGTD
 FTLTISSLQPEDFATYYCQQSYSWPWTFGQGTKVEIKR (SEQ ID NO: 196)

VH in FIG. 1B

EVQLVESGGGLVQPGGSLRLSCAASGFTFTSYGIHWVRQAPGKLEWVSGISGAGDTTYADSVKGRFTIS
 RDNSKNLTYLQLNSLRAEDTAVYYCARERDYDFDYWGQGLVTVSS (SEQ ID NO:197)

Formula (I)

$X_1TFX_2X_3YX_4IHWV$, wherein X_1 is F or Y, X_2 is S or T, X_3 is D, G, N, or S, and X_4 is A, G, or W (SEQ ID NO:198)

Formula (II)

$YSIX_1SGX_2X_3WX_4WI$, wherein X_1 is S or T, X_2 is H or Y, X_3 is H or Y, and X_4 is A, D, G, N, S, or T (SEQ ID NO:199)

Formula (III)

$FSLSTX_1GVX_2VX_3WI$, wherein X_1 is G or S, X_2 is A or G, and X_3 is A, G, S, or T (SEQ ID NO:200)

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)

VSX₁ISGX₂GX₃X₄TYADSVKGRF, 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)

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)

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)

Formula (XIII)

VGRIX₁SKX₂X₃GX₄TTEYAAX₅VKGRF, 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 (SEQ ID NO:210)

Primer F_1999

CGTTTGTCCCTGTGCAGCTTCCGG (SEQ ID NO:211)

Primer R_1999

CGAGGCCCTTACCCGGGGCCTGACG (SEQ ID NO:212)

Primer F_2003

CCGGGTAAGGGCCTCGAGTGG (SEQ ID NO:213)

Primer R_2003

GAGCACGTCCGTTCTGAATTGTCGCGACTTATAG (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: ARGGGGYFDV (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: ARGSSGYFDY (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: ARGYSYFDY (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: ARVGESGGIESPYYYYYGLDV (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: SASSRVGGSVY (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: FCLQGTTFPWT (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

What is claimed is:

1. A library comprising polynucleotides, wherein one 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) $X_1TFX_2X_3YX_4IHWV$ (SEQ ID NO:198), wherein X_1 is F or Y, X_2 is S or T, X_3 is D, G, N, or S, and X_4 is A, G, or W;

(Formula II) $YSIX_1SGX_2X_3WX_4WI$ (SEQ ID NO:199), wherein X_1 is S or T, X_2 is H or Y, X_3 is H or Y, and X_4 is A, D, G, N, S, or T; and

(Formula III) $FSLSTX_1GVX_2VX_3WI$ (SEQ ID NO:200), wherein X_1 is G or S, X_2 is A or G, and X_3 is A, G, S, or T; and

wherein the HVR-H2 comprises an amino acid sequence according to a formula selected from the group consisting of:

(Formula IV) $LAX_1IX_2WX_3X_4DKX_5YSX_6SLKSRL$ (SEQ ID NO:201), wherein X_1 is L or R, X_2 is D or Y, X_3 is A, D, S, or Y, X_4 is D or G, X_5 is R, S, or Y, and X_6 is P or T;

(Formula V) $IGX_1IX_2X_3SGSTYYSPSLKSRV$ (SEQ ID NO:202), wherein X_1 is A, D, E, S, or Y, X_2 is S or Y, and X_3 is H or Y;

(Formula VI) $IGX_1IYX_2SGX_3TX_4YNPSLKSRV$ (SEQ ID NO:203), wherein X_1 is D, E, R, S, or Y, X_2 is H or Y, X_3 is N or S, and X_4 is N or Y;

(Formula VII) $VSX_1ISGX_2GX_3X_4TYYADSVKGRF$ (SEQ ID NO:204), wherein X_1 is A, G, S, V, or Y, X_2 is A, D, S, or Y, X_3 is D, G, or S, and X_4 is S or T;

(Formula VIII) $IGX_1INPNX_2GX_3TX_4YAQKFQGRV$ (SEQ ID NO:205), wherein X_1 is I, R, or W, X_2 is F or R, X_3 is D, G, or S, and X_4 is K or N;

(Formula IX) $IGX_1IX_2PSX_3GX_4TX_5YAQKFQGRV$ (SEQ ID NO:206), wherein X_1 is I, R, or W, X_2 is S or Y, X_3 is G or S, X_4 is D, G, or S, and X_5 is K or N; and

(Formula X) $VGRIX_1SKX_2X_3GX_4TTX_5YAAX_6VKGRF$ (SEQ ID NO:207), wherein X_1 is K or R, X_2 is A or T, X_3 is D or Y, X_4 is G or Y, X_5 is D or E, and X_6 is P or S.

2. The library of claim 1, wherein at least two, at least three, at least four, at least five or at least ten of the polynucleotides encode 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 according to a formula selected from the group consisting of:

(Formula I) $X_1TFX_2X_3YX_4IHWV$ (SEQ ID NO:198), wherein X_1 is F or Y, X_2 is S or T, X_3 is D, G, N, or S, and X_4 is A, G, or W;

(Formula II) $YSIX_1SGX_2X_3WX_4WI$ (SEQ ID NO:199), wherein X_1 is S or T, X_2 is H or Y, X_3 is H or Y, and X_4 is A, D, G, N, S, or T; and

(Formula III) $FSLSTX_1GVX_2VX_3WI$ (SEQ ID NO:200), wherein X_1 is G or S, X_2 is A or G, and X_3 is A, G, S, or T; and

wherein the HVR-H2 comprises an amino acid sequence according to a formula selected from the group consisting of:

(Formula IV) $LAX_1IX_2WX_3X_4DKX_5YSX_6SLKSRL$ (SEQ ID NO:201), wherein X_1 is L or R, X_2 is D or Y, X_3 is A, D, S, or Y, X_4 is D or G, X_5 is R, S, or Y, and X_6 is P or T;

(Formula V) $IGX_1IX_2X_3SGSTYYSPSLKSRV$ (SEQ ID NO:202), wherein X_1 is A, D, E, S, or Y, X_2 is S or Y, and X_3 is H or Y;

(Formula VI) $IGX_1IYX_2SGX_3TX_4YNPSLKSRV$ (SEQ ID NO:203), wherein X_1 is D, E, R, S, or Y, X_2 is H or Y, X_3 is N or S, and X_4 is N or Y;

(Formula VII) $VSX_1ISGX_2GX_3X_4TYYADSVKGRF$ (SEQ ID NO:204), wherein X_1 is A, G, S, V, or Y, X_2 is A, D, S, or Y, X_3 is D, G, or S, and X_4 is S or T;

(Formula VIII) $IGX_1INPNX_2GX_3TX_4YAQKFQGRV$ (SEQ ID NO:205), wherein X_1 is I, R, or W, X_2 is F or R, X_3 is D, G, or S, and X_4 is K or N;

(Formula IX) $IGX_1IX_2PSX_3GX_4TX_5YAQKFQGRV$ (SEQ ID NO:206), wherein X_1 is I, R, or W, X_2 is S or Y, X_3 is G or S, X_4 is D, G, or S, and X_5 is K or N; and

(Formula X) $VGRIX_1SKX_2X_3GX_4TTX_5YAAX_6VKGRF$ (SEQ ID NO:207), wherein X_1 is K or R, X_2 is A or T, X_3 is D or Y, X_4 is G or Y, X_5 is D or E, and X_6 is P or S.

3. The library of claim 1 or claim 2, wherein the HVR-H2 comprises an amino acid sequence according to a formula selected from the group consisting of:

(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) IGX₁IYX₂SGX₃TX₄YNPSLKSRV (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) VGRIX₁SKX₂X₃GX₄TTEYAAX₅VKGRF (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.
4. The library of any one of claims 1-3, wherein each of the polynucleotides encode a heavy chain comprising a HVR-H1, a HVR-H2 and a HVR-H3, and wherein the HVR-H1 comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:1-52 and 137-158.
5. The library of any one of claims 1-4, wherein each of the polynucleotides encode a heavy chain comprising a HVR-H1, a HVR-H2 and a HVR-H3, and wherein the HVR-H1 comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:1-52.
6. The library of any one of claims 1-5, wherein each of the polynucleotides encode a heavy chain comprising a HVR-H1, a HVR-H2 and a HVR-H3, and wherein the HVR-H2 comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:53-136 and 159-164.
7. The library of any one of claims 1-6, wherein each of the polynucleotides encode a heavy chain comprising a HVR-H1, a HVR-H2 and a HVR-H3, and wherein the HVR-H2 comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:53-136.
8. The library of any one of claims 1-7, wherein the polynucleotides contain less than about 6.5×10^4 unique combinations of HVR-H1 and HVR-H2 sequences.

9. The library of claim 8, wherein the polynucleotides contain less than about 6700 unique combinations of HVR-H1 and HVR-H2 sequences.
10. The library of claim 9, wherein the polynucleotides contain about 6660 or less unique combinations of HVR-H1 and HVR-H2 sequences.
11. The library of any one of claims 1-10, wherein the heavy chain variable region 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 library of any one of claims 1-11, wherein the heavy chain variable region 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 library of claim 1, wherein the 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).

14. The library of claim 1, wherein the 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.
15. The library of any one of claims 1-14, wherein the heavy chain variable region comprises a HVR-H3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 223-256.
16. The library of any one of claims 1-15, wherein the heavy chain variable region comprises 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 library of claim 1, wherein 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.
18. The library of any one of claims 1-17, wherein the polynucleotides encode full-length antibody heavy chains.
19. The library of any one of claims 1-18, further comprising polynucleotides that encode antibody light chain variable regions.
20. The library of claim 19, wherein 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.
21. The library of claim 19 or claim 20, wherein the polynucleotides that encode antibody light chain variable regions include at least one unique sequence.
22. The library of any one of claims 19-21, wherein the polynucleotides that encode antibody light chain variable regions include at least about 280 unique sequences.
23. The library of any one of claims 19-22, wherein the polynucleotides that encode antibody light chain variable regions include at least about 10^5 unique sequences.
24. A library comprising 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 comprises a HVR-H1, a HVR-H2 and a HVR-H3, and wherein the HVR-H1 comprises an amino acid sequence according to a formula selected from the group consisting of:

(Formula I) $X_1TFX_2X_3YX_4IHWV$ (SEQ ID NO:198), wherein X_1 is F or Y, X_2 is S or T, X_3 is D, G, N, or S, and X_4 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; and

wherein the HVR-H2 comprises an amino acid sequence according to a formula selected from the group consisting of:

(Formula IV) LAX₁IX₂WX₃X₄DKX₅YSX₆SLKSRV (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) IGX₁IYX₂SGX₃TX₄YNPSLKSRV (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) VSX₁ISGX₂GX₃X₄TYADSVKGRF (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) IGX₁INPNX₂GX₃TX₄YAQKFQGRV (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) VGRIX₁SKX₂X₃GX₄TTX₅YAAX₆VKGRF (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.

25. The library of claim 24, wherein the HVR-H2 comprises an amino acid sequence according to a formula selected from the group consisting of:

(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) IGX₁IYX₂SGX₃TX₄YNPSLKSRV (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) VGRIX₁SKX₂X₃GX₄TTEYAAX₅VKGRF (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.

26. The library of claim 24 or claim 25, wherein the heavy chain variable region comprises a HVR-H1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOS:1-52 and 137-158.
27. The library of any one of claims 24-26, wherein the heavy chain variable region comprises a HVR-H1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOS:1-52.
28. The library of any one of claims 24-27, wherein the heavy chain variable region comprises a HVR-H2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOS:53-136 and 159-164.
29. The library of any one of claims 24-28, wherein the heavy chain variable region comprises a HVR-H2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOS:53-136.
30. The library of any one of claims 24-29, wherein the heavy chain variable region comprises a HVR-H1 comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 1-52 and 137-158 and a HVR-H2 comprising an amino acid sequence selected from the group consisting of SEQ ID NO:53-136 and 159-164.
31. The library of any one of claims 24-30, wherein the heavy chain variable region comprises a HVR-H1 comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-52 and a HVR-H2 of the antibody comprises an amino acid sequence selected from the group consisting of SEQ ID NO:53-136.
32. The library of claim 24, wherein the 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).

33. The library of claim 24, wherein the 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.

34. The library of any one of claims 24-33, wherein the heavy chain variable region comprises a HVR-H3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 223-256.

35. The library of any one of claims 24-34, wherein the heavy chain variable region comprises 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.
36. The library of claim 24, wherein the heavy chain variable region comprises a sequence selected from the group consisting of SEQ ID NOs: SEQ ID NOs: 169, 171, 173, 175, 177, 179, 181, 183, 185, 187, 189, 191, 193, and 195.
37. The library of any one of claims 24-36, wherein 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.
38. The library of any one of claims 24-37, wherein the light chain variable regions of the antibodies in the library have at least one unique sequence.
39. The library of any one of claims 24-38, wherein the light chain variable regions of the antibodies in the library have at least about 280 unique sequences.
40. The library of any one of claims 24-39, wherein the light chain variable regions of the antibodies in the library have at least about 10^5 unique sequences.
41. The library of any one of claims 1-40, wherein 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
42. The library of any one of claims 1-41, wherein at least one of the polynucleotides encoding the antibody heavy chain variable region is in a vector.
43. The library of claim 42, wherein the vector is an expression vector.
44. The library of claim 42, wherein the vector is a display vector.

45. The library of any one of claims 1-44, wherein at least one of the polynucleotides encoding the antibody heavy chain variable region is in a cell.
46. The library of claim 45, wherein the cell is a bacterial, yeast, or mammalian cell.
47. A non-human animal comprising polynucleotides, wherein one 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) $X_1TFX_2X_3YX_4IHWV$ (SEQ ID NO:198), wherein X_1 is F or Y, X_2 is S or T, X_3 is D, G, N, or S, and X_4 is A, G, or W;

(Formula II) $YSIX_1SGX_2X_3WX_4WI$ (SEQ ID NO:199), wherein X_1 is S or T, X_2 is H or Y, X_3 is H or Y, and X_4 is A, D, G, N, S, or T; and

(Formula III) $FSLSTX_1GVX_2VX_3WI$ (SEQ ID NO:200), wherein X_1 is G or S, X_2 is A or G, and X_3 is A, G, S, or T; and

wherein the HVR-H2 comprises an amino acid sequence according to a formula selected from the group consisting of:

(Formula IV) $LAX_1IX_2WX_3X_4DKX_5YSX_6SLKSRL$ (SEQ ID NO:201), wherein X_1 is L or R, X_2 is D or Y, X_3 is A, D, S, or Y, X_4 is D or G, X_5 is R, S, or Y, and X_6 is P or T;

(Formula V) $IGX_1IX_2X_3SGSTYYSPSLKSRV$ (SEQ ID NO:202), wherein X_1 is A, D, E, S, or Y, X_2 is S or Y, and X_3 is H or Y;

(Formula VI) $IGX_1IYX_2SGX_3TX_4YNPSLKSRV$ (SEQ ID NO:203), wherein X_1 is D, E, R, S, or Y, X_2 is H or Y, X_3 is N or S, and X_4 is N or Y;

(Formula VII) $VSX_1ISGX_2GX_3X_4TYYADSVKGRF$ (SEQ ID NO:204), wherein X_1 is A, G, S, V, or Y, X_2 is A, D, S, or Y, X_3 is D, G, or S, and X_4 is S or T;

(Formula VIII) $IGX_1INPNX_2GX_3TX_4YAQKFQGRV$ (SEQ ID NO:205), wherein X_1 is I, R, or W, X_2 is F or R, X_3 is D, G, or S, and X_4 is K or N;

(Formula IX) $IGX_1IX_2PSX_3GX_4TX_5YAQKFQGRV$ (SEQ ID NO:206), wherein X_1 is I, R, or W, X_2 is S or Y, X_3 is G or S, X_4 is D, G, or S, and X_5 is K or N; and

(Formula X) VGRIX₁SKX₂X₃GX₄TTX₅YAAX₆VKGRF (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.

48. The non-human animal of claim 47, wherein the non-human animal is a mammal.
49. A phage comprising at least one polypeptide displayed on its surface, wherein the at least one polypeptide comprises an antigen binding domain that comprises an antibody heavy chain variable region comprising a HVR-H1, a HVR-H2 and a HVR-H3, and 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; and

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) IGX₁IYX₂SGX₃TX₄YNPSLKSRV (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) VSX₁ISGX₂GX₃X₄TYYADSVKGRF (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) IGX₁INPNX₂GX₃TX₄YAQKFQGRV (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) VGRIX₁SKX₂X₃GX₄TTX₅YAAX₆VKGRF (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.

50. An antibody heavy chain comprising 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 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; and

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) IGX₁IYX₂SGX₃TX₄YNPSLKSRV (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) VSX₁ISGX₂GX₃X₄TYADSVKGRF (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) IGX₁INPNX₂GX₃TX₄YAQKFQGRV (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) VGRIX₁SKX₂X₃GX₄TTX₅YAAX₆VKGRF (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.

51. The antibody heavy chain of claim 50, wherein the heavy chain variable region comprises a HVR-H1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOS:1-52 and 137-158.
52. The antibody heavy chain of claim 50 or claim 51, wherein the heavy chain variable region comprises a HVR-H1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOS:1-52.
53. The antibody heavy chain of any one of claims 50-52, wherein the heavy chain variable region comprises a HVR-H2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOS:53-136 and 159-164.
54. The antibody heavy chain of any one of claims 50-53, wherein the heavy chain variable region comprises a HVR-H2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOS:53-136.
55. The antibody heavy chain of any one of claims 50-54, wherein the heavy chain variable region comprises a HVR-H1 comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-52 and 137-158, and a HVR-H2 of the antibody comprising an amino acid sequence selected from the group consisting of SEQ ID NO:53-136 and 159-164.
56. The antibody heavy chain of any one of claims 50-55, wherein the heavy chain variable region comprises a HVR-H1 comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-52, and a HVR-H2 of the antibody comprising an amino acid sequence selected from the group consisting of SEQ ID NO:53-136.
57. The antibody heavy chain of claim 50, wherein the 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).

58. The antibody heavy chain of claim 50, wherein the 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.
59. The antibody heavy chain of any one of claims 50-58, wherein the heavy chain variable region comprises a HVR-H3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 223-256.
60. The antibody heavy chain of any one of claims 50-59, wherein the heavy chain variable region comprises 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.
61. The antibody heavy chain of claim 50, wherein 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.
62. An antibody comprising a heavy chain and a light chain, wherein the heavy chain is a heavy chain of any one of claims 50-61.
63. The antibody of claim 62, wherein the antibody binds at least 1 target with an equilibrium dissociation constant (Kd) of between about 10^{-7} and about 10^{-11} M.
64. The antibody of claim 62 or claim 63, wherein the antibody has a melting temperature (Tm) of between about 60°C and about 90°C.
65. A library comprising antigen binding domains, wherein one of the antigen binding domains comprises an antibody heavy chain variable region comprising a HVR-H1, a HVR-H2 and a HVR-H3, and wherein the HVR-H1 comprises an amino acid sequence according to a formula selected from the group consisting of:

(Formula I) $X_1TFX_2X_3YX_4IHWV$ (SEQ ID NO:198), wherein X_1 is F or Y, X_2 is S or T, X_3 is D, G, N, or S, and X_4 is A, G, or W;

(Formula II) $YSIX_1SGX_2X_3WX_4WI$ (SEQ ID NO:199), wherein X_1 is S or T, X_2 is H or Y, X_3 is H or Y, and X_4 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; and 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) IGX₁IYX₂SGX₃TX₄YNPSLKSRV (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) VSX₁ISGX₂GX₃X₄TYADSVKGRF (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) IGX₁INPNX₂GX₃TX₄YAQKFQGRV (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) VGRIX₁SKX₂X₃GX₄TTX₅YAAX₆VKGRF (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.

66. The library of claim 65, wherein the heavy chain variable region comprises a HVR-H3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 223-256.
67. The library of claim 65 or claim 66, wherein the antigen binding domain further comprises an antibody light chain variable region.
68. The library of claim 67, wherein 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.

69. The library of any one of claims 65-68, wherein the library comprises phages, and wherein the antigen binding domain is displayed on the surface of at least one phage of the library.
70. A method of preparing a library comprising providing and assembling the polynucleotide sequences of the library of any one of claims 1-46.
71. A method 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 polynucleotides encoding a plurality of antibody heavy chain variable region sequences.
72. The method of claim 71, wherein the antibody heavy chain variable region sequences are human antibody sequences.
73. The method of claim 71, wherein the antibody heavy chain variable region 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) $X_1TFX_2X_3YX_4IHWV$ (SEQ ID NO:198), wherein X_1 is F or Y, X_2 is S or T, X_3 is D, G, N, or S, and X_4 is A, G, or W;
- (Formula II) $YSIX_1SGX_2X_3WX_4WI$ (SEQ ID NO:199), wherein X_1 is S or T, X_2 is H or Y, X_3 is H or Y, and X_4 is A, D, G, N, S, or T; and
- (Formula III) $FSLSTX_1GVX_2VX_3WI$ (SEQ ID NO:200), wherein X_1 is G or S, X_2 is A or G, and X_3 is A, G, S, or T; and
- wherein the HVR-H2 comprises an amino acid sequence according to a formula selected from the group consisting of:
- (Formula IV) $LAX_1IX_2WX_3X_4DKX_5YSX_6SLKSRL$ (SEQ ID NO:201), wherein X_1 is L or R, X_2 is D or Y, X_3 is A, D, S, or Y, X_4 is D or G, X_5 is R, S, or Y, and X_6 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) IGX₁IYX₂SGX₃TX₄YNPSLKSRV (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) VSX₁ISGX₂GX₃X₄TYADSVKGRF (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) IGX₁INPNX₂GX₃TX₄YAQKFQGRV (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) VGRIX₁SKX₂X₃GX₄TTX₅YAAX₆VKGRF (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.

74. A method 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 a HVR-H1, a HVR-H2, and a HVR-H3, and 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; and

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) IGX₁IYX₂SGX₃TX₄YNPSLKSRV (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) VSX₁ISGX₂GX₃X₄TYADSVKGRF (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) IGX₁INPNX₂GX₃TX₄YAQKFQGRV (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) VGRIX₁SKX₂X₃GX₄TTX₅YAAX₆VKGRF (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;

(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.

75. A bispecific antibody 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 comprise a HVR-L1, a HVR-L2 and a HVR-L3, and wherein the HVR-H1 comprises an amino acid sequence according to a formula selected from the group consisting of:

(Formula I) $X_1TFX_2X_3YX_4IHWV$ (SEQ ID NO:198), wherein X_1 is F or Y, X_2 is S or T, X_3 is D, G, N, or S, and X_4 is A, G, or W;

(Formula II) $YSIX_1SGX_2X_3WX_4WI$ (SEQ ID NO:199), wherein X_1 is S or T, X_2 is H or Y, X_3 is H or Y, and X_4 is A, D, G, N, S, or T; and

(Formula III) $FSLSTX_1GVX_2VX_3WI$ (SEQ ID NO:200), wherein X_1 is G or S, X_2 is A or G, and X_3 is A, G, S, or T; and

wherein the HVR-H2 comprises an amino acid sequence according to a formula selected from the group consisting of:

(Formula IV) $LAX_1IX_2WX_3X_4DKX_5YSX_6SLKSRL$ (SEQ ID NO:201), wherein X_1 is L or R, X_2 is D or Y, X_3 is A, D, S, or Y, X_4 is D or G, X_5 is R, S, or Y, and X_6 is P or T;

(Formula V) $IGX_1IX_2X_3SGSTYYSPSLKSRV$ (SEQ ID NO:202), wherein X_1 is A, D, E, S, or Y, X_2 is S or Y, and X_3 is H or Y;

(Formula VI) $IGX_1IYX_2SGX_3TX_4YNPSLKSRV$ (SEQ ID NO:203), wherein X_1 is D, E, R, S, or Y, X_2 is H or Y, X_3 is N or S, and X_4 is N or Y;

(Formula VII) $VSX_1ISGX_2GX_3X_4TYYADSVKGRF$ (SEQ ID NO:204), wherein X_1 is A, G, S, V, or Y, X_2 is A, D, S, or Y, X_3 is D, G, or S, and X_4 is S or T;

(Formula VIII) $IGX_1INPNX_2GX_3TX_4YAQKFQGRV$ (SEQ ID NO:205), wherein X_1 is I, R, or W, X_2 is F or R, X_3 is D, G, or S, and X_4 is K or N;

(Formula IX) $IGX_1IX_2PSX_3GX_4TX_5YAQKFQGRV$ (SEQ ID NO:206), wherein X_1 is I, R, or W, X_2 is S or Y, X_3 is G or S, X_4 is D, G, or S, and X_5 is K or N; and

(Formula X) $VGRIX_1SKX_2X_3GX_4TTX_5YAAX_6VKGRF$ (SEQ ID NO:207), wherein X_1 is K or R, X_2 is A or T, X_3 is D or Y, X_4 is G or Y, X_5 is D or E, and X_6 is P or S.

76. The bispecific antibody of claim 75, wherein the first heavy chain variable region is linked to a first heavy chain constant region, wherein the second heavy chain variable region is linked to a second heavy chain constant region, wherein the first antibody light chain variable region is linked to a first light chain constant region, wherein the second

antibody light chain variable region is linked to a second light chain constant region, and wherein the first and the second antibody heavy chains have identical sequences.

77. A kit comprising the library of polynucleotides of any one of claims 1-46.
78. A library comprising polynucleotides, wherein one 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 selected from the group consisting of SEQ ID NOs: 1-52, and/or wherein the HVR-H2 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 53-136.
79. The library of claim 78, wherein 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/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.
80. The library of claim 78 or claim 79, wherein the heavy chain variable region comprises a HVR-H3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 223-256.

FIG. 1A

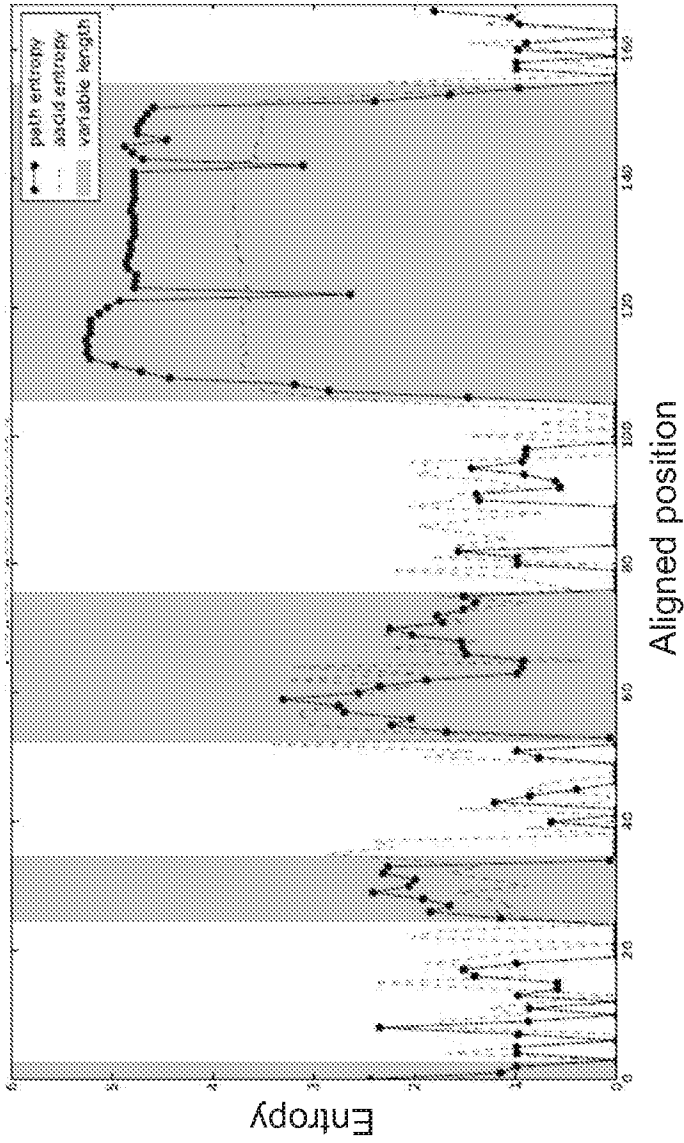


FIG. 1B

VH EYQLVSSGGSLVQPGGSLRLSCAASGFTTTSYGTHWVRQAPGKGLKRVSGISGAGDTTYTADSVKSRFTISRDNKNTLYLDINSLRAEFTAVYICARERDYDFYWGQETLIVTSS
ADG <-----FW_H1-----><-----HVR_H1-----><-----FW_H2-----><-----HVR_H2-----><-----FW_H3-----><-----HVR_H3-----><-----FW_H4----->
VH EYQLVSSGGSLVQPGGSLRLSCAASGFTTTSYGTHWVRQAPGKGLKRVSGISGAGDTTYTADSVKSRFTISRDNKNTLYLDINSLRAEFTAVYICARERDYDFYWGQETLIVTSS
Kabat <-----FW1-----><-----CDR1-----><-----FW2-----><-----CDR2-----><-----FW3-----><-----CDR3-----><-----FW4----->

FIG. 2A

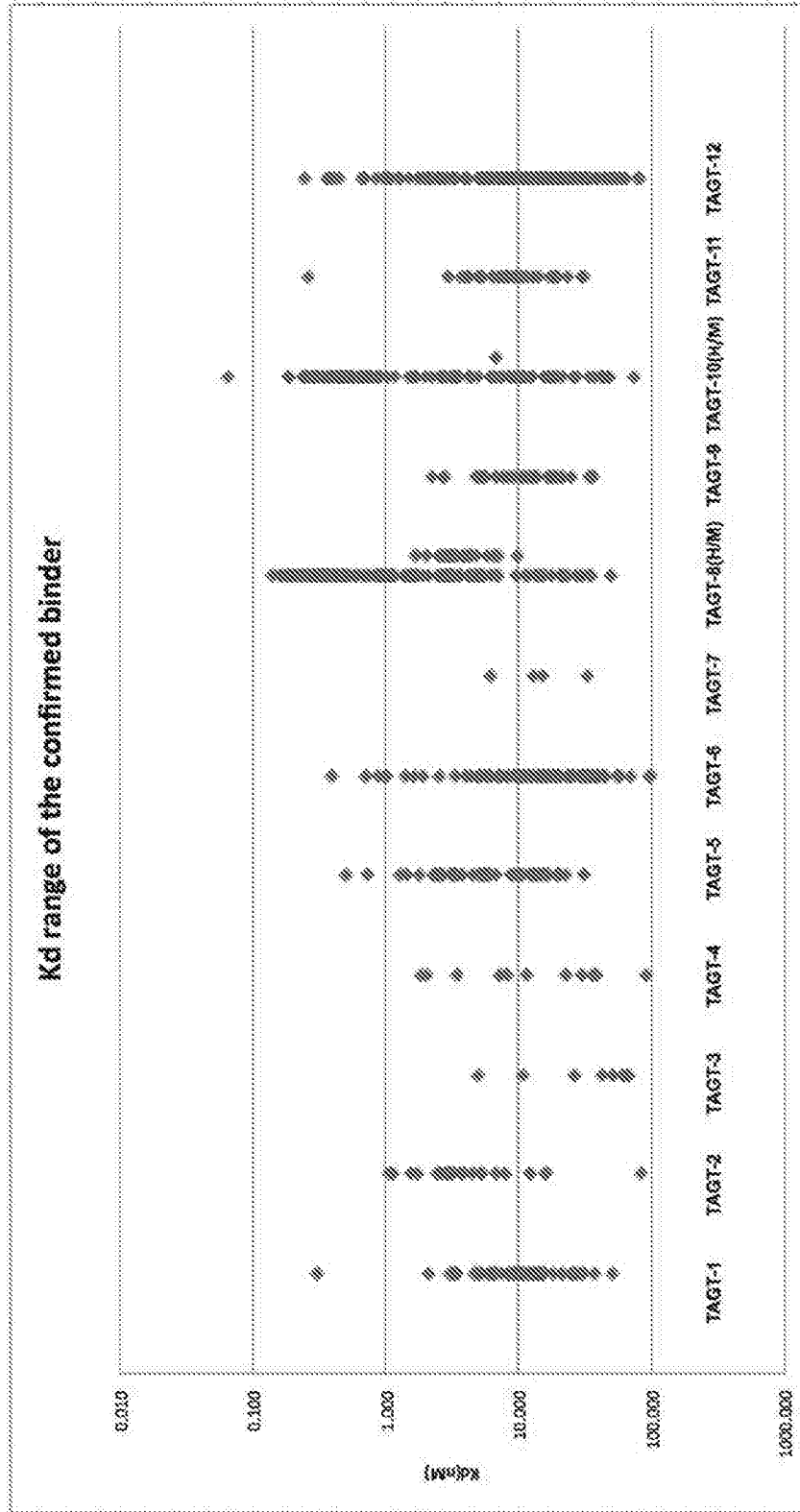
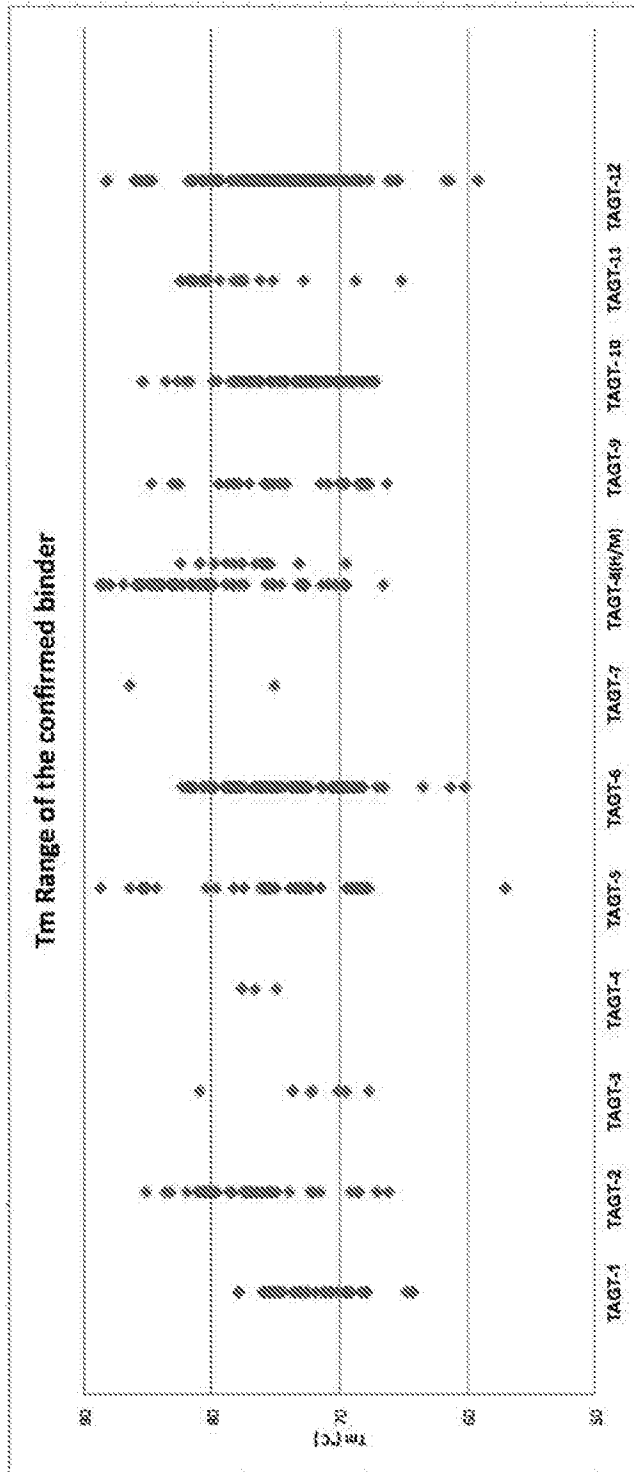


FIG. 2B



INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2017/098299

A. CLASSIFICATION OF SUBJECT MATTER

C40B 40/08(2006.01)i; C40B 50/04(2006.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C40B

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

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

CNABS, CPRSABS, DWPI, SIPOABS, CNKI, WANFANG, ISI Web of Knowledge, BAIDU and searched terms: antibody, library, heavy chain, hypervariable region, HVR, nucleotide, phage, dynamic motif, degenerate oligos, bispecific antibody and the like; GENBANK, EMBL, Chinese Patent Biological Sequence Retrieval System, STN and searched sequences: SEQ ID NOs: 1-64, 198-210.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0440146 A2 (BEHRINGWERKE AG) 07 August 1991 (1991-08-07) see the whole document	1-80
A	WO 2016062989 A1 (CRESCENDO BIOLOG LTD) 28 April 2016 (2016-04-28) see the whole document	1-80
A	CN 103603057 A (UNIV SHEN ZHEN) 26 February 2014 (2014-02-26) see the whole document	1-80
A	Chingwei V. Lee et al. "High-affinity Human Antibodies from Phage-displayed Synthetic Fab Libraries with a Single Framework Scaffold" 《 <i>J. Mol. Biol.</i> 》, Vol. 5, No. 340, 23 July 2004 (2004-07-23), see the whole document	1-80

 Further documents are listed in the continuation of Box C. See patent family annex.

* Special categories of cited documents:

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

"E" earlier application or patent but published on or after the international filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

07 May 2018

Date of mailing of the international search report

24 May 2018

Name and mailing address of the ISA/CN

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2017/098299

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

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:
 - a. forming part of the international application as filed:
 - in the form of an Annex C/ST.25 text file.
 - on paper or in the form of an image file.
 - b. furnished together with the international application under PCT Rule 13ter.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.
 - c. furnished subsequent to the international filing date for the purposes of international search only:
 - in the form of an Annex C/ST.25 text file (Rule 13ter.1(a)).
 - on paper or in the form of an image file (Rule 13ter.1(b) and Administrative Instructions, Section 713).
2. In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
3. Additional comments: