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(45) Date of Patent: Aug. 12, 2025(54) DYNAMIC HUMAN HEAVY CHAIN
ANTIBODY LIBRARIES

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(58) Field of Classification Search

None

See application file for complete search history.

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(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.

32 Claims, 3 Drawing Sheets

Specification includes a Sequence Listing.

VB EVQLVESGGGLVQPGGSLRLSCAASGFTFTSYGIGWVRQAPGKGLEWVSGIISGAGDTYYADSVKRGRFTISRDNSKNTLYLQLNLRAEDTAVYYCARERDVFDFDYWGQGTLVTVSS
ADC <----FW_H1----><----HVR_B1----><----FW_H2----><----HVR_B2----><----FW_H3----><----HVR_H3----><----FW_H4---->
VR EVQLVESGGGLVQPGGSLRLSCAASGFTFTSYGIGWVRQAPGKGLEWVSGIISGAGDTYYADSVKRGRFTISRDNSKNTLYLQLNLRAEDTAVYYCARERDVFDFDYWGQGTLVTVSS
Kabat <----FW1----><----CDR1----><----FW2----><----CDR2----><----FW3----><----CDR3----><----FW4---->

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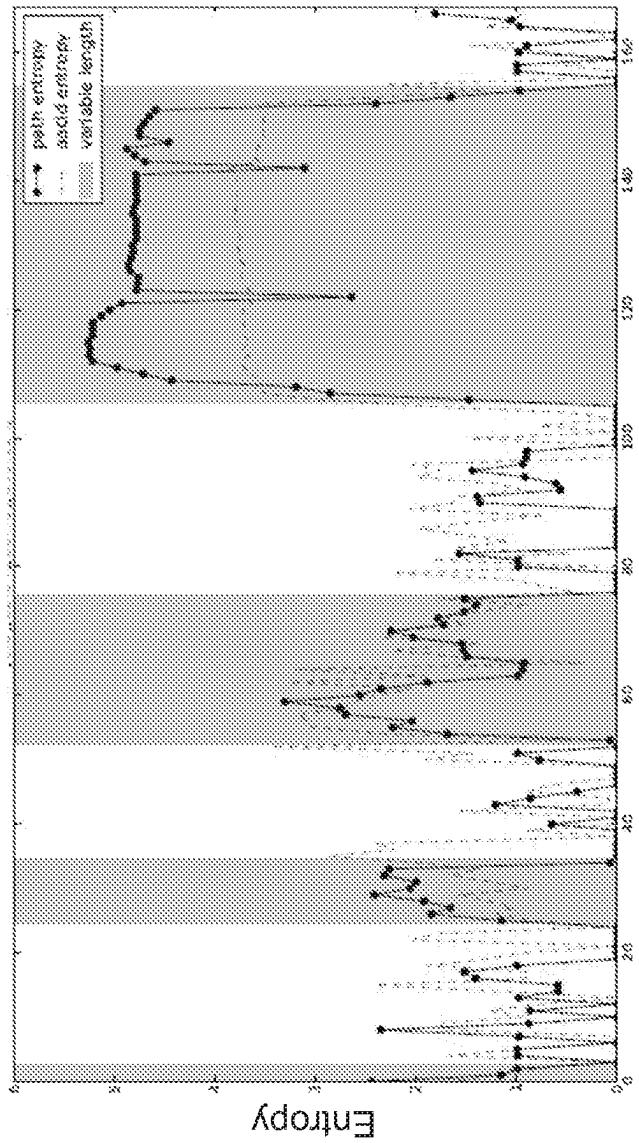
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FIG. 1A



Aligned position

FIG. 1B

VH EVIYVSESGEGLYQPGSESRILSCAQGETETAYGCBWVHQAPKGLSERGSIAGCAUTTYADSVEGRIGRONSRTYLQLNSLRAEDTAVYCARERDDEDYGGCLTVVSS
<----FW_1----->----HVR_H1----<----FW_H2---->----HVR_H2---->----FW_H3---->----HVR_H3---->----FW_H4---->
ADG <----FW_1----->----HVR_H1---->----FW_H2---->----HVR_H2---->----FW_H3---->----HVR_H3---->----FW_H4---->
VH EVQVYESGGLYQPGSESRILSCAQGETETAYGCBWVHQAPKGLSERGSIAGCAUTTYADSVEGRIGRONSRTYLQLNSLRAEDTAVYCARERDDEDYGGCLTVVSS
<----FW_1----->----HVR_H1---->----FW_H2---->----HVR_H2---->----FW_H3---->----HVR_H3---->----FW_H4---->
Kabat <----FW_1----->----CDR1---->----FW2---->----CDR2---->----FW3---->----CDR3---->----FW4---->

FIG. 2A
Kd range of the confirmed binder

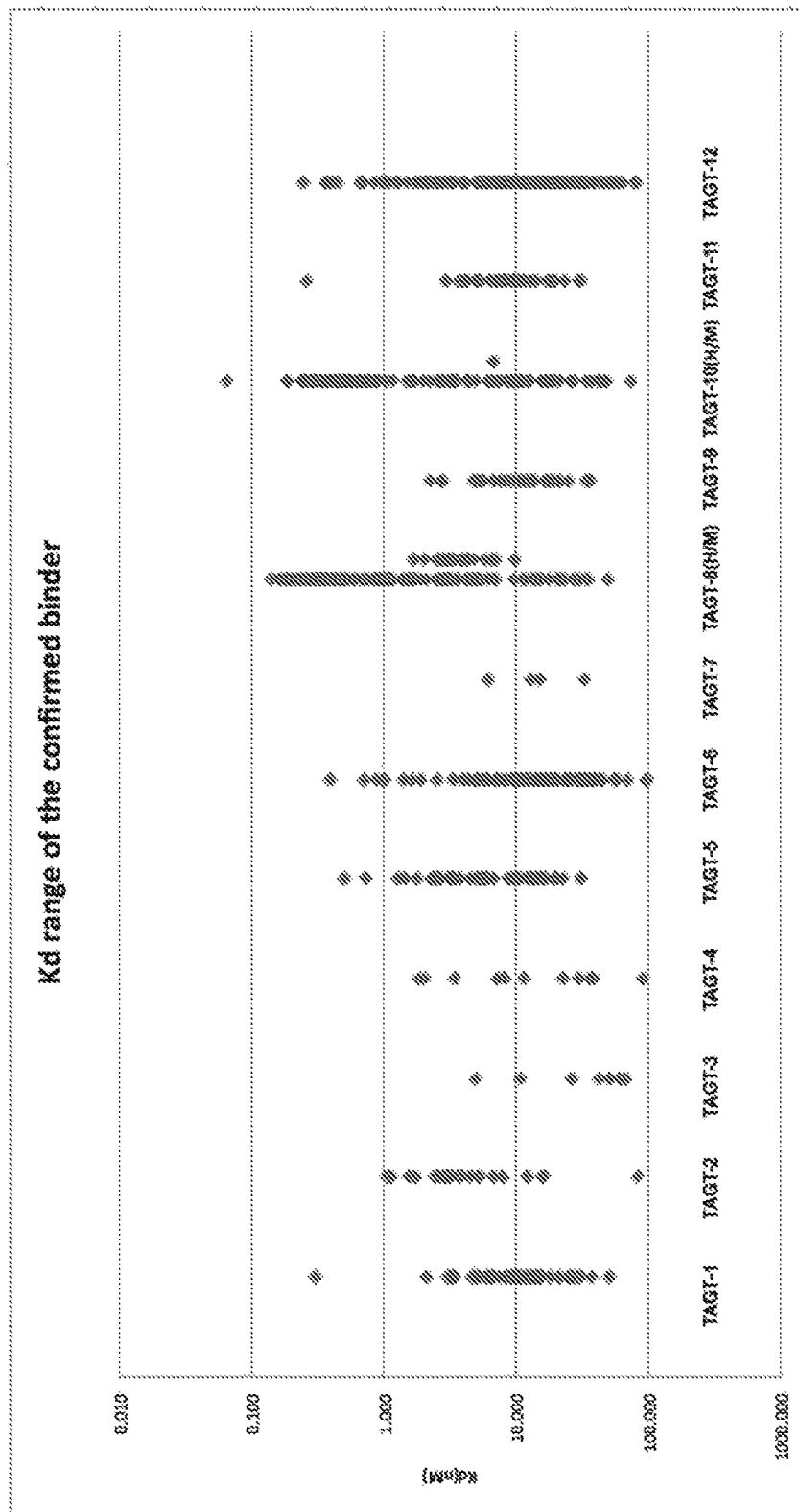
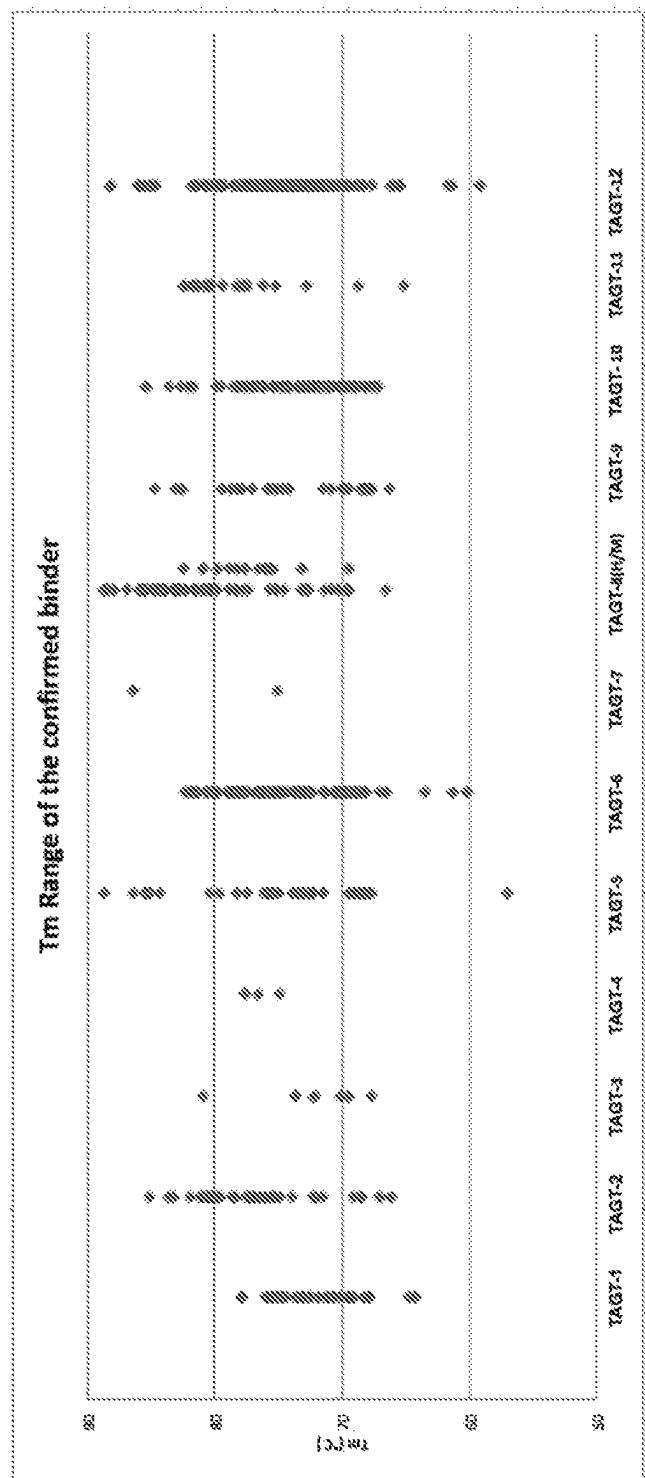


FIG. 2B



**DYNAMIC HUMAN HEAVY CHAIN
ANTIBODY LIBRARIES**

**CROSS REFERENCE TO RELATED
APPLICATIONS**

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

**REFERENCE TO AN ELECTRONIC SEQUENCE
LISTING**

The content of the electronic sequence listing (6954020002012SeqList.xml; Size: 367,770 bytes; and Date of Creation: Jan. 10, 2023) is herein incorporated by reference in its entirety.

FIELD OF THE INVENTION

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

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.

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.

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.

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

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 evolutionarily conserved sites on a given antigen from different species with low sequence identity (e.g., below 60% to 70%).

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.

In another aspect, provided herein are one or more HVR-H2 amino acid sequences, and/or one or more polynucleotides (e.g., synthetic polynucleotides) encoding the same, wherein the HVR-H2 comprises an amino acid sequence according to a formula selected from the group consisting of: Formula (IV): LAX1IX2WX3X4DKX5YSX6SLKSRL (SEQ ID NO:201), wherein X1 is L or R, X2 is D or Y, X3 is A, D, S, or Y, X4 is D or G, X5 is R, S, or Y, and X6 is P or T; Formula (V): IGX1IX2X3SGSTYYSPSLKSRV (SEQ ID NO:202), wherein X1 is A, D, E, S, or Y, X2 is S or Y, and X3 is H or Y; Formula (VI):

IGXIIYX2SGX3TX4YNPSLKSrv (SEQ ID NO:203), wherein X1 is D, E, R, S, or Y, X2 is H or Y, X3 is N or S, and X4 is N or Y; Formula (VII): VSXIISGX2GX3X4TYYADSVKGRF (SEQ ID NO: 204), wherein X1 is A, G, S, V, or Y, X2 is A, D, S, or Y, X3 is D, G, or S, and X4 is S or T; Formula (VIII): IGXIINPNX2GX3TX4YAQKFQGRV (SEQ ID NO:205), wherein X1 is I, R, or W, X2 is F or R, X3 is D, G, or S, and X4 is K or N; Formula (IX): IGX1IX2PSX3GX4TX5YAQKFQGRV (SEQ ID NO:206), wherein X1 is I, R, or W, X2 is S or Y, X3 is G or S, X4 is D, G, or S, and X5 is K or N; and Formula (X): VGRIXISKX2X3GX4TTX5YAAX6VKGRF (SEQ ID NO: 207), wherein X1 is K or R, X2 is A or T, X3 is D or Y, X4 is G or Y, X5 is D or E, and X6 is P or S. In some embodiments, the HVR-H2 comprises an amino acid sequence according to a formula selected from the group consisting of: Formula (IV); Formula (VII); Formula (VIII); Formula (IX); Formula (XI): IGX1IX2X3SGSTYYSPSLKSrv (SEQ ID NO:208), wherein X1 is A, D, or E, X2 is S or Y, and X3 is H or Y; Formula (XII): IGXIIYX2SGX3TX4YNPSLKSrv (SEQ ID NO:209), wherein X1 is D, E, or S, X2 is H or Y, X3 is N or S, and X4 is N or Y; and Formula (XIII): VGRIXISKX2X3GX4TTEYAAX5VKGRF (SEQ ID NO:210), wherein X1 is K or R, X2 is A or T, X3 is D or Y, X4 is G or Y, X5 is P or S. In some embodiments, the HVR-H2 comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 53-136 and 159-164. In some embodiments, the HVR-H2 comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 53-136.

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.

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.

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.

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 poly-

nucleotides), 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).

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.

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.

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 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).

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).

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.

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.

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 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).

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).

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.

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

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

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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.

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.

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.

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

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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.

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.

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.

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 108 unique sequences, or least about 109 unique sequences.

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 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.

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).

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).

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.

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.

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 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

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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).

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).

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.

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.

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

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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 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). 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).

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).

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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

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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.

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.

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.

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.

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

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

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.

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.

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

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.

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.

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).

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.

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.

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 poly-

nucleotides 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.

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.

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.

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

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).

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.

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

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.

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.

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

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

DETAILED DESCRIPTION

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

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 Molecu-

lar 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

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.

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.

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.

It is understood that aspects and embodiments of the present disclosure described herein include "comprising," "consisting," and "consisting essentially of" aspects and embodiments.

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.

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.

The L chain from any vertebrate species can be assigned to one of two clearly distinct types, called kappa ("u") and lambda ("2"), based on the amino acid sequences of their constant domains. Depending on the amino acid sequence of the constant domain of their heavy chains (CH), immunoglobulins can be assigned to different classes or isotypes. There are five classes of immunoglobulins: IgA, IgD, IgE,

IgG, and IgM, having heavy chains designated alpha ("a"), delta ("6"), epsilon ("c"), gamma ("y") and mu ("p"), respectively. The y and a classes are further divided into subclasses (isotypes) on the basis of relatively minor differences in the CH sequence and function, e.g., humans express the following subclasses: IgG1, IgG2, IgG3, IgG4, IgA1, and IgA2. The subunit structures and three dimensional configurations of different classes of immunoglobulins are well known and described generally in, for example, Abbas et al., *Cellular and Molecular Immunology*, 4th ed. (W. B. Saunders Co., 2000).

The "variable region" or "variable domain" of an antibody refers to the amino-terminal domains of the heavy or light chain of the antibody. The variable domain of the heavy chain may be referred to as "VH." The variable domain of the light chain may be referred to as "V_L." These domains are generally the most variable parts of an antibody and contain the antigen-binding sites.

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.

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.

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, C_H) of the heavy chain and the CHL (or CL) domain of the light chain.

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.

The term "monoclonal antibody" as used herein refers to an antibody obtained from a population of substantially homogeneous antibodies, i.e., the individual antibodies comprising the population are identical except for possible naturally occurring mutations and/or post-translation modifications (e.g., isomerizations, amidations) that may be present in minor amounts. Monoclonal antibodies are highly specific, being directed against a single antigenic site. In contrast to polyclonal antibody preparations which typically include different antibodies directed against different determinants (epitopes), each monoclonal antibody is directed against a single determinant on the antigen. The modifier "monoclonal" indicates the character of the antibody as being obtained from a substantially homogeneous population of antibodies, and is not to be construed as requiring production of the antibody by any particular method. For example, the monoclonal antibodies to be used in accordance with the present disclosure may be made by a variety of techniques, including, for example, the hybridoma method (e.g., Kohler and Milstein, *Nature*, 256:495-97 (1975); Hongo et al., *Hybridoma*, 14 (3):253-260 (1995), Harlow et al., *Antibodies: A Laboratory Manual*, (Cold Spring Harbor Laboratory Press, 2d ed. 1988); Hammerling et al., in: *Monoclonal Antibodies and T-Cell Hybridomas* 563-681 (Elsevier, N.Y., 1981)), recombinant DNA methods (see, e.g., U.S. Pat. No. 4,816,567), phage-display technologies (see, e.g., Clackson et al., *Nature*, 352:624-628 (1991); Marks et al., *J. Mol. Biol.* 222:581-597 (1992); Sidhu et al., *J. Mol. Biol.* 338(2): 299-310 (2004); Lee et al., *J. Mol. Biol.* 340(5):1073-1093 (2004); Fellouse, *Proc. Nat'l Acad. Sci. USA* 101(34):12467-472 (2004); and Lee et al., *J. Immunol. Methods* 284(1-2):119-132 (2004), and technologies for producing human or human-like antibodies in animals that have parts or all of the human immunoglobulin loci or genes encoding human immunoglobulin sequences (see, e.g., WO 1998/24893; WO 1996/34096; WO 1996/33735; WO 1991/10741; Jakobovits et al., *Proc. Nat'l Acad. Sci. USA* 90:2551 (1993); Jakobovits et al., *Nature* 362:255-258 (1993); Bruggemann et al., *Year in Immunol.* 7:33 (1993); U.S. Pat. Nos. 5,545,807; 5,545,806; 5,569,825; 5,625,126; 5,633,425; and U.S. Pat. No. 5,661,016; Marks et al., *Bio/Technology* 10:779-783 (1992); Lonberg et al., *Nature* 368:856-859 (1994); Morrison, *Nature* 368:812-813 (1994); Fishwild et al., *Nature Biotechnol.* 14:845-851 (1996); Neuberger, *Nature Biotechnol.* 14:826 (1996); and Lonberg and Huszar, *Intern. Rev. Immunol.* 13:65-93 (1995).

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.

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.

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.

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.

The terms "polypeptide," "protein," and "peptide" are used interchangeably herein and may refer to polymers of two or more amino acids.

"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, phosphoramidates, 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 ("amide"), 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.

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).

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

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.

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.

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).

In some embodiments, one or more of the polynucleotides encode an antibody heavy chain variable region comprising a HVR-H1, a HVR-H2, and a HVR-H3, wherein the HVR-H1 comprises an amino acid sequence according to a formula selected from the group consisting of (Formula I) X1TFX2X3YX4IHWV, wherein X1 is F or Y, X2 is S or T, X3 is D, G, N, or S, and X4 is A, G, or W(SEQ ID NO:198); (Formula II) YSIX1SGX2X3WX4WI, wherein X1 is S or T, X2 is H or Y, X3 is H or Y, and X4 is A, D, G, N, S, or T (SEQ ID NO:199); and (Formula III) FSLSTX1GVX2VX3WI, wherein X1 is G or S, X2 is A or G, and X3 is A, G, S, or T(SEQ ID NO:200). In some embodiments, one or more of the polynucleotides encode an antibody heavy chain variable region comprising a HVR-H1, a HVR-H2, and a HVR-H3, wherein the HVR-H2 comprises an amino acid sequence according to a formula selected from the group consisting of (Formula IV) LAX1IX2WX3X4DKX5YSX6SLKSRL, wherein X1 is L or R, X2 is D or Y, X3 is A, D, S, or Y, X4 is D or G, X5 is R, S, or Y, and X6 is P or T(SEQ ID NO:201); (Formula V) IGX1IX2X3SGSTYYSPSLKSRV, wherein X1 is A, D, E, S, or Y, X2 is S or Y, and X3 is H or Y(SEQ ID NO:202); (Formula VI) IGX1IYX2SGX3TX4YNPSLKSRV, wherein X1 is D, E, R, S, or Y, X2 is H or Y, X3 is N or S, and X4 is N or Y(SEQ ID NO:203); (Formula VII) VSX1ISGX2GX3X4TYYADSVKGRF, wherein X1 is A, G, S, V, or Y, X2 is A, D, S, or Y, X3 is D, G, or S, and X4 is S or T(SEQ ID NO:204); (Formula VIII) IGX1INPNX2GX3TX4YAQKFQGRV, wherein X1 is I, R, or W, X2 is F or R, X3 is D, G, or S, and X4 is K or N(SEQ ID NO:205); (Formula IX) 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) VGRIXISKX2X3GX4TTEYAAAX5VKGRF, wherein X1 is K or R, X2 is A or T, X3 is D or Y, X4 is G or Y, and X5 is P or S(SEQ ID NO:210). In some embodiments, one or more of the polynucleotides encode an antibody heavy chain variable region comprising a HVR-H1, a HVR-H2, and a HVR-H3, wherein the HVR-H1 comprises an amino acid sequence according to a formula selected from the group consisting of (Formula I) X1TFX2X3YX4IHWV, wherein X1 is F or Y, X2 is S or T, X3 is D, G, N, or S, and X4 is A, G, or W(SEQ ID NO:198); (Formula II) YSIX1SGX2X3WX4WI, wherein X1 is S or T, X2 is H or Y, X3 is H or Y, and X4 is A, D, G, N, S, or T (SEQ ID NO:199); and (Formula III) FSLSTX1GVX2VX3WI, wherein X1 is G or S, X2 is A or G, and X3 is A, G, S, or T(SEQ ID NO:200); and an HVR-H2 comprises an amino acid sequence according to a formula selected from the group consisting of (Formula IV) LAX1IX2WX3X4DKX5YSX6SLKSRL, wherein X1 is L or R, X2 is D or Y, X3 is A, D, S, or Y, X4 is D or G, X5

is R, S, or Y, and X6 is P or T(SEQ ID NO:201); (Formula V) IGX1IX2X3SGSTYYSPSLKSRV, wherein X1 is A, D, E, S, or Y, X2 is S or Y, and X3 is H or Y(SEQ ID NO:202); (Formula VI) IGXIIYX2SGX3TX4YNPSLKSRV, wherein X1 is D, E, R, S, or Y, X2 is H or Y, X3 is N or S, and X4 is N or Y(SEQ ID NO:203); (Formula VII) VSXIISGX2GX3X4TYYADSVKGRF, wherein X1 is A, G, S, V, or Y, X2 is A, D, S, or Y, X3 is D, G, or S, and X4 is S or T(SEQ ID NO:204); (Formula VIII) IGX1INPNX2GX3TX4YAQKFQGRV, wherein X1 is I, R, or W, X2 is F or R, X3 is D, G, or S, and X4 is K or N(SEQ ID NO:205); (Formula IX) IGX1IX2PSX3GX4TX5YAQKFQGRV, wherein X1 is I, R, or W, X2 is S or Y, X3 is G or S, X4 is D, G, or S, and X5 is K or N(SEQ ID NO:206); and (Formula X) VGRIXISKX2X3GX4TTX5YAAX6VKGRF, wherein X1 is K or R, X2 is A or T, X3 is D or Y, X4 is G or Y, X5 is D or E, and X6 is P or S(SEQ ID NO:207). In some embodiments, one or more of the polynucleotides encode an antibody heavy chain variable region comprising a HVR-H1, a HVR-H2, and a HVR-H3, wherein the HVR-H1 comprises an amino acid sequence according to a formula selected from the group consisting of (Formula I) X1TFX2X3YX4IHWV, wherein X1 is F or Y, X2 is S or T, X3 is D, G, N, or S, and X4 is A, G, or W(SEQ ID NO:198); (Formula II) YSIX1SGX2X3WX4WI, wherein X1 is S or T, X2 is H or Y, X3 is H or Y, and X4 is A, D, G, N, S, or T (SEQ ID NO:199); and (Formula III) FSLSTX1GVX2VX3WI, wherein X1 is G or S, X2 is A or G, and X3 is A, G, S, or T(SEQ ID NO:200); and an HVR-H2 comprises an amino acid sequence according to a formula selected from the group consisting of (Formula XI) IGX1IX2X3SGSTYYSPSLKSRV, wherein X1 is A, D, or E, X2 is S or Y, and X3 is H or Y (SEQ ID NO:208); (Formula XI) IGXIIYX2SGX3TX4YNPSLKSRV, wherein X1 is D, E, or S, X2 is H or Y, X3 is N or S, and X4 is N or Y(SEQ ID NO:209); and (Formula XII) VGRIXISKX2X3GX4TTEYAAAX5VKGRF, 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).

In some embodiments, at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 15, at least 20, at least 25, at least 30, at least 35, at least 40, at least 45, at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 95, at least 100, at least 110, at least 120, at least 130, at least 140, at least 150, at least 160, at least 170, at least 180, at least 190, at least 200, at least 225, at least 250, at least 500, at least 1000, at least 1250, at least 1500, at least 1750, at least 2000, at least 2250, at least 2500, at least 2750, at least 3000, at least 3250, at least 3500, at least 3750, at least 4000, at least 4250, at least 4500, at least 4750, at least 5000, at least 5250, at least 5500, at least 5750, at least 6000, at least 6250, or at least 6500 of the polynucleotides encodes an antibody heavy chain variable region comprising a HVR-H1, a HVR-H2 and a HVR-H3, wherein the HVR-H1 comprises an amino acid sequence according to a formula selected from the group consisting of (Formula I) X1TFX2X3YX4IHWV, wherein X1 is F or Y, X2 is S or T, X3 is D, G, N, or S, and X4 is A, G, or W(SEQ ID NO:198); (Formula II) YSIX1SGX2X3WX4WI, wherein X1 is S or T, X2 is H or Y, X3 is H or Y, and X4 is A, D, G, N, S, or T (SEQ ID NO:199); and (Formula III) FSLSTX1GVX2VX3WI, wherein X1 is G or S, X2 is A or G, and X3 is A, G, S, or T(SEQ ID NO:200); and/or an

HVR-H2 comprising the amino acid sequence according to a formula selected from the group consisting of (Formula IV) LAX1IX2WX3X4DKX5YSX6SLKSRL, wherein X1 is L or R, X2 is D or Y, X3 is A, D, S, or Y, X4 is D or G, X5 is R, S, or Y, and X6 is P or T(SEQ ID NO:201); (Formula V) IGX1IX2X3SGSTYYSPSLKSRV, wherein X1 is A, D, E, S, or Y, X2 is S or Y, and X3 is H or Y(SEQ ID NO:202); (Formula VI) IGXIIYX2SGX3TX4YNPSLKSRV, wherein X1 is D, E, R, S, or Y, X2 is H or Y, X3 is N or S, and X4 is N or Y(SEQ ID NO:203); (Formula VII) VSX1ISGX2GX3X4TYYADSVKGRF, wherein X1 is A, G, S, V, or Y, X2 is A, D, S, or Y, X3 is D, G, or S, and X4 is S or T(SEQ ID NO:204); (Formula VIII) IGX1INPNX2GX3TX4YAQKFQGRV, wherein X1 is I, R, or W, X2 is F or R, X3 is D, G, or S, and X4 is K or N(SEQ ID NO:205); (Formula IX) IGX1IX2PSX3GX4TX5YAQKFQGRV, wherein X1 is I, R, or W, X2 is S or Y, X3 is G or S, X4 is D, G, or S, and X5 is K or N(SEQ ID NO:206); and (Formula X) VGRIXISKX2X3GX4TTX5YAAX6VKGRF, wherein X1 is K or R, X2 is A or T, X3 is D or Y, X4 is G or Y, X5 is D or E, and X6 is P or S(SEQ ID NO:207); and/or less than about 6.5*10⁴ (e.g., less than about 6.5*10⁴, less than about 5.5*10⁴, less than about 2.5*10⁴, less than about 1*10⁴, less than about 6700, less than about 6660, less than about 5000, less than about 2500, less than about 1000, less than about 690, less than about 500, less than about 100, less than about 50, etc.), less than or equal to 62272, less than or equal to 60928, less than or equal to 54656, or less than or equal to 6660 of the polynucleotides encodes an antibody heavy chain variable region comprising and HVR-H1, HVR-H2, and HVR-H3, wherein the HVR-H1 comprises an amino acid sequence according to a formula selected from the group consisting of (Formula I) X1TFX2X3YX4IHWV, wherein X1 is F or Y, X2 is S or T, X3 is D, G, N, or S, and X4 is A, G, or W(SEQ ID NO:198); (Formula II) YSIX1SGX2X3WX4WI, wherein X1 is S or T, X2 is H or Y, X3 is H or Y, and X4 is A, D, G, N, S, or T (SEQ ID NO:199); and (Formula III) FSLSTX1GVX2VX3WI, wherein X1 is G or S, X2 is A or G, and X3 is A, G, S, or T(SEQ ID NO:200); and an HVR-H2 comprising the amino acid sequence according to a formula selected from the group consisting of (Formula IV) LAX1IX2WX3X4DKX5YSX6SLKSRL, wherein X1 is L or R, X2 is D or Y, X3 is A, D, S, or Y, X4 is D or G, X5 is R, S, or Y, and X6 is P or T(SEQ ID NO:201); (Formula V) IGX1IX2X3SGSTYYSPSLKSRV, wherein X1 is A, D, E, S, or Y, X2 is S or Y, and X3 is H or Y(SEQ ID NO:202); (Formula VI) IGXIIYX2SGX3TX4YNPSLKSRV, wherein X1 is D, E, R, S, or Y, X2 is H or Y, X3 is N or S, and X4 is N or Y(SEQ ID NO:203); (Formula VII) VSX1ISGX2GX3X4TYYADSVKGRF, wherein X1 is A, G, S, V, or Y, X2 is A, D, S, or Y, X3 is D, G, or S, and X4 is S or T(SEQ ID NO:204); (Formula VIII) IGX1INPNX2GX3TX4YAQKFQGRV, wherein X1 is I, R, or W, X2 is F or R, X3 is D, G, or S, and X4 is K or N(SEQ ID NO:205); (Formula IX) IGX1IX2PSX3GX4TX5YAQKFQGRV, wherein X1 is I, R, or W, X2 is S or Y, X3 is G or S, X4 is D, G, or S, and X5 is K or N(SEQ ID NO:206); and (Formula X) VGRIXISKX2X3GX4TTX5YAAX6VKGRF, wherein X1 is K or R, X2 is A or T, X3 is D or Y, X4 is G or Y, X5 is D or E, and X6 is P or S(SEQ ID NO:207). In some embodiments, one or more polynucleotides of the library are in a vector (e.g., an expression vector or display vector).

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 X1) IGX1IX2X3SGSTYYSPSLKSRV, wherein X1 is A, D, or E, X2 is S or Y, and X3 is H or Y (SEQ ID NO:208); (Formula XI) IGXIIYX2SGX3TX4YNPSLKSRV, wherein X1 is D, E, or S, X2 is H or Y, X3 is N or S, and X4 is N or Y(SEQ ID NO:209); and (Formula XII) VGRIX1SKX2X3GX4TTEYAAAX5VKGRF, 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 XII) VGRIX1SKX2X3GX4TTEYAAAX5VKGRF, 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).

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). 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) IGXIIYX2SGX3TX4YNPSLKSRV, wherein X1 is D, E, or S, X2 is H or Y, X3 is N or S, and X4 is N or Y(SEQ ID NO:209); and (Formula XII) VGRIX1SKX2X3GX4TTEYAAAX5VKGRF, 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, 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 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).

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) 10 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) 15 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) 20 VGRIIX1SKX2X3GX4TTEYAAAX5VKGRF, 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, 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) 25 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) 30 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) 35 IGXIIYX2SGX3TX4YNPSLKSRV, wherein X1 is D, E, R, S, or Y, X2 is H or Y, X3 is N or S, and X4 is N or Y(SEQ ID NO:203); (Formula VII) 40 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) 45 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) 50 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) 55 VGRIIX1SKX2X3GX4TTX5YAAX6VKGRF, 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 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) 60 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) 65 IGXIIYX2SGX3TX4YNPSLKSRV, wherein X1 is D, E, or S, X2 is H or Y, X3 is N or S, and X4 is N or Y(SEQ ID NO:209); and (Formula XII) 70 VGRIIX1SKX2X3GX4TTEYAAAX5VKGRF, 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, 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.

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.

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.

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.

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

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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

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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.

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.

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 TISRDNSKNTLYLQLQLNSLRAEDTAVYYC
(SEQ ID NO:167)

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

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.

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

10³, at least 10⁴, at least 10⁵, at least 10⁶, at least 10⁷, at least 10⁸, at least 10⁹, at least 10¹⁰, at least 10¹¹, or at least 10¹² unique sequences of antibody light chain variable regions. In some embodiments, a library contains a plurality of polynucleotides that encodes at least 10³ unique sequences of antibody light chain variable regions. In some embodiments, a library contains a plurality of polynucleotides that encodes at least 10⁵ unique sequences of antibody light chain variable regions. In some embodiments, a library contains a plurality of polynucleotides that encodes at least 10⁹ 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 10³ unique sequences of antibody light chain variable regions. In some embodiments, the antibody light chain variable region is any of the antibody light chain variable regions found in International Application No. PCT/CN2017/098333 and/or U.S. patent application Ser. No. 16/640,673 (the disclosures of which are each incorporated herein by reference in their entireties). In some embodiments, the antibody light chain variable region comprises any of the HVR-L1, HVR-L2, and/or HVR-L3 sequences found in International Application No. PCT/CN2017/098333 and/or U.S. patent application Ser. No. 16/640,673 (the disclosures of which are each incorporated herein by reference in their entireties).

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).

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); IGXIYYX2SGX3TX4YNPSLKSRV, 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); VSX1ISGX2GX3X4TYYADSVKGKF, 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 VGRIIX1SKX2X3GX4TTEYAAAX5VKGRF, 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).

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.

Further provided herein is a method of preparing a library, e.g., by providing and assembling the polynucleotide sequences (e.g., synthetic polynucleotide(s)) of a library of the present disclosure. Further provided herein is a method of making a library, e.g., by selecting one, two, or three heavy chain HVRs (e.g., one or two heavy chain HVRs of the present disclosure) comprising a sequence having multiple conformations and assembling polynucleotide sequences to produce a library of polynucleotides (e.g., synthetic polynucleotides) encoding a plurality of antibody heavy chain variable region sequences. In some embodiments, the antibody heavy chain variable region sequences are human antibody sequences. In some embodiments, the antibody heavy chain variable region comprises a HVR-H1, a HVR-H2 and a HVR-H3, and the HVR-H1 and/or HVR-H2 comprise an amino acid sequence selected from a HVR-H1 sequence of the present disclosure (e.g., X1TFX2X3YX4IHWV, wherein X1 is F or Y, X2 is S or T, X3 is D, G, N, or S, and X4 is A, G, or W (SEQ ID NO:198); YSIX1SGX2X3WX4WI, wherein X1 is S or T, X2 is H or Y, X3 is H or Y, and X4 is A, D, G, N, S, or T (SEQ ID NO:199); and FSLSTX1GVX2VX3WI, wherein X1 is G or S, X2 is A or G, and X3 is A, G, S, or T (SEQ ID NO:200); and SEQ ID NOS:1-52 and 137-158), and a HVR-H2 sequence of the present disclosure (e.g., LAX1IX2WX3X4DKX5YSX6SLKSR, 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); VGRIIX1SKX2X3GX4TTEYAAAX5VKGRF, 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 VGRIIX1SKX2X3GX4TTEYAAAX5VKGRF,

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, 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.

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.

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.

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 VL are each attached to the 3' end of a sequence encoding a signal sequence, such as the ompA, phoA or pe1B signal sequence (Lei et al., J. Bacteriol., 1987, 169: 4379). These gene fusions are assembled in a dicistronic construct, so that they can be expressed from a single vector and secreted into the periplasmic space of *E. coli* where they will refold and can be recovered in active form. (Skerra et al., Biotechnology, 1991, 9: 273). For example, antibody heavy chain genes can be concurrently expressed with antibody light chain genes to produce antibodies or antibody fragments.

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.

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.

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).

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.

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™).

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). 5 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 10 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.

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 15 protein expression.

IV. Antibodies and Antibody Production

Provided herein are antibodies identified and selected 20 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 25 fragment, full-length antibody, or single-chain variable fragment (scFv).

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 30 to a formula selected from the group consisting of (Formula I) X1TFX2X3YX4IH WV, 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, 35 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 40 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 45 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 50

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) VGRIX1SKX2X3GX4TTX5YAAAX6VKGRF, 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) VGRIX1SKX2X3GX4TTEYAAAX5VKGRF, 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) LAX1IX2WX3X4DKX5YSX6SLKSR, 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) VGRIX1SKX2X3GX4TTX5YAAAX6VKGRF, 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).

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) IGX1IYX2SGX3TX4YNPLSLSRV, 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) VSX1ISGX2GX3X4TYYADSVKGKF, 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) VGRIX1SKX2X3GX4TTX5YAAAX6VKGRF, 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).

40 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
45 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) IGX1IYX2SGX3TX4YNPSLKSRSV,
50 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) VGRIX1SKX2X3GX4TTEYAAAX5VKGRF, 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).

55 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 60 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 65 V) IGX1IX2X3SGSTYYSPSLKSRV, wherein X1 is A, D, E, S, or Y, X2 is S or Y, and X3 is H or Y (SEQ ID NO:202); (Formula VI) IGXIIYX2SGX3TX4YNPSLKSRV, wherein

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X1 is D, E, R, S, or Y, X2 is H or Y, X3 is N or S, and X4 is N or Y (SEQ ID NO:203); (Formula VII) VSXIISGX2GX3X4TYYADSVKGRF, wherein X1 is A, G, S, V, or Y, X2 is A, D, S, or Y, X3 is D, G, or S, and X4 is S or T (SEQ ID NO:204); (Formula VIII) IGXIINPNX2GX3TX4YAQKFQGRV, wherein X1 is I, R, or W, X2 is F or R, X3 is D, G, or S, and X4 is K or N (SEQ ID NO:205); (Formula IX) IGX1IX2PSX3GX4TX5YAQKFQGRV, wherein X1 is I, R, or W, X2 is S or Y, X3 is G or S, X4 is D, G, or S, and X5 is K or N (SEQ ID NO: 206); and (Formula X) VGRIIX1SKX2X3GX4TTX5YAAAX6VKGRF, 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 heavy chain variable region comprises an HVR-H1 comprising the amino acid sequence according to the formula YSIX1SGX2X3WX4WI, wherein X1 is S or T, X2 is H or Y, X3 is H or Y, and X4 is A, D, G, N, S, or T (SEQ ID NO:199); and an HVR-H2 comprising an amino acid sequence according to a formula selected from the group consisting of (Formula XI) IGX1IX2X3SGSTYYSPSLKSRV, wherein X1 is A, D, or E, X2 is S or Y, and X3 is H or Y (SEQ ID NO:208); (Formula XII) IGX1IYX2SGX3TX4YNPSLKSRV, wherein X1 is D, E, or S, X2 is H or Y, X3 is N or S, and X4 is N or Y (SEQ ID NO:209); and (Formula XII) VGRIIX1SKX2X3GX4TTYEAAAX5VKGRF, 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, 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) LAX1IX2WX3X4DKX5YSX6SLKSR, wherein X1 is L or R, X2 is D or Y, X3 is A, D, S, or Y, X4 is D or G, X5 is R, S, or Y, and X6 is P or T (SEQ ID NO:201); (Formula V) IGX1IX2X3SGSTYYSPSLKSRV, wherein X1 is A, D, E, S, or Y, X2 is S or Y, and X3 is H or Y (SEQ ID NO:202); (Formula VI) IGXIIYX2SGX3TX4YNPSLKSRV, wherein X1 is D, E, R, S, or Y, X2 is H or Y, X3 is N or S, and X4 is N or Y (SEQ ID NO:203); (Formula VII) VSX1ISGX2GX3X4TYYADSVKGRF, wherein X1 is A, G, S, V, or Y, X2 is A, D, S, or Y, X3 is D, G, or S, and X4 is S or T (SEQ ID NO:204); (Formula VIII) IGX1INPNX2GX3TX4YAQKFQGRV, wherein X1 is I, R, or W, X2 is F or R, X3 is D, G, or S, and X4 is K or N (SEQ ID NO:205); (Formula IX) IGX1IX2PSX3GX4TX5YAQKFQGRV, wherein X1 is I, R, or W, X2 is S or Y, X3 is G or S, X4 is D, G, or S, and X5 is K or N (SEQ ID NO: 206); and (Formula X) VGRIIX1SKX2X3GX4TTX5YAAAX6VKGRF, 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 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

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X4 is N or Y (SEQ ID NO:209); and (Formula XII) VGRIIX1SKX2X3GX4TTYEAAAX5VKGRF, 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, 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

SEQ ID NO.	Heavy chain HVR sequences	
	Designed Sequence	HVR-H1
1	FTFTDYGIHWV	
2	FTFTGYAIHWV	
3	FTFTNYGIHWV	
4	YTFSDYAIHWV	
5	YTFSDYGIHWV	
6	YTFSGYAIHWV	
7	YTFSGYGIHWV	
8	YTFSNYGIHWV	
9	YTFSYYGIHWV	
10	YTFSGYWIHWV	
11	YTFSNYWIHWV	
12	FTFSGYWIHWV	
13	FTFSNYWIHWV	
14	YTFSDYWIHWV	
15	YSISSGHHWAWI	
16	YSISSGHYWNWI	
17	YSISSGHYWSWI	
18	YSISSGHYWTWI	
19	YSISSGYHWAWI	
20	YSISSSGYHWDWI	
21	YSISSGGYHWGWI	
22	YSISSGGYHWNWI	
23	YSISSGGYHWSWI	
24	YSISSGGHHDWI	
25	YSISSGGYWDWI	
26	YSISSGGYWNWI	
27	YSISSGGYWTWI	
28	YSITSGHHWAWI	
29	YSITSGHHWDWI	
30	YSITSGHHWGWI	
31	YSITSGHHWNWI	
32	YSITSGHHWSWI	

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TABLE 1-continued

Heavy chain HVR sequences	
SEQ ID NO.	Designed Sequence
33	YSISSHGHHWGWI
34	YSITSGHYWAWI
35	YSITSGHYWDWI
36	YSITSGHYWGWI
37	YSITSGHYWNWI
38	YSITSGHYWSWI
39	YSITSGYHWAWI
40	YSITSGYHWGWI
41	YSISSHHNWI
42	YSITSGYHWNWI
43	YSITSGYHWSWI
44	YSITSGYYWDWI
45	YSISSHHTWI
46	YSISSHGHWI
47	FSLSTSGVAVSWI
48	FSLSTGGVAVGWI
49	FSLSTGGVAVSWI
50	FSLSTGGVGVAWI
51	FSLSTGGVGWSWI
52	FSLSTSGVAVAWI
137	FTPSDYAIHWV
138	FTPSDYGIHWV
139	YTFSNYAIHWV
140	YTFSYYAIHWV
141	YTFTDYAIHWV
142	YTFTDYGIHWV
143	YTFTNYAIHWV
144	YTFTNYGIHWV
145	FTPSGYGIHWV
146	FTFSNYAIHWV
147	FTFSSYGIHWV
148	FTFDSDYIHWV
149	FTFTSYWIHWV
150	YSISSLGYYWGWI
151	YSITSGYYWNWI
152	YSITSGYYWSWI
153	YSISSHGHWAWI
154	YSISSHGHWGWI

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TABLE 1-continued

Heavy chain HVR sequences		
SEQ ID NO.	Designed Sequence	
5		
155	FSLSTSGVAVGWI	
156	FSLSTSGVGVAWI	
10	157	FSLSTSGVGVGWI
	158	FSLSTGGVGVGWI
	HVR-H2	
15	53	LALIDWDDDKEYSPSLKSRL
	54	LALIDWDDDKEYSPSLKSRL
	55	LALIDWDDDKEYSPSLKSRL
20	56	LALIDWDDDKEYSPSLKSRL
	57	LALIDWADDKEYSPSLKSRL
	58	LALIDWAGDKSYSTSLKSRL
25	59	LARIDWDDDKEYSPSLKSRL
	60	LARIDWDDDKEYSTSLKSRL
	61	LARIDWDGDKEYSTSLKSRL
	62	IGDIYHSGSTYYSPSLKSRV
30	63	IGEIHSGSTYYSPSLKSRV
	64	IGEIIYSGSTYYSPSLKSRV
	65	IGSIYHSGNTNYPNSLKSRL
35	66	IGEIYHSGNTYYNPNSLKSRL
	67	IGEIYHSGSTYYNPNSLKSRL
	68	IGEIYYSGSTYYNPNSLKSRL
40	69	IGDIYHSGNTYYNPNSLKSRL
	70	IGDIYHSGSTYYNPNSLKSRL
	71	VSAISGYGDTYYADSVKGRF
45	72	VSAISGYGGSTYYADSVKGRF
	73	VSAISGYGGTYYADSVKGRF
	74	VSGISGAGDTYYADSVKGRF
50	75	VSGISGDDGDTYYADSVKGRF
	76	VSGISGDDGTTYYADSVKGRF
	77	VSGISGYGDTYYADSVKGRF
55	78	VSGISGYGGTYYADSVKGRF
	79	VSVISGDGDTYYADSVKGRF
	80	VSVISGYGGSTYYADSVKGRF
60	81	VSGISGDDGTTYYADSVKGRF
	82	VSGISGYGDTYYADSVKGRF
	83	VSVISGSGSTYYADSVKGRF
	84	VSVISGYGSSTYYADSVKGRF
65	85	VSVISGYGDTYYADSVKGRF

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TABLE 1-continued

Heavy chain HVR sequences	
SEQ ID NO.	Designed Sequence
86	VSAISGYGSTTYYADSVKGRF
87	VSSISGYGDTTYYADSVKGRF
88	VSSISGYGGSTTYYADSVKGRF
89	VSSISGYGGTTYYADSVKGRF
90	VSYISGAGDTTYYADSVKGRF
91	VSSISGAGDTTYYADSVKGRF
92	VSYISGAGGTTYYADSVKGRF
93	VSYISGAGGTTYYADSVKGRF
94	VSYISGAGGTTYYADSVKGRF
95	VSYISGAGGTTYYADSVKGRF
96	VSYISGSGDTTYYADSVKGRF
97	VSSISGAGGTTYYADSVKGRF
98	VSYISGYGDTTYYADSVKGRF
99	VSYISGYGGTTYYADSVKGRF
100	VSSISGAGGTTYYADSVKGRF
101	VSSISGAGGTTYYADSVKGRF
102	VSSISGAGGTTYYADSVKGRF
103	VSSISGAGSSTYYADSVKGRF
104	VSSISGAGSTTYYADSVKGRF
105	VSSISGDSSTYYADSVKGRF
106	VSSISGDGDTYYADSVKGRF
107	VSSISGYGSSTYYADSVKGRF
108	VSSISGYGSTYYADSVKGRF
109	IGWINPNRGDTKYAQKFQGRV
110	IGWINPNRGDTNYAQKFQGRV
111	IGWINPNRGDTKYAQKFQGRV
112	IGWINPNRGDTNYAQKFQGRV
113	IGWINPNRGDTKYAQKFQGRV
114	IGWINPNRGSTNYAQKFQGRV
115	IGRINPNFGDTNYAQKFQGRV
116	IGWINPNFGDTNYAQKFQGRV
117	IGWINPNFGSTKYAQKFQGRV
118	IGWINPNFGSTNYAQKFQGRV
119	IGIIINPNRGDTKYAQKFQGRV
120	IGIIINPNRGDTNYAQKFQGRV
121	IGIIINPNFGDTNYAQKFQGRV
122	IGWISPSGGGTKYAQKFQGRV
123	IGWISPSGGGTNYAQKFQGRV

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TABLE 1-continued

Heavy chain HVR sequences	
SEQ ID NO.	Designed Sequence
5	IGWISPSGGTAKYQKFQGRV
124	IGWISPSGGTAKYQKFQGRV
125	IGWISPSGGTNYAQKFQGRV
10	IGWIYPGGTAKYQKFQGRV
126	IGWIYPGGTNYAQKFQGRV
127	IGWIYPGGTNYAQKFQGRV
128	IGWISPGGTNYAQKFQGRV
15	IGWISPSGGAKYQKFQGRV
129	IGWIIPSGGAKYQKFQGRV
130	IGWIIPSGGAKYQKFQGRV
131	IGWIIPSGGAKYQKFQGRV
20	IGIIIPSGGAKYQKFQGRV
132	IGIIIPSGGAKYQKFQGRV
133	IGIIIPSGGAKYQKFQGRV
134	IGIIIPSGGAKYQKFQGRV
25	IGIIIPSGGAKYQKFQGRV
135	IGIIIPSGGAKYQKFQGRV
136	VGRIKSKTDGYTTEAAPVKGRF
159	VSAISGSGSTYYADSVKGRF
30	VSSISGSGDTYYADSVKGRF
160	VSSISGSGDTYYADSVKGRF
161	VSSISGSGGAKYQKFQGRV
162	VSSISGSGGAKYQKFQGRV
163	VSSISGAGGTTYYADSVKGRF
35	VSSISGAGGTTYYADSVKGRF
164	VSSISGAGGTTYYADSVKGRF

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.

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., LAX1IX2WX3X4DKX5YSX6LKSRL, 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); VGRIIX1SKX2X3GX4TTX5YAAAX6VKGRF, 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); IGXIIFYX2SGX3TX4YNPSSLKSRV, 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 VGRIIXSKX2X3GX4TTEYAAAX5VKGRF, 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, 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.

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.

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.

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.

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 (XII); a HVR-H1 comprising the amino acid sequence of Formula (III) and a HVR-H2 comprising the amino acid sequence of Formula (XI); and a HVR-H1 comprising the amino acid sequence of Formula (XI) and a HVR-H2 comprising the amino acid sequence of Formula (XI). In

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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

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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.

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.

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:

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(SEQ ID NO: 165)

FW-H1 is EVQLVESGGGLVQPGGSLRLSCAASG

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(SEQ ID NO: 166)

FW-H2 is RQAPGKGLEW

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-continued

(SEQ ID NO: 167)

FW-H3 is TISRDNSKNTLYLQLNLSRAEDTAVYYC

(SEQ ID NO: 168)

FW-H4 is WGQGTLTVVSS.

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.

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

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

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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.

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); IGXIYX2SGX3TX4YNPSLKSRV, 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); VSX1ISGX2GX3X4TYYADSVKGKF, 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); IGXIYX2SGX3TX4YNPSLKSRV, 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 VGRIX1SKX2X3GX4TTEYAA5VKGRF, 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).

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-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.

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.

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 (K_d) 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 (K_d) 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).

In some embodiments, an antibody or antibody fragment of the present disclosure has a melting temperature (T_m) of at least 60° C. For example, in some embodiments, an antibody or antibody fragment of the present disclosure has a T_m 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 T_m of between about 60° C. and about 90° C. Various methods of measuring T_m for an antibody or antibody fragment are known in the art. Exemplary assays for deter-

mining antibody T_m are described and exemplified infra (See e.g., the DSF assay of Example 4 below).

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

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).

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

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

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 *Sophoptera frugiperda* cells.

Plant cell cultures can also be utilized as hosts. See, e.g., U.S. Pat. Nos. 5,959,177, 6,040,498, 6,420,548, 7,125,978,

and 6,417,429 (describing PLANTIBODIES™ technology for producing antibodies in transgenic plants).

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

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 CL domain are known in the art (See e.g., Fischer et al. (2015), *Nat. Commun.* 6:6113; US20140179547). For example, a bispecific antibody comprising: a) two identical heavy chain variable regions (e.g., any one of the heavy chain variable regions described herein), b) a first light chain comprising a first light chain variable region and a kappa C_L domain, and c) a second light chain comprising a second light chain variable region and a lambda CL domain (e.g., the constant region of a second light chain comprising a kappa C_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-C_H1 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 CL domains are eliminated in the column flow through; finally, pure bispecific kappa-lambda-bodies are recovered using LambdaFab-Select 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.).

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.

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.

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.

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

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

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

To understand variability of antibody variable domains at a structural level, an algorithm was developed to map the geometric alignment for antibody variable domains, and further, to calculate the structural and sequence entropy based upon the geometric alignment. Taking such an approach combines the classical theory of antibody diversity being determined by the well-established process of V(D)J recombination coupled with conformational diversity from dynamic units (template-directed conformational selection by Linus Pauling; See e.g., James, L. and Tawfik, D. "Conformational diversity and protein evolution—a 60-year-old hypothesis revisited", *Trends Biochem Sci*. 2003 July; 28(7):361-8) to allow sampling of an almost infinite epitope space by selection and adaptation of antibody binding sites. As an example, this algorithm was used to analyze the structural and sequence variability of 113 high-resolution crystal structures of human antibody variable heavy chain domains. Entropy was calculated and plotted for every position of the variable heavy chain domain, (FIG. 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).

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

To begin construction of the heavy chain libraries, 3 groups of degenerate oligos were designed for the variable region HVR-H1 based on the formulas shown in Table 2, resulting in 112 unique HVR-H1 sequences. 7 groups of degenerate oligos were designed for the variable region HVR-H2 based on the formulas shown in Table 2, resulting in 565 unique HVR-H2 sequences. The synthesized degenerate oligos were converted into double stranded DNA through the following protocol: 0.75 pL of 0.2 μM template oligos were mixed with 10 pL 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 (CGTTTGTCTGTGCAGCTTCGG) (SEQ ID NO:211) and R_1999 (CGAGGCCCT-TACCCGGGGCTGACG) (SEQ ID NO:212), while VH_vr2s were amplified using the primer pair F_2003 (CCGGGTAAGGGCCTGAGTGG) (SEQ ID NO:213) and R_2003 (GAGCACGTCGTTCAAT-TGTCGCACTTATAG) (SEQ ID NO:214).

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 Prime-

STAR buffer, 4 μ L dNTP mixture, 1 μ L of 100 μ M F_1999 primer, 1 μ L of 100 μ M R_2003 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 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

entific), 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.

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 desalting (QIAquick® PCR Purification Kit (QIAGEN)) before rolling circle amplification (RCA) was performed. RCA was carried out as follows: 40 ng ligation

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 N, S,	A, D, G, 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 SX6SLKSR	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)	VGRIIX1SKX2X3GX4TT X5YAAAX6VKGRF	K, R	A, T	D, Y	G, Y	D, E	P, S	

n/a, not applicable.

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/pL), 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 (ACAAC-TAACAGCTTAAGAGCTGAGGACACTGCCGTATT-ATTG) (SEQ ID NO:215) and the reverse primer was S1090 (GAGGAGACGGTGACTAGTGTCCCTTGACCCCA) (SEQ ID NO:216). The resulting synthesized DNAs were then purified through gel electrophoresis (GENEray Gel Extraction kit), digested with AflII and SpeI (Thermo Sci-

50 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 tL), heated to 95° C. for three minutes, and annealed for 65 cycles (30 second each cycle) with each cycle decreasing by 1° C. The annealed reactions were incubated overnight at 30° C. after the addition of 10 μ L of 10 mM dNTP mix, 1 μ L of 100× 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 XbaI. 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).

55 The above-mentioned mixtures of plasmids for the two heavy chain libraries were digested with PvuI and Acc65I,

60 65

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

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 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 VL_vr1s were amplified using the primer pair F_2898 (TACTTATGTAGGCGATCGGGT-CACCATCACCTGC) (SEQ ID NO:217) and R_2898 (CG-GAGCTTTCTGGTTCTGTTGATAC) (SEQ ID NO:218), while VL_vr2s were amplified using the primer pair F_2013 (GAAACCAGGAAAAGCTCCGAAG) (SEQ ID NO:219) and R_2013 (CGTCCCAGAACCG-GATCCAGAGAAGCGAG) (SEQ ID NO:220).

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 Pvul 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.

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 (ACCATCAGCAGTCTGCAGCCGGAA-GACTTCGCAAC) (SEQ ID NO:221), 1 μ L of 100 μ M reverse primer R2929 (GATCTCACCTGGTACCTGTCCGAA) (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.

To assemble the full length VL library, the purified VL-vr3 library plasmid mixture was digested with PstI and 5 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 10 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 15 Fad40, using the restriction enzymes Pvul and Acc65I. The size of the library containing Fad40-vr123 reached 4*10⁷. Construction of the Complete Dynamic Library

The dynamic library was composed of the heavy chain library derived from the VH-vr123 library and the light 20 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 25 vector backbones derived from Fad40-vr123 library. The ligation products were desaltsed (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× 30 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 35 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*10¹⁰ colonies were collected from plates (2×YT, 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

50 To prepare the dynamic library phagemid particles for antigen panning, 5.0 liters of ER2738 cells harboring the dynamic library (described in Example 2 above) were inoculated in media containing 2×YT, 2% glucose, 100 μ g/mL ampicillin and 12.5 g/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 55 media containing 2×YT, 100 μ g/mL ampicillin and 50 μ g/mL kanamycin. Culture supernatants were then harvested by centrifugation at 10,000 rpm for 15 minutes, and filtered through a 0.45 μ m low-binding membrane filter (Corning). The phagemid particles were then precipitated from the 60 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 65

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

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).

Alternatively, phagemid library panning was performed using Dynabeads (M280, Streptavidin, Invitrogen, Cat. No. 60210) through KingFisher (Thermo Scientific) according to the manufacturer's instructions. 300 µL of Dynabeads were washed with PBS and incubated with biotinylated anti-human Fc for 20 minutes at room temperature. The beads were then blocked with 5% BSA in PBS for one hour at room temperature. Fc-fusion antigens (70-100 pmols) were captured by one hour incubation at room temperature. The beads were then washed once with PBS, and incubated with 1 mL of phage library solution (typically 5*10¹² to 1*10¹³ phage particles in 5% BSA-PBS) for 1-2 hours. The beads were then washed several times with PBS/Tween (0.1% to 0.3%) and PBS, and the bound phages were eluted from the beads with 100 µL of 0.2 M glycine-HCl for 10 minutes at room temperature. The eluted phages were immediately neutralized with 18 µL of 1 M Tris-HCl (pH 9.1). A total of three or four rounds of panning were conducted against each of the antigens, and more than 10 fold excess of purified human Fc was included to reduce background binding.

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

Amplification of Enriched Phage

The eluted, enriched phage pool was further amplified as follows: ER2738 cells were infected with the eluted phagemid particles at 37° C. for 30 minutes. The infected cells were then plated out on 2×YT agar plates with 2% glucose, 100 µg/mL ampicillin and 12.5 µg/mL tetracycline. The colonies were harvested from plates, grown in 100 ml of 2% glucose, 100 µg/mL ampicillin and 12.5 g/mL tetracycline, and infected with M13KO7 helper phage. The amplified phages were purified and quantified by the processes described above. Usually, the eluted phages after the final round of panning were used to infect ER2738 cells, and the resulting ER2738 colonies were picked for supernatant ELISA screening assays.

Supernatant Sandwich EELISA Assay

A sensitive sandwich Elisa assay was developed to measure the Fabs present in bacterial supernatant. Microplates were coated with polyclonal anti-human IgG (Fab specific) (Sigma 15260) to capture Fabs present in the bacterial supernatant, and then HRP labeled goat anti-human Fc was used to detect the amount of Fabs captured. The 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).

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)	X1TFX2X3YX4IHNV	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)	IGX1IX2X3GSTYYSPS LKSRV	A, D, E	S, Y	H, Y	n/a	n/a	n/a
HVR-H2_3 (SEQ ID NO: 209)	IGX1IYX2SGX3TX4YNP SLKSRV	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

TABLE 3-continued

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-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 EYAXX5VKGRF	K, R	A, T	D, Y	G, Y	P, S	n/a	

n/a, not applicable.

Example 4: Characterization of Antibodies In Vitro

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

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 20 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 Tm ranges shown in FIG. 2B.

Example 5: Application of the Dynamic Heavy Chain Libraries

To further examine the robustness and flexibility of the heavy chain libraries, the libraries were screened against the 30 14 target antigens described in Example 4 above by pairing the heavy chains with different light chain libraries having a diversity varying from 10⁷ 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 35 was explored by trimming the physical size of their respective pairing partners (e.g., light chain libraries with a diversity ranging from 10⁷ to 280, 20, and to a single light chain) while exploring the flexibility and/or the dynamic diversity 40 of the light chain itself. The capacity of these dynamic light chain libraries in pairing with the dynamic heavy chain libraries provided a strong rational for the library design when generating and engineering the diverse antibody hits/ 45 leads against known and challenging target antigens. Positive hits having high affinity were identified from each of the 50 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 55 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 60 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 65 targets for therapeutic, diagnostic and/or research reagents when they are grafted on or designed into antibody (and/or alternative protein) scaffolds. The dynamic nature of these heavy chain hypervariable region units in designing and constructing antibody (and/or non-antibody) scaffolds, when paired with light chain libraries having a wide diversity (e.g., ranging from 10⁷ to 280, down to a single unique sequence), 66 is a strong validation of the dynamic antibody design concept for creating novel binding reagents useful in therapeutic, diagnostic and/or research settings.

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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

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TABLE 4-continued

Affinity data for confirmed hits				
5	HVR-H1 and H2 Usage	Hit ID	Target ID	Kd (M)
		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

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TABLE 4-continued

Affinity data for confirmed hits			
HVR-H1 and H2 Usage	Hit ID	Target ID	Kd (M)
HVR-H1 and H2 Usage	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
HVR-H1_3 and HVR-H2_4	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
HVR-H1_3 and HVR-H2_4	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
	4074	TAGT-6	1.95E-08
	4131	TAGT-6	<1.0E-12
HVR-H1_3 and HVR-H2_4	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
HVR-H1_3 and HVR-H2_4	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
HVR-H1_3 and HVR-H2_4	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
HVR-H1_3 and HVR-H2_4	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

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TABLE 4-continued

Affinity data for confirmed hits			
HVR-H1 and H2 Usage	Hit ID	Target ID	Kd (M)
HVR-H1_3 and HVR-H2_4	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
HVR-H1_3 and HVR-H2_4	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
HVR-H1_3 and HVR-H2_4	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
HVR-H1_3 and HVR-H2_4	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
HVR-H1_3 and HVR-H2_4	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
HVR-H1_3 and HVR-H2_4	7257	TAGT-12	1.11E-08
	7420	TAGT-9	1.38E-08
	7425	TAGT-9	1.77E-08
	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
HVR-H1_3 and HVR-H2_4	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
HVR-H1_3 and HVR-H2_4	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

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TABLE 4-continued

Affinity data for confirmed hits			
HVR-H1 and H2 Usage	Hit ID	Target ID	Kd (M)
HVR-H1_1 and HVR-H2_4	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
HVR-H1_2 and HVR-H2_6	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
HVR-H1_1 and HVR-H2_4	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
HVR-H1_1 and HVR-H2_4	7427	TAGT-9	5.58E-09
	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
HVR-H1_2 and HVR-H2_6	4723	TAGT-10	9.11E-10
	4733	TAGT-10	3.05E-10
	4734	TAGT-10	5.72E-10

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TABLE 4-continued

Affinity data for confirmed hits			
HVR-H1 and H2 Usage	Hit ID	Target ID	Kd (M)
HVR-H1_2 and HVR-H2_6	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
	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

TABLE 4-continued

Affinity data for confirmed hits			
HVR-H1 and H2 Usage	Hit ID	Target ID	Kd (M)
HVR-H1 and H2 Usage	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
HVR-H1_2 and HVR-H2_2 Usage	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
HVR-H1_2 and HVR-H2_3 Usage	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
HVR-H1_2 and HVR-H2_1 Usage	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
HVR-H1_1 and HVR-H2_1 Usage	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
HVR-H1 and H2 Usage	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
HVR-H1 and H2 Usage	7443	TAGT-9	1.27E-08
	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
HVR-H1 and H2 Usage	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

TABLE 4-continued

Affinity data for confirmed hits			
HVR-H1 and H2 Usage	Hit ID	Target ID	Kd (M)
HVR-H1 and H2 Usage	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
HVR-H1_2 and HVR-H2_2 Usage	7513	TAGT-9	8.43E-09
	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
HVR-H1_2 and HVR-H2_3 Usage	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
HVR-H1_2 and HVR-H2_1 Usage	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
	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
HVR-H1 and H2 Usage	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
HVR-H1 and H2 Usage	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
	5202	TAGT-1	1.50E-08
	5203	TAGT-1	1.31E-08
	5207	TAGT-1	7.44E-09
	5221	TAGT-1	1.18E-08
HVR-H1 and H2 Usage	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
HVR-H1 and H2 Usage	7277	TAGT-5	2.56E-09
	7278	TAGT-5	1.53E-08
	7390	TAGT-5	1.44E-09

TABLE 4-continued

Affinity data for confirmed hits			
HVR-H1 and H2 Usage	Hit ID	Target ID	Kd (M)
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
	5208	TAGT-1	3.36E-09
	5283	TAGT-1	2.88E-08
	5303	TAGT-6	5.12E-09
HVR-H1_3 and HVR-H2_1	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
	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
HVR-H1_1 and HVR-H2_2	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
	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

TABLE 4-continued

Affinity data for confirmed hits				
5	HVR-H1 and H2 Usage	Hit ID	Target ID	Kd (M)
10	HVR-H1_3 and HVR-H2_6	4857	TAGT-12	4.05E-09
		5227	TAGT-1	1.04E-08
	HVR-H1_2 and HVR-H2_7	7221	TAGT-12	5.58E-09
		7229	TAGT-12	8.91E-09
	HVR-H1_2 and HVR-H2_5	4220	TAGT-6	5.72E-08
		4861	TAGT-12	5.11E-09
	HVR-H1_3 and HVR-H2_7	5284	TAGT-1	1.84E-08
15		4079	TAGT-6	3.15E-08
HVR-H2_7	7129	TAGT-6	1.90E-08	
	4072	TAGT-6	6.95E-09	
HVR-H1_3 and HVR-H2_5	5333	TAGT-6	5.02E-09	
	HVR-H2_7			

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).

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
55	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
60	HVR-H2_5	16.8%	8
	HVR-H2_6	21.8%	13
	HVR-H2_7	0.9%	3

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

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TABLE 6

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

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

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TABLE 7-continued

Usage of new HVR-H1 and HVR-H2 sequences		
SEQ ID NO:	Number of hits	Number of Antigens hit out of 14
5	20	3
10	33	3
10	42	3
10	45	3
15	13	27
15	34	7
15	35	5
15	41	5
15	3	2
15	15	3
15	30	3
15	44	3
15	46	3
15	32	2
15	37	2
20	39	2
20	2	2
20	14	2
20	48	6
20	29	3
20	6	3
25	17	2
25	36	2
25	52	1
25	10	1
25	63	7
25	93	5
25	66	5
25	122	5
25	65	5
25	105	5
25	124	4
25	123	4
25	70	4
25	110	3
25	129	3
25	121	3
25	89	3
25	134	3
25	128	3
25	60	3
40	67	3
40	95	3
40	117	2
40	82	2
40	130	2
40	132	2
45	53	2
45	131	2
45	109	2
45	118	2
45	100	2
45	103	2
45	106	2
45	61	2
45	71	2
45	75	2
45	77	2
45	79	2
45	108	2
45	112	2
45	113	2
45	55	2
45	56	2
45	59	2
45	62	2
45	64	2
45	68	2
45	69	2
45	73	2
45	74	2
45	76	2
45	78	2
55	60	2

TABLE 7-continued

Usage of new HVR-H1 and HVR-H2 sequences		
SEQ ID NO:	Number of hits	Number of Antigens hit out of 14
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

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

TABLE 8-continued

new HVR-H1 and HVR-H2 combination usage				
5	Preference Ranking	HVR-H1 SEQ ID NO:	HVR-H2 SEQ ID NO:	Number of Antigens hit out of 14
10	Tier 2	26	53	4
	Tier 2	151	53	4
	Tier 2	34	63	3
	Tier 2	50	162	3
	Tier 2	158	104	3
	Tier 2	5	121	3
	Tier 2	6	116	3
	Tier 2	7	121	3
	Tier 2	17	63	2
	Tier 2	25	101	2
15	Tier 2	25	114	2
	Tier 2	29	112	2
	Tier 2	152	63	2
	Tier 2	156	89	2
	Tier 2	157	94	2
	Tier 2	48	58	2
	Tier 2	50	89	2
	Tier 2	50	163	2
	Tier 2	158	160	2
	Tier 2	158	87	2
20	Tier 2	158	92	2
	Tier 2	158	93	2
	Tier 2	158	97	2
	Tier 2	158	103	2
	Tier 2	158	164	2
	Tier 2	137	54	2
	Tier 2	3	127	2
	Tier 2	4	85	2
	Tier 2	4	110	2
	Tier 2	139	109	2
25	Tier 2	139	121	2
	Tier 2	8	120	2
	Tier 2	140	131	2
	Tier 2	141	116	2
	Tier 2	142	159	2
	Tier 2	143	116	2
	Tier 2	144	121	2
	Tier 2	146	110	2
	Tier 2	147	133	2
	Tier 2	148	63	2
30	Tier 2	13	118	2
	Tier 2	8	4025	2.89E-09
	Tier 2	8	4033	8.75E-10
	Tier 2	8	4614	3.53E-10
	Tier 2	8	4615	2.28E-10
	Tier 2	8	4617	2.88E-10
	Tier 2	8	4622	2.74E-10
	Tier 2	8	4627	1.82E-10
	Tier 2	8	4631	1.83E-10
	Tier 2	8	4633	3.22E-10
35	Tier 2	8	4634	2.07E-10
	Tier 2	8	4638	3.14E-10
	Tier 2	8	4642	1.89E-10
	Tier 2	8	4644	2.48E-10
	Tier 2	8	4645	2.96E-10
	Tier 2	8	4650	3.57E-10
	Tier 2	8	4651	3.01E-10
	Tier 2	8	4652	2.94E-10
	Tier 2	8	4654	2.32E-10
	Tier 2	8	4658	1.42E-10
40	Affinity data for confirmed hits using new HVR-H1 and HVR-H2 sequences			

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)
50	8	TAGT-8	2.89E-09
55	8	TAGT-8	8.75E-10
60	8	TAGT-8	3.53E-10
65	8	TAGT-8	2.28E-10
70	8	TAGT-8	2.88E-10
75	8	TAGT-8	2.74E-10
80	8	TAGT-8	1.82E-10
85	8	TAGT-8	1.83E-10
90	8	TAGT-8	3.22E-10
95	8	TAGT-8	2.07E-10
100	8	TAGT-8	3.14E-10
105	8	TAGT-8	1.89E-10
110	8	TAGT-8	2.48E-10
115	8	TAGT-8	2.96E-10
120	8	TAGT-8	3.57E-10
125	8	TAGT-8	3.01E-10
130	8	TAGT-8	2.94E-10
135	8	TAGT-8	2.32E-10
140	8	TAGT-8	1.42E-10

TABLE 9-continued

Affinity data for confirmed hits using new HVR-H1 and HVR-H2 sequences			
HVR SEQ ID NO(S):	Hit ID	Antigen	Kd (M)
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

TABLE 9-continued

Affinity data for confirmed hits using new HVR-H1 and HVR-H2 sequences			
HVR SEQ ID NO(S):	Hit ID	Antigen	Kd (M)
31	5040	TAGT-8M	3.13E-09
31	5045	TAGT-8	1.00E-09
31	5045	TAGT-8M	3.91E-09
10	31	TAGT-8	5.10E-10
10	31	TAGT-8M	2.52E-09
10	31	TAGT-8	5.23E-09
10	31	TAGT-8M	9.99E-09
10	31	TAGT-8	1.34E-09
10	31	TAGT-8M	6.63E-09
15	31	TAGT-11	2.61E-10
15	31	TAGT-12	3.23E-08
15	31	TAGT-5	8.75E-09
15	50	TAGT-12	3.20E-08
15	50	TAGT-12	3.25E-08
15	50	TAGT-12	6.29E-08
20	50	TAGT-6	1.88E-08
20	50	TAGT-6	5.55E-08
20	50	TAGT-6	3.97E-08
20	50	TAGT-12	9.36E-09
20	50	TAGT-12	1.44E-08
20	50	TAGT-12	2.18E-08
20	50	TAGT-12	1.17E-08
25	50	TAGT-12	7.08E-09
25	50	TAGT-12	1.11E-08
25	50	TAGT-5	6.03E-09
25	22	TAGT-10	<1.0E-12
25	22	TAGT-6	<1.0E-12
25	22	TAGT-6	<1.0E-12
30	22	TAGT-12	4.01E-10
30	22	TAGT-1	9.19E-09
30	22	TAGT-1	6.04E-09
30	22	TAGT-1	1.24E-08
30	22	TAGT-1	1.84E-08
30	22	TAGT-6	2.61E-07
35	22	TAGT-6	6.04E-07
35	22	TAGT-12	1.50E-08
35	22	TAGT-5	4.99E-10
35	1	TAGT-6	1.84E-08
35	1	TAGT-11	2.35E-08
35	1	TAGT-10	2.67E-09
40	1	TAGT-11	1.71E-08
40	1	TAGT-1	5.33E-09
40	1	TAGT-1	1.02E-08
40	1	TAGT-6	2.10E-06
40	1	TAGT-2	7.85E-09
45	1	TAGT-5	2.02E-08
45	1	TAGT-4	3.82E-08
45	1	TAGT-9	1.72E-08
45	12	TAGT-10	3.24E-09
45	12	TAGT-8	1.37E-08
45	12	TAGT-10	9.11E-10
45	12	TAGT-10	3.05E-10
50	12	TAGT-10	5.72E-10
50	12	TAGT-10	2.77E-10
50	12	TAGT-10	7.23E-10
55	12	TAGT-10	5.63E-10
55	12	TAGT-10	1.17E-09
55	12	TAGT-8	1.53E-08
55	12	TAGT-8	3.47E-08
55	12	TAGT-5	5.68E-09
60	4	TAGT-10	1.58E-08
60	4	TAGT-1	1.31E-08
60	4	TAGT-6	4.96E-09
60	4	TAGT-10	1.99E-09
60	4	TAGT-10	2.70E-09
60	4	TAGT-10	3.44E-09
60	4	TAGT-10	4.99E-09
60	4	TAGT-5	2.30E-09
65	7	TAGT-5	1.53E-08
65	7	TAGT-5	2.31E-08
65	7	TAGT-11	1.97E-08
65	7	TAGT-11	1.83E-08
65	7	TAGT-10	4.31E-08

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TABLE 9-continued

Affinity data for confirmed hits using new HVR-H1 and HVR-H2 sequences			
HVR SEQ ID NO(S):	Hit ID	Antigen	Kd (M)
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

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TABLE 9-continued

Affinity data for confirmed hits using new HVR-H1 and HVR-H2 sequences			
HVR SEQ ID NO(S):	Hit ID	Antigen	Kd (M)
5	48	TAGT-6	3.89E-08
5	48	TAGT-6	1.02E-08
5	48	TAGT-6	7.26E-09
10	48	TAGT-6	9.93E-10
10	18	TAGT-12	3.69E-10
10	18	TAGT-12	5.11E-09
10	18	TAGT-6	9.87E-09
10	18	TAGT-3	4.18E-08
10	18	TAGT-9	8.43E-09
15	24	TAGT-6	2.43E-08
15	24	TAGT-12	7.62E-09
15	24	TAGT-12	1.05E-08
15	24	TAGT-5	2.72E-09
15	24	TAGT-9	2.47E-08
15	27	TAGT-6	<1.0E-12
20	27	TAGT-12	3.19E-09
20	27	TAGT-12	4.19E-09
20	27	TAGT-6	1.49E-08
20	27	TAGT-1	5.15E-09
20	28	TAGT-5	8.40E-10
20	35	TAGT-12	1.23E-09
20	35	TAGT-12	3.84E-10
20	35	TAGT-11	9.45E-09
30	35	TAGT-12	1.14E-08
30	41	TAGT-12	1.66E-08
30	41	TAGT-12	2.09E-08
30	41	TAGT-12	1.13E-08
30	41	TAGT-12	1.42E-08
30	41	TAGT-4	7.22E-09
35	9	TAGT-6	1.77E-06
35	9	TAGT-2	1.64E-08
35	9	TAGT-2	1.14E-09
35	9	TAGT-5	3.76E-09
35	9	TAGT-9	3.53E-08
40	11	TAGT-10	1.80E-08
40	11	TAGT-10	1.97E-08
40	11	TAGT-8	3.59E-10
40	11	TAGT-6	1.53E-08
40	11	TAGT-8	2.15E-08
40	38	TAGT-10	6.83E-09
40	38	TAGT-10M	6.89E-09
40	38	TAGT-12	3.64E-10
45	38	TAGT-9	1.97E-08
45	40	TAGT-8	1.89E-09
45	40	TAGT-6	7.44E-09
50	43	TAGT-12	1.70E-08
50	43	TAGT-12	5.36E-09
50	43	TAGT-5	3.17E-09
50	43	TAGT-11	3.00E-08
50	43	TAGT-3	6.78E-08
50	43	TAGT-9	1.38E-08
55	3	TAGT-2	5.29E-09
55	3	TAGT-2	3.84E-09
55	3	TAGT-8	1.12E-09
55	3	TAGT-8	1.11E-09
55	15	TAGT-6	<1.0E-12
60	20	TAGT-8	5.53E-09
60	20	TAGT-11	5.24E-09
60	20	TAGT-12	9.72E-09
60	29	TAGT-12	5.66E-09
60	29	TAGT-12	1.12E-08
60	29	TAGT-6	1.07E-08
65	30	TAGT-6	1.25E-08
65	30	TAGT-6	1.41E-08

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TABLE 9-continued

Affinity data for confirmed hits using new HVR-H1 and HVR-H2 sequences			
HVR SEQ ID NO(S):	Hit ID	Antigen	Kd (M)
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

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TABLE 9-continued

Affinity data for confirmed hits using new HVR-H1 and HVR-H2 sequences			
HVR SEQ ID NO(S):	Hit ID	Antigen	Kd (M)
5	110	TAGT-10	8.28E-10
10	110	TAGT-10	2.90E-10
10	6010	TAGT-12	2.83E-08
10	6183	TAGT-10	2.70E-09
10	6191	TAGT-10	6.58E-11
10	6206	TAGT-10	3.44E-09
10	7066	TAGT-8	1.80E-08
10	63	TAGT-8	3.13E-09
10	4096	TAGT-8	2.70E-09
15	63	TAGT-12	2.89E-09
15	63	TAGT-12	5.91E-09
15	4817	TAGT-12	2.06E-09
15	4818	TAGT-12	1.02E-09
15	4836	TAGT-12	2.49E-09
15	4840	TAGT-12	2.08E-09
20	63	TAGT-12	4.50E-10
20	63	TAGT-12	3.19E-09
20	4846	TAGT-12	2.26E-09
20	63	TAGT-12	2.44E-09
20	4876	TAGT-12	7.75E-09
20	4880	TAGT-12	2.77E-09
25	63	TAGT-12	6.83E-10
25	63	TAGT-12	3.19E-09
25	4901	TAGT-12	5.39E-09
25	63	TAGT-12	5.115
25	5195	TAGT-1	2.62E-08
25	5216	TAGT-1	3.08E-09
25	5286	TAGT-1	6.34E-09
30	63	TAGT-1	1.02E-08
30	63	TAGT-1	5.290
30	63	TAGT-6	1.04E-08
30	5387	TAGT-8	1.13E-09
30	5404	TAGT-6	3.30E-09
30	63	TAGT-9	1.05E-08
35	63	TAGT-9	5.12E-09
35	63	TAGT-11	2.61E-10
35	5722	TAGT-11	3.08E-08
35	5756	TAGT-11	3.00E-08
35	5985	TAGT-12	3.92E-08
35	5986	TAGT-12	4.65E-08
40	63	TAGT-5	6.01E-09
40	63	TAGT-5	7.316
40	63	TAGT-5	7.370
40	126	TAGT-5	7.375
40	126	TAGT-5	7.385
40	126	TAGT-5	7.391
40	126	TAGT-5	7.394
45	126	TAGT-8	8.75E-10
45	126	TAGT-8	4.614
45	126	TAGT-8	4.615
45	126	TAGT-8	4.617
45	126	TAGT-8	4.622
45	126	TAGT-8	4.627
50	126	TAGT-8	4.631
50	126	TAGT-8	4.633
50	126	TAGT-8	4.634
50	126	TAGT-8	4.638
50	126	TAGT-8	4.642
50	126	TAGT-8	4.644
50	126	TAGT-8	4.645
55	126	TAGT-8	4.650
55	126	TAGT-8	4.651
55	126	TAGT-8	4.652
55	126	TAGT-8	4.654
55	126	TAGT-8	4.658
55	126	TAGT-8	4.665
60	126	TAGT-8	4.673
60	126	TAGT-8	4.674
60	126	TAGT-8	4.681
60	126	TAGT-8	4.689
60	126	TAGT-8	4.690
65	126	TAGT-8	7.043
65	126	TAGT-8	BH3002
65	126	TAGT-8	BH3004

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TABLE 9-continued

Affinity data for confirmed hits using new HVR-H1 and HVR-H2 sequences			
HVR SEQ ID NO(S):	Hit ID	Antigen	Kd (M)
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

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TABLE 9-continued

Affinity data for confirmed hits using new HVR-H1 and HVR-H2 sequences			
HVR SEQ ID NO(S):	Hit ID	Antigen	Kd (M)
5	124	TAGT-12	1.58E-08
10	124	TAGT-9	6.83E-09
10	93	TAGT-10	2.11E-08
10	93	TAGT-6	<1.0E-12
10	93	TAGT-6	1.41E-08
10	93	TAGT-6	1.53E-08
10	93	TAGT-11	9.45E-09
10	93	TAGT-12	1.50E-08
10	93	TAGT-12	3.23E-08
15	93	TAGT-6	2.52E-08
15	93	TAGT-6	6.96E-08
15	93	TAGT-6	3.45E-08
15	93	TAGT-6	1.03E-08
15	93	TAGT-5	3.13E-08
15	82	TAGT-10	3.24E-09
20	82	TAGT-10	1.80E-08
20	82	TAGT-10	9.11E-10
20	82	TAGT-10	3.05E-10
20	82	TAGT-10	5.72E-10
20	82	TAGT-10	2.77E-10
20	82	TAGT-10	7.23E-10
25	82	TAGT-10	5.63E-10
25	82	TAGT-10	1.17E-09
25	82	TAGT-6	1.61E-08
30	130	TAGT-10	6.92E-10
30	130	TAGT-12	2.45E-10
30	130	TAGT-12	6.80E-09
30	130	TAGT-12	3.42E-08
30	130	TAGT-12	1.46E-08
35	130	TAGT-12	8.55E-09
35	116	TAGT-10	3.34E-09
35	116	TAGT-10	2.49E-10
35	116	TAGT-10	<1.0E-12
35	116	TAGT-10	1.03E-09
35	116	TAGT-10	6.46E-09
40	116	TAGT-10	3.50E-09
40	116	TAGT-10	5.17E-10
40	116	TAGT-10	2.25E-09
40	116	TAGT-10	1.51E-09
40	116	TAGT-10	4.99E-09
45	132	TAGT-8	5.11E-09
45	132	TAGT-8M	4.84E-09
45	132	TAGT-10	1.65E-08
45	132	TAGT-8	1.76E-09
45	132	TAGT-8M	2.03E-09
50	132	TAGT-8	2.43E-09
50	132	TAGT-8M	3.87E-09
50	132	TAGT-8	3.56E-09
50	132	TAGT-8M	2.84E-09
50	132	TAGT-8	3.68E-09
50	132	TAGT-8M	3.03E-09
50	132	TAGT-8	4.52E-09
50	132	TAGT-8M	3.48E-09
50	132	TAGT-8	1.68E-09
55	132	TAGT-8M	1.67E-09
55	132	TAGT-8	4.31E-09
55	132	TAGT-8M	2.98E-09
55	132	TAGT-8	4.79E-09
55	132	TAGT-8M	3.23E-09
60	53	TAGT-10	9.73E-09
60	53	TAGT-10	3.30E-07
60	53	TAGT-10	4.34E-08
60	53	TAGT-10	1.27E-08
60	53	TAGT-10	1.27E-08
60	53	TAGT-10	4.20E-08
60	53	TAGT-10	2.59E-08
65	53	TAGT-1	8.43E-09
65	53	TAGT-10	1.75E-08
65	89	TAGT-8	1.10E-09

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TABLE 9-continued

Affinity data for confirmed hits using new HVR-H1 and HVR-H2 sequences			
HVR SEQ ID NO(S):	Hit ID	Antigen	Kd (M)
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

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TABLE 9-continued

Affinity data for confirmed hits using new HVR-H1 and HVR-H2 sequences			
HVR SEQ ID NO(S):	Hit ID	Antigen	Kd (M)
5	87	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
67	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
92	7378	TAGT-5	5.66E-09
92	7260	TAGT-5	2.30E-09
92	7365	TAGT-5	1.82E-09
92	7369	TAGT-5	2.46E-09
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

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TABLE 9-continued

Affinity data for confirmed hits using new HVR-H1 and HVR-H2 sequences			
HVR SEQ ID NO(S):	Hit ID	Antigen	Kd (M)
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

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TABLE 9-continued

Affinity data for confirmed hits using new HVR-H1 and HVR-H2 sequences			
HVR SEQ ID NO(S):	Hit ID	Antigen	Kd (M)
5	102	TAGT-12	2.69E-08
	107	4133	3.90E-10
	107	7262	2.63E-09
10	115	7310	1.41E-08
	115	7379	5.43E-09
10	119	6193	3.18E-09
	119	6220	3.45E-09
10	125	4030	4.90E-09
	125	7038	2.33E-08
15	127	7044	1.12E-09
	127	7045	1.11E-09
	135	4204	6.83E-09
	135	4204	6.89E-09
11	135	5423	4.90E-09
	136	4861	5.11E-09
	136	7129	1.90E-08
20	139 and 110	4181	4.27E-08
	139 and 110	4693	4.87E-10
	139 and 110	4696	4.58E-10
	139 and 110	4697	6.21E-10
	139 and 110	4698	5.70E-10
25	139 and 110	4700	2.62E-10
	139 and 110	4701	5.60E-10
	139 and 110	4702	5.02E-10
	139 and 110	4703	2.85E-10
	139 and 110	4704	6.65E-10
	139 and 110	4705	3.02E-10
	139 and 110	4706	2.50E-10
30	139 and 110	4707	4.29E-10
	139 and 110	4708	5.29E-10
	139 and 110	4710	6.26E-10
	139 and 110	4714	4.46E-10
	139 and 110	4717	4.61E-10
	139 and 110	4718	5.32E-10
35	139 and 110	4722	7.46E-10
	139 and 110	4725	4.84E-10
	139 and 110	4729	8.80E-10
	139 and 110	4731	4.67E-10
	139 and 110	4732	3.33E-10
	139 and 110	4738	5.34E-10
	139 and 110	4744	3.73E-10
40	139 and 110	4748	3.92E-10
	139 and 110	4749	2.55E-10
	139 and 110	4750	7.86E-10
	139 and 110	4753	3.43E-10
	139 and 110	4759	6.59E-10
	139 and 110	4766	4.09E-10
	139 and 110	4768	2.88E-10
45	139 and 110	4794	5.56E-10
	139 and 110	4803	1.88E-10
	139 and 110	4805	4.26E-10
	139 and 110	4808	8.28E-10
	139 and 110	4909	2.90E-10
50	139 and 110	6191	6.58E-11
	8 and 126	4033	8.75E-10
	8 and 126	4614	3.53E-10
	8 and 126	4615	2.28E-10
	8 and 126	4617	2.88E-10
	8 and 126	4622	2.74E-10
55	8 and 126	4627	1.82E-10
	8 and 126	4631	1.83E-10
	8 and 126	4633	3.22E-10
	8 and 126	4634	2.07E-10
	8 and 126	4638	3.14E-10
	8 and 126	4642	1.89E-10
	8 and 126	4644	2.48E-10
60	8 and 126	4645	2.96E-10
	8 and 126	4650	3.57E-10
	8 and 126	4651	3.01E-10
	8 and 126	4652	2.94E-10
	8 and 126	4654	2.32E-10
	8 and 126	4658	1.42E-10
65	8 and 126	4665	3.69E-10
	8 and 126	4673	3.23E-10

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TABLE 9-continued

Affinity data for confirmed hits using new HVR-H1 and HVR-H2 sequences			
HVR SEQ ID NO(S):	Hit ID	Antigen	Kd (M)
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

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TABLE 9-continued

Affinity data for confirmed hits using new HVR-H1 and HVR-H2 sequences			
HVR SEQ ID NO(S):	Hit ID	Antigen	Kd (M)
5	150 and 132	TAGT-8	1.68E-09
10	150 and 132	TAGT-8M	1.67E-09
15	150 and 132	TAGT-8	4.31E-09
15	150 and 132	TAGT-8M	2.98E-09
15	150 and 132	TAGT-8	4.79E-09
15	150 and 132	TAGT-8M	3.23E-09
15	150 and 132	TAGT-12	8.06E-08
15	150 and 132	TAGT-12	2.21E-08
15	150 and 132	6000	7.86E-08
15	150 and 132	7210	9.85E-09
15	150 and 132	7218	1.49E-08
15	150 and 132	7225	9.53E-09
15	150 and 132	7241	6.43E-09
15	150 and 132	7247	8.93E-09
20	12 and 82	4048	3.24E-09
20	12 and 82	4723	9.11E-10
20	12 and 82	4733	3.05E-10
20	12 and 82	4734	5.72E-10
20	12 and 82	4767	2.77E-10
25	149 and 117	4031	1.06E-09
25	149 and 117	5126	9.54E-09
25	149 and 117	5129	1.12E-09
25	149 and 117	5132	3.06E-09
25	149 and 117	5145	7.00E-09
25	149 and 117	7068	1.11E-08
30	149 and 117	7073	3.19E-09
35	7 and 134	3898	1.83E-08
35	7 and 134	5149	2.91E-09
35	7 and 134	5159	4.09E-09
35	7 and 134	5160	8.07E-09
35	7 and 134	5162	9.87E-09
35	7 and 134	5165	4.06E-09
35	154 and 63	4812	2.89E-09
35	154 and 63	4904	5.39E-09
35	154 and 63	5115	1.16E-08
35	154 and 63	5421	1.05E-08
35	154 and 63	5422	5.12E-09
40	158 and 161	5922	1.95E-08
40	158 and 161	7135	3.17E-08
40	158 and 161	7245	1.38E-08
40	158 and 161	7246	6.22E-09
40	158 and 161	7252	9.56E-09
45	26 and 53	4052	9.73E-09
45	26 and 53	5094	4.34E-08
45	26 and 53	5097	1.27E-08
45	26 and 53	5109	2.59E-08
45	151 and 53	4059	3.30E-07
45	151 and 53	5095	1.27E-08
45	151 and 53	5099	4.20E-08
45	151 and 53	5936	1.75E-08
50	157 and 63	4036	3.13E-09
50	157 and 63	4096	2.70E-09
50	157 and 63	5323	1.04E-08
50	157 and 63	7391	1.35E-08
55	1 and 122	3757	1.84E-08
55	1 and 122	3869	2.35E-08
55	1 and 122	5103	2.67E-09
55	1 and 122	5163	1.71E-08
60	34 and 63	4836	2.49E-09
60	34 and 63	4852	2.26E-09
60	34 and 63	4876	7.75E-09
60	50 and 162	7256	7.08E-09
60	50 and 162	7257	1.11E-08
65	158 and 63	5387	1.13E-09
65	158 and 63	5985	3.92E-08
65	158 and 63	5986	4.65E-08
65	158 and 104	5912	1.68E-08
65	158 and 104	5923	1.60E-08
65	158 and 104	7226	7.57E-09
65	5 and 121	4060	1.10E-08

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TABLE 9-continued

Affinity data for confirmed hits using new HVR-H1 and HVR-H2 sequences			
HVR SEQ ID NO(S):	Hit ID	Antigen	Kd (M)
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

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TABLE 9-continued

Affinity data for confirmed hits using new HVR-H1 and HVR-H2 sequences			
HVR SEQ ID NO(S):	Hit ID	Antigen	Kd (M)
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
10 140 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
20 148 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

25 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.

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.

Exemplary hit IDs 3757 and 5103 contained the same 40 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 35 HVR-H1 and HVR-H2 sequences could bind to another target antigen, TAGT-11.

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 50 species (TAGT-8H and TAGT-8M). Several other hits with these same HVR-H1 and HVR-H2 sequences demonstrated species cross-reactivity.

The novel methodology employed to identify the dynamic motif of the redefined hyper-variable regions of antibodies 55 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 60 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.

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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) 5
 Designed HVR-H1 sequence 3: FTFTNYGIHWV (SEQ ID NO:3)
 Designed HVR-H1 sequence 4: YTFSDYAIHWV (SEQ ID NO:4) 10
 Designed HVR-H1 sequence 5: YTFSDYGIHWV (SEQ ID NO:5)
 Designed HVR-H1 sequence 6: YTFSGYAIHWV (SEQ ID NO:6) 15
 Designed HVR-H1 sequence 7: YTFSGYGIHWV (SEQ ID NO:7)
 Designed HVR-H1 sequence 8: YTFSNYGIHWV (SEQ ID NO:8)
 Designed HVR-H1 sequence 9: YTFSYYGIHWV (SEQ ID NO:9) 20
 Designed HVR-H1 sequence 10: YTFSGYWIHWV (SEQ ID NO:10)
 Designed HVR-H1 sequence 11: YTFSNYWIHWV (SEQ ID NO:11) 25
 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) 30
 Designed HVR-H1 sequence 15: YSISSGHHWAWI (SEQ ID NO:15)
 Designed HVR-H1 sequence 16: YSISSGHYWNWI (SEQ ID NO:16) 35
 Designed HVR-H1 sequence 17: YSISSGHYWSWI (SEQ ID NO:17)
 Designed HVR-H1 sequence 18: YSISSGHYWTWI (SEQ ID NO:18)
 Designed HVR-H1 sequence 19: YSISSGYHAWI (SEQ ID NO:19) 40
 Designed HVR-H1 sequence 20: YSISSGYHWDWI (SEQ ID NO:20)
 Designed HVR-H1 sequence 21: YSISSGYHWGWI (SEQ ID NO:21) 45
 Designed HVR-H1 sequence 22: YSISSGYHWNWI (SEQ ID NO:22)
 Designed HVR-H1 sequence 23: YSISSGYHWSWI (SEQ ID NO:23)
 Designed HVR-H1 sequence 24: YSISSGHHWDWI (SEQ ID NO:24) 50
 Designed HVR-H1 sequence 25: YSISSGYYWDWI (SEQ ID NO:25)
 Designed HVR-H1 sequence 26: YSISSGYYWNWI (SEQ ID NO:26) 55
 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) 60
 Designed HVR-H1 sequence 30: YSITSGHHWGWI (SEQ ID NO:30)
 Designed HVR-H1 sequence 31: YSITSGHHWNWI (SEQ ID NO:31) 65
 Designed HVR-H1 sequence 32: YSITSGHHWSWI (SEQ ID NO:32)

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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: YSITSGYHAWI (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: FSLSTSGVAWSWI (SEQ ID NO:47)
 Designed HVR-H1 sequence 48: FSLSTGGVAVGWI (SEQ ID NO:48)
 Designed HVR-H1 sequence 49: FSLSTGGVAWSWI (SEQ ID NO:49)
 Designed HVR-H1 sequence 50: FSLSTGGVGVAWI (SEQ ID NO:50)
 Designed HVR-H1 sequence 51: FSLSTGGVGWSWI (SEQ ID NO:51)
 Designed HVR-H1 sequence 52: FSLSTSGVAVAWI (SEQ ID NO:52)
 Designed HVR-H1 sequence 53: FTFSDYAIHWV (SEQ ID NO:137)
 Designed HVR-H1 sequence 54: FTFSYYGIHWV (SEQ ID NO:138)
 Designed HVR-H1 sequence 55: YTFSNYAIHWV (SEQ ID NO:139)
 Designed HVR-H1 sequence 56: YTFSYYAIHWV (SEQ ID NO:140)
 Designed HVR-H1 sequence 57: YTFTDYAIHWV (SEQ ID NO:141)
 Designed HVR-H1 sequence 58: YTFTDYGIHWV (SEQ ID NO:142)
 Designed HVR-H1 sequence 59: YTFTNYAIHWV (SEQ ID NO:143)
 Designed HVR-H1 sequence 60: YTFTNYGIHWV (SEQ ID NO:144)
 Designed HVR-H1 sequence 61: FTFSGYGIHWV (SEQ ID NO:145)
 Designed HVR-H1 sequence 62: FTFSNYAIHWV (SEQ ID NO:146)
 Designed HVR-H1 sequence 63: FTFSYYGIHWV (SEQ ID NO:147)
 Designed HVR-H1 sequence 64: FTFSDYWIHWV (SEQ ID NO:148)
 Designed HVR-H1 sequence 65: FTFTSYWIHWV (SEQ ID NO:149)

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Designed HVR-H1 sequence 66: YSISSGYYWGWI
(SEQ ID NO:150)

Designed HVR-H1 sequence 67: YSITSGYYWNWI
(SEQ ID NO:151)

Designed HVR-H1 sequence 68: YSITSGYYWSWI 5
(SEQ ID NO:152)

Designed HVR-H1 sequence 69: YSISSGHYWAWI
(SEQ ID NO:153)

Designed HVR-H1 sequence 70: YSISSGHYWGWI 10
(SEQ ID NO:154)

Designed HVR-H1 sequence 71: FSLSTSGVAVGWI
(SEQ ID NO:155)

Designed HVR-H1 sequence 72: FSLSTSGVGVAWI 15
(SEQ ID NO:156)

Designed HVR-H1 sequence 73: FSLSTSGVGVGWI
(SEQ ID NO:157)

Designed HVR-H1 sequence 74: FSLSTGGVGVGWI
(SEQ ID NO:158)

Designed HVR-H2 sequence 1: LAR- 20
IDWDDDCKRYSPSLKSRL (SEQ ID NO:53)

Designed HVR-H2 sequence 2: 2:
LALIDWDDDCKRYSPSLKSRL (SEQ ID NO:54)

Designed HVR-H2 sequence 3: LALIDWDDDCKRYST- 25
SLKSRL (SEQ ID NO:55)

Designed HVR-H2 sequence 4: 4:
LALIDWDDDCKYYSPSLKSRL (SEQ ID NO:56)

Designed HVR-H2 sequence 5: LALID- 30
WADDKYYSPSLKSRL (SEQ ID NO:57)

Designed HVR-H2 sequence 6: LALIDWAGDKSYST-
SLKSRL (SEQ ID NO:58)

Designed HVR-H2 sequence 7: LAR- 35
IDWDDDCKYYSPSLKSRL (SEQ ID NO:59)

Designed HVR-H2 sequence 8: LARIDWDDDCKYYST-
SLKSRL (SEQ ID NO:60)

Designed HVR-H2 sequence 9: LARIDWDGDCKYYST- 35
SLKSRL (SEQ ID NO:61)

Designed HVR-H2 sequence 10: IGDIYHSG-
STYYSPSLKSRV (SEQ ID NO:62)

Designed HVR-H2 sequence 11: IGEIYHSG- 40
STYYSPSLKSRV (SEQ ID NO:63)

Designed HVR-H2 sequence 12: IGEIYYSG-
STYYSPSLKSRV (SEQ ID NO:64)

Designed HVR-H2 sequence 13: 13:
IGSIYHSGNTNYNPSLKSRV (SEQ ID NO:65) 45

Designed HVR-H2 sequence 14: IGEIYHSGN-
TYYNPSLKSRV (SEQ ID NO:66)

Designed HVR-H2 sequence 15: IGEIYHSG-
STYYNPSLKSRV (SEQ ID NO:67)

Designed HVR-H2 sequence 16: IGEIYYSG- 50
STYYNPSLKSRV (SEQ ID NO:68)

Designed HVR-H2 sequence 17: IGDIYHSGN-
TYYNPSLKSRV (SEQ ID NO:69)

Designed HVR-H2 sequence 18: IGDIYHSG- 55
STYYNPSLKSRV (SEQ ID NO:70)

Designed HVR-H2 sequence 19: VSAISGYGDTTYY-
ADSVKGRF (SEQ ID NO:71)

Designed HVR-H2 sequence 20: VSAISGYGGSTYY-
ADSVKGRF (SEQ ID NO:72)

Designed HVR-H2 sequence 21: VSAISGYGGTTYY- 60
ADSVKGRF (SEQ ID NO:73)

Designed HVR-H2 sequence 22: VSGISGAGDTTYY-
ADSVKGRF (SEQ ID NO:74)

Designed HVR-H2 sequence 23: VSGISGDGDTTYY-
ADSVKGRF (SEQ ID NO:75) 65

Designed HVR-H2 sequence 24: VSGISGDGGSTYY-
ADSVKGRF (SEQ ID NO:76)

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Designed HVR-H2 sequence 25: VSGISGYGDTTYY-
ADSVKGRF (SEQ ID NO:77)

Designed HVR-H2 sequence 26: VSGISGYGGTTYY-
ADSVKGRF (SEQ ID NO:78)

Designed HVR-H2 sequence 27: VSVISGDGDTTYY-
ADSVKGRF (SEQ ID NO:79)

Designed HVR-H2 sequence 28: VSVISGYGGSTYY-
ADSVKGRF (SEQ ID NO:80)

Designed HVR-H2 sequence 29: VSGISGDGSTTYY-
ADSVKGRF (SEQ ID NO:81)

Designed HVR-H2 sequence 30: VSGISGYGDTTYY-
ADSVKGRF (SEQ ID NO:82)

Designed HVR-H2 sequence 31: VSVISGSGGSTTYY-
ADSVKGRF (SEQ ID NO:83)

Designed HVR-H2 sequence 32: VSVISGYGSSTYY-
ADSVKGRF (SEQ ID NO:84)

Designed HVR-H2 sequence 33: VSVISGYGDTTYY-
ADSVKGRF (SEQ ID NO:85)

Designed HVR-H2 sequence 34: VSAISGYGDTTYY-
ADSVKGRF (SEQ ID NO:86)

Designed HVR-H2 sequence 35: VSSISGYGDTTYY-
ADSVKGRF (SEQ ID NO:87)

Designed HVR-H2 sequence 36: VSSISGYGGSTYY-
ADSVKGRF (SEQ ID NO:88)

Designed HVR-H2 sequence 37: VSSISGYGGTTYY-
ADSVKGRF (SEQ ID NO:89)

Designed HVR-H2 sequence 38: VSYISGAGDTTYY-
ADSVKGRF (SEQ ID NO:90)

Designed HVR-H2 sequence 39: VSSISGAGDTTYY-
ADSVKGRF (SEQ ID NO:91)

Designed HVR-H2 sequence 40: VSYISGAGGTTYY-
ADSVKGRF (SEQ ID NO:92)

Designed HVR-H2 sequence 41: VSYISGDGDTTYY-
ADSVKGRF (SEQ ID NO:93)

Designed HVR-H2 sequence 42: VSYISGDGGSTYY-
ADSVKGRF (SEQ ID NO:94)

Designed HVR-H2 sequence 43: VSYISGDGGTTYY-
ADSVKGRF (SEQ ID NO:95)

Designed HVR-H2 sequence 44: VSYISGSGDTTYY-
ADSVKGRF (SEQ ID NO:96)

Designed HVR-H2 sequence 45: VSSISGAGGSTYY-
ADSVKGRF (SEQ ID NO:97)

Designed HVR-H2 sequence 46: VSYISGYGDTTYY-
ADSVKGRF (SEQ ID NO:98)

Designed HVR-H2 sequence 47: VSYISGYGGTTYY-
ADSVKGRF (SEQ ID NO:99)

Designed HVR-H2 sequence 48: VSSISGAGGTTYY-
ADSVKGRF (SEQ ID NO:100)

Designed HVR-H2 sequence 49: VSSISGDGDTTYY-
ADSVKGRF (SEQ ID NO:101)

Designed HVR-H2 sequence 50: VSSISGDGGTTYY-
ADSVKGRF (SEQ ID NO:102)

Designed HVR-H2 sequence 51: VSSISGAGSSTYY-
ADSVKGRF (SEQ ID NO:103)

Designed HVR-H2 sequence 52: VSSISGAGSTTYY-
ADSVKGRF (SEQ ID NO:104)

Designed HVR-H2 sequence 53: VSSISGDGSSTYY-
ADSVKGRF (SEQ ID NO:105)

Designed HVR-H2 sequence 54: VSSISGDGSTTYY-
ADSVKGRF (SEQ ID NO:106)

Designed HVR-H2 sequence 55: VSSISGYGSSTYY-
ADSVKGRF (SEQ ID NO:107)

Designed HVR-H2 sequence 56: VSSISGYGDTTYY-
ADSVKGRF (SEQ ID NO:108)

Designed HVR-H2 sequence 57: IGWINPNRGDT-
KYAQKFQGRV (SEQ ID NO:109)

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Designed HVR-H2 sequence 58: IGVINPNRGDTNYAQKFQGRV (SEQ ID NO:110)
 Designed HVR-H2 sequence 59: IGVINPNRGGT-KYAQKFQGRV (SEQ ID NO:111)
 Designed HVR-H2 sequence 60: IGVINPNRGDTNYAQKFQGRV (SEQ ID NO: 112)
 Designed HVR-H2 sequence 61: IGVINPNRGST-KYAQKFQGRV (SEQ ID NO:113)
 Designed HVR-H2 sequence 62: IGVINPNRG-STNYAQKFQGRV (SEQ ID NO:114) 10
 Designed HVR-H2 sequence 63: IGRINPNFGDTNYAQKFQGRV (SEQ ID NO: 115)
 Designed HVR-H2 sequence 64: IGVINPNFGDTNYAQKFQGRV (SEQ ID NO:116) 15
 Designed HVR-H2 sequence 65: IGVINPNFGST-KYAQKFQGRV (SEQ ID NO: 117)
 Designed HVR-H2 sequence 66: IGVINPNFG-STNYAQKFQGRV (SEQ ID NO: 118)
 Designed HVR-H2 sequence 67: IGIINPNRGDT-KYAQKFQGRV (SEQ ID NO: 119) 20
 Designed HVR-H2 sequence 68: IGI-INPNRGDTNYAQKFQGRV (SEQ ID NO:120)
 Designed HVR-H2 sequence 69: IGI-INPNFGDTNYAQKFQGRV (SEQ ID NO:121) 25
 Designed HVR-H2 sequence 70: IGWISPSGGT-KYAQKFQGRV (SEQ ID NO:122)
 Designed HVR-H2 sequence 71: IGWISPSGGGTNYAQKFQGRV (SEQ ID NO:123)
 Designed HVR-H2 sequence 72: IGWISPSGGT- 30
 KYAQKFQGRV (SEQ ID NO:124)
 Designed HVR-H2 sequence 73: IGWISPSGGGTNYAQKFQGRV (SEQ ID NO:125)
 Designed HVR-H2 sequence 74: IGWIYPSGGT-KYAQKFQGRV (SEQ ID NO:126) 35
 Designed HVR-H2 sequence 75: IGWIYPSGGGTNYAQKFQGRV (SEQ ID NO:127)
 Designed HVR-H2 sequence 76: IGWISPSGG-STNYAQKFQGRV (SEQ ID NO:128)
 Designed HVR-H2 sequence 77: IGWISPSGGST-KYAQKFQGRV (SEQ ID NO:129) 40
 Designed HVR-H2 sequence 78: IGWISPSGG-STNYAQKFQGRV (SEQ ID NO:130)
 Designed HVR-H2 sequence 79: IGWISPSGGST-KYAQKFQGRV (SEQ ID NO:131) 45
 Designed HVR-H2 sequence 80: IGIYPSGGGTNYAQKFQGRV (SEQ ID NO:132)
 Designed HVR-H2 sequence 81: IGIISPSGGT-KYAQKFQGRV (SEQ ID NO:133)
 Designed HVR-H2 sequence 82: IGI- 50
 ISPSGGGTNYAQKFQGRV (SEQ ID NO134)
 Designed HVR-H2 sequence 83: IGIYPSGG-STNYAQKFQGRV (SEQ ID NO:135)
 Designed HVR-H2 sequence 84: VGRIK-SKTDGYTTEYAAPVKGRF (SEQ ID NO:136) 55
 Designed HVR-H2 sequence 85: VSAISGSGSTTYY-ADSVKGRF (SEQ ID NO:159)
 Designed HVR-H2 sequence 86: VSSISGSGDITTYY-ADSVKGRF (SEQ ID NO:160)
 Designed HVR-H2 sequence 87: VSSISGSGGSTYY- 60
 ADSVKGRF (SEQ ID NO:161)
 Designed HVR-H2 sequence 88: VSSISGSGGTTYY-ADSVKGRF (SEQ ID NO:162)
 Designed HVR-H2 sequence 89: VSSISGDGGSTYY- 65
 ADSVKGRF (SEQ ID NO:163)
 Designed HVR-H2 sequence 90: VSSISGSGSTTYY-ADSVKGRF (SEQ ID NO:164)

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Framework FW-H1 sequence: EVQLVESGG-GLVQPGGSLRLSCAASG (SEQ ID NO:165)
 Framework FW-H2 sequence: RQAPGKGLEW (SEQ ID NO:166)
 Framework FW-H3 sequence: TISSRDN SKNT-LYLQLNSLRAEDTAVYYC (SEQ ID NO:167)
 Framework FW-H4 sequence: WGQGTLVTVSS (SEQ ID NO: 168)
 Hit ID 4029—VH
 EVQLVESGGGLVQPGGSLRLS-CAASGYSITSGYHWGWRQAPGKGLEWVSYIS-GAGDTYYYADSVKGRFTIISRDNSKNT-LYLQLNSLRAEDTAVYYC (SEQ ID NO: 169)
 HIT ID 4029—VL
 DIQLTQSPSSLSASVGDRVTITCRASQSVDYFYGISF-LAWYQQKPGKAPKLLIYDASN-LETGVPSRFSGS GSGT DFTLTISSLQPEDFATYYCQQSYRTPLTFGQGTKVEIKR (SEQ ID NO: 170)
 Hit ID 7097—VH
 EVQLVESGGGLVQPGGSLRLSCAASGYSIS-SGHHDWWRQAPGKGLEWVSYISGAGDTYY-ADSVKGRFTIISRDNSKNTLYLQLNSLRAEDTAVYYCAREGSDAVLGDWFAYWGQGTLVTVSS (SEQ ID NO: 171)
 HIT ID 7097—VL
 DIQLTQSPSSLSASVGDRVTITCRASQGISSY-LAWYQQKPGKAPKLLIYDASN-LETGVPSRFSGS GSGT DFTLTISSLQPEDFATYYCQQSYSTPLTFGQGTKVEIKR (SEQ ID NO: 172)
 Hit ID 5906—VH
 EVQLVESGGGLVQPGGSLRLSCAASGYSIS-SGYHWNWIRQAPGKGLEWVSYISGAGDTYY-ADSVKGRFTIISRDNSKNTLYLQLNSLRAEDTAVYYCARDLGGYYYWGGRYFDYWGQGTLVTVSS (SEQ ID NO: 173)
 HIT ID 5906—VL
 DIQLTQSPSSLSASVGDRVTITCRASQSVDYFYGISF-LAWYQQKPGKAPKLLIYDASN-LETGVPSRFSGS GSGT DFTLTISSLQPEDFATYYCQQSYSTPLTFGQGTKVEIKR (SEQ ID NO: 174)
 Hit ID 7040—VH
 EVQLVESGGGLVQPGGSLRLSCAASGYSIS-SGYYWNWIRQAPGKGLEWIGWISPSGG-STNYAQKFQGRVTIISRDNSKNTLYLQLNSLRAEDTAVYYCARDLTTAGGF DYWGQGTLVTVSS (SEQ ID NO: 175)
 HIT ID 7040—VL
 DIQLTQSPSSLSASVGDRVTITCRASQGISSY-LAWYQQKPGKAPKLLIYDASN-LETGVPSRFSGS GSGT DFTLTISSLQPEDFATYYCQQSYSTPLTFGQGTKVEIKR (SEQ ID NO: 176)
 Hit ID 5924—VH
 EVQLVESGGGLVQPGGSLRLSCAASGYSIS-SGYHWGWRQAPGKGLEWIGIISPSGGST-KYAQKFQGRVTIISRDNSKNTLYLQLNSLRAEDTAVYYCARGAGVHYALDYWGQGTLVTVSS (SEQ ID NO: 177)
 HIT ID 5924—VL
 DIQLTQSPSSLSASVGDRVTITCRASQSVDYFYGISF-LAWYQQKPGKAPKLLIYDASN-

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LETGVPSRFSGSGSGTDFL TISSLPEDFA-
TYYCQQSYSTPLTFGQGTKEIKR (SEQ ID NO:
178)

Hit ID 4034—VH

EVQLVESGGGLVQPGGSLRLSCAASGYSIS-
SGHYWNWIRQAPGKGLEWVSSISGYGTTYY-
ADSVKGRFTI SRDNSKNTLYLQLNSLRAED-
TAVYYCARERYYGYSTDYAFDYWGQGTLTVSS
(SEQ ID NO: 179)

Hit ID 4034—VL

DIQLTQSPSSL-
SASVGDRVTITCSASSRVSHWFYWQQKPGKAP
KLLIYAASLQLSGVPSRSGSGSGTDFLT
SSLQPEDFATYFCLQGTHFPWTFGQGTLVKEIKR
(SEQ ID NO: 180)

Hit ID 6010—VH

EVQLVESGGGLVQPGGSLRLSCAASGYSIS-
SGHYWNWIRQAPGK-
GLEWIGWINPNRGDTNYAQKFQGRVT
ISRDNSKNTLYLQLNSLRAEDTAVYY-
CARDYYGDFDYWGQGTLTVSS (SEQ ID NO:
181)

Hit ID 6010—VL

DIQLTQSPSSLASAVGDRVTITCRASQSIS-
SYLNWYQQKPGKAPKLLIYDASN-
LETGVPSRSGSGSGTDFL TISSLPEDFA-
TYYCQHGYTPTLFGQGTLVKEIKR (SEQ ID NO:
182)

Hit ID 7183—VH

EVQLVESGGGLVQPGGSLRLSCAASGYSIS-
SGHYWNWIRQAPGKGLEWVSSISGYGDTYY-
ADSVKGRFTI SRDNSKNTLYLQLNSLRAED-
TAVYYCAREGSDTFLGDWFAYWGQGTLTVSS
(SEQ ID NO: 183)

Hit ID 7183—VL

DIQLTQSPSSLASAVGDRVTITCRASQSIS-
SYLNWYQQKPGKAPKLLIYDASNAT-
GIPSRSFGSGSGTDFLT ISSLQPEDFATYYCQQ-
SYSTPPTFGQGTLVKEIKR (SEQ ID NO: 184)

Hit ID 4036—VH

EVQLVESGGGLVQPGGSLRLSCAASGFLST-
SGVGVWIRQAPGKGLEWIGEIYHSG-
STYYSPSLKSRVTIS RDNSKNTLYLQLNSLRAE-
DTAVYYCARERYGSYYFDYWGQGTLTVSS
(SEQ ID NO: 185)

Hit ID 4036—VL

DIQLTQSPSSLASAVGDRVTITCRASQSIS-
CRASQSVDFYGKSLDWFYQQKPGKAPKLLIY-
DASSLESGVPSRSGSGSGT DFTLTISLQPEDFA-
TYYCQQYYRIPPTFGQGTLVKEIKR (SEQ ID NO:
186)

Hit ID 5115—VH

EVQLVESGGGLVQPGGSLRLSCAASGYSIS-
SGHYWGIRQAPGKGLEWIGEIYHSG-
STYYSPSLKSRVTIS RDNSKNTLYLQLNSLRAE-
DTAVYYCARESYYAFDYWGQGTLTVSS (SEQ
ID NO: 187)

Hit ID 5115—VL

DIQLTQSPSSLASAVGDRVTITCRASQSIS-
LAWYQQKPGKAPKLLI-
YAASLQLSGVPSRSGSGSGTDFL TISSLPED-
FATYYCQQYYTPTLFGQGTLVKEIKR (SEQ ID
NO: 188)

Hit ID 5404—VH

EVQLVESGGGLVQPGGSLRLSCAASGYSIS-
SGYHWAWIRQAPGKGLEWIGEIYHSG-

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STYYSPSLKSRVTISR DNSKNTLYLQLNSLRAE-
DTAVYYCARS PYYYYGVFDYWGQGTLTVSS
(SEQ ID NO: 189)

Hit ID 5404—VL

DIQLTQSPSSL-
SASVGDRVTITCSASSRVGSVWYQQKPGKAP
KLLIYDASNLETGVPSRSGSGSGTDFLT
ISSLQPEDFATYYCQQYTHDPVTFGQGTLVKEIKR
(SEQ ID NO: 190)

Hit ID 3757—VH

EVQLVESGGGLVQPGGSLRLSCAASGFTFTDY-
GIHWVRQAPGKGLEWIGWISPSGGGT-
KYAQKFQGRVTIS RDNSKNTLYLQLNSLRAED-
TAVYYCARHSYYGVGDFDYWGQGTLTVSS
(SEQ ID NO: 191)

Hit ID 3757—VL

DIQLTQSPSSLASAVGDRVTITCRASQSIS-
LAWYQQKPGKAPKLLIYDASN-
LETGVPSRSGSGSGTDFL TISSLPEDFA-
TYYCQQSYSTPLTFGQGTLVKEIKR (SEQ ID NO:
192)

Hit ID 5103—VH

EVQLVESGGGLVQPGGSLRLSCAASGFTFTDY-
GIHWVRQAPGKGLEWIGWISPSGGGT-
KYAQKFQGRVTIS RDNSKNTLYLQLNSLRAED-
TAVYYCARHSYYGVGDFDYWGQGTLTVSS
(SEQ ID NO: 193)

Hit ID 5103—VL

DIQLTQSPSSLASAVGDRVTITCRASQSIS-
LAWYQQKPGKAPKLLIYDASN-
LETGVPSRSGSGSGTDFL TISSLPEDFA-
TYYCQQSYSTPLTFGQGTLVKEIKR (SEQ ID NO:
194)

Hit ID 4027—VH

EVQLVESGGGLVQPGGSLRLSCAASGFTFTSY-
CAASGYSITSGHHNWIRQAPGK-
GLEWIGWISPSGGT KYAQKFQGRVTIS
SRDNSKNTLYLQLNSLRAEDTAVYY-
CARGFDGFHYWGQGTLTVSS (SEQ ID NO: 195)

Hit ID 4027—VL

DIQLTQSPSSLASAVGDRVTITCRASESVDYFYGIS-
FLPWYQQKPGKAPKLLIYDASNAT-
GIPSRSFGSGSGTD FTLTISLQPEDFATYYCQQ-
SYSWPWTFGQGTLVKEIKR (SEQ ID NO: 196)

VH in FIG. 1B

EVQLVESGGGLVQPGGSLRLSCAASGFTFTSY-
GIHWVRQAPGKGLEWVSGISGAGDTYY-
ADSVKGRFTIS RDNSKNTLYLQLNSLRAED-
TAVYYCARERDYDFDYWGQGTLTVSS (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)

$LAX_1X_2WX_3X_4DKX_5YSX_6SLKSRL$, 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 (SEQ ID NO:201)

Formula (V)

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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)

Formula (X)

VGRIX₁SKX₂X₃GX₄TTX₅YAAX₆VKGFR, 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)

VGRIX₁SKX₂X₃GX₄TTEYAAAX₅VKGFR, 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

CGTTTGTCTGTGCAGCTTCGG (SEQ ID NO:211)

Primer R_1999

CGAGGCCCTTACCCGGGGCCTGACG (SEQ ID NO:212)

Primer F_2003

CCGGGTAAGGGCCTCGAGTGG (SEQ ID NO:213)

Primer R_2003

GAGCACGTCGTTGAATTGTCGCGACTTATAG (SEQ ID NO:214)

Primer S1089

ACAACTAACAGCTTAAGAGCT-GAGACACTGCCGTCTATTATTG (SEQ ID NO:215)

Primer S1090

GAGGAGACGGTGACTAGTGTTCCTTGACCCCCA (SEQ ID NO:216)

Primer F_2898

TACTTATGTAGGCATGGTCACCATCACCTGC (SEQ ID NO:217)

Primer R_2898

CGGAGCTTTCCTGGTTCTGTTGATAC (SEQ ID NO:218)

Primer F_2013

GAAACCAGGAAAAGCTCCGAAG (SEQ ID NO:219)

Primer R_2013

CGTCCCGGAACCGGATCCAGAGAAAGCGAG (SEQ ID NO:220)

Primer F2929

ACCATCAGCAGTCTGCAGCCGGAA-GACTTCGCAAC (SEQ ID NO:221)

Primer R2929

GATCTCACCTTGGTACCCGTCCGAA (SEQ ID NO:222)

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HVR-H3 sequence 1: ARDLGGYYGWGRYFDY (SEQ ID NO:223)

HVR-H3 sequence 2: ARDLTAGGF DY (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: ARGGGGYYYFDV (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: ARGGSDTVLGDWFAY (SEQ ID NO:241)

HVR-H3 sequence 20: ARGGVGPFDI (SEQ ID NO:242)

HVR-H3 sequence 21: ARGGYGGYLDV (SEQ ID NO:243)

HVR-H3 sequence 22: ARGLSSGYFDY (SEQ ID NO:244)

HVR-H3 sequence 23: ARGSWYFDV (SEQ ID NO:245)

HVR-H3 sequence 24: ARGTRGLDY (SEQ ID NO:246)

HVR-H3 sequence 25: ARGYSDYFDY (SEQ ID NO:247)

HVR-H3 sequence 26: ARGYYYGRAFDY (SEQ ID NO:248)

HVR-H3 sequence 27: ARHSYYVGDFDY (SEQ ID NO:249)

HVR-H3 sequence 28: ARLFEGFPY (SEQ ID NO:250)

HVR-H3 sequence 29: ARLYDYFAY (SEQ ID NO:251)

HVR-H3 sequence 30: ARSGYYALDY (SEQ ID NO:252)

HVR-H3 sequence 31: ARSPYYYGVFDY (SEQ ID NO:253)

HVR-H3 sequence 32: ARSYVYFDY (SEQ ID NO:254)

HVR-H3 sequence 33: ARDGLGLRGVYYYYYGLDV (SEQ ID NO:255)

HVR-H3 sequence 34: ARVGESGGIESPYYYYGLDV (SEQ ID NO:256)

HVR-L1 sequence 1: RASESVDFYGISFLP (SEQ ID NO:257)

HVR-L1 sequence 2: RASQSVDFYGISFLA (SEQ ID NO:258)

HVR-L1 sequence 3: RASQSVDFYGKSFLD (SEQ ID NO:259)

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HVR-L1 sequence 4: SASSRVRGSVY (SEQ ID NO:260)
 HVR-L1 sequence 5: SASSRVSHVF (SEQ ID NO:261)
 HVR-L1 sequence 6: RASQGISSYLA (SEQ ID NO:262)
 HVR-L1 sequence 7: RASQSVSSYLA (SEQ ID NO:263)
 HVR-L1 sequence 8: RASQSISSYLN (SEQ ID NO:264)
 HVR-L3 sequence 1: FCLQGTHFPWT (SEQ ID NO:265)
 HVR-L3 sequence 2: YCQQSYRTPFT (SEQ ID NO:266)
 HVR-L3 sequence 3: YCQQSYSWPWT (SEQ ID NO:267)

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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)

SEQUENCE LISTING

```
Sequence total quantity: 274
SEQ ID NO: 1      moltype = AA  length = 11
FEATURE
REGION
source
SEQUENCE: 1
PTFTDYGIAHW V

SEQ ID NO: 2      moltype = AA  length = 11
FEATURE
REGION
source
SEQUENCE: 2
PTFTGYAIHW V

SEQ ID NO: 3      moltype = AA  length = 11
FEATURE
REGION
source
SEQUENCE: 3
PTFTNYGIHW V

SEQ ID NO: 4      moltype = AA  length = 11
FEATURE
REGION
source
SEQUENCE: 4
YTFSDYAIHW V

SEQ ID NO: 5      moltype = AA  length = 11
FEATURE
REGION
source
SEQUENCE: 5
YTFSDYGIHW V

SEQ ID NO: 6      moltype = AA  length = 11
FEATURE
REGION
source
SEQUENCE: 6
YTFSGYAIHW V

SEQ ID NO: 7      moltype = AA  length = 11
```

11

11

11

11

11

11

11

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FEATURE REGION	Location/Qualifiers 1..11 note = Designed HVR-H1 sequence 7
source	1..11 mol_type = protein organism = synthetic construct
SEQUENCE: 7 YTFSGYGIHW V	
SEQ ID NO: 8	11
FEATURE REGION	moltype = AA length = 11 Location/Qualifiers 1..11 note = Designed HVR-H1 sequence 8
source	1..11 mol_type = protein organism = synthetic construct
SEQUENCE: 8 YTFSNYGIHW V	
SEQ ID NO: 9	11
FEATURE REGION	moltype = AA length = 11 Location/Qualifiers 1..11 note = Designed HVR-H1 sequence 9
source	1..11 mol_type = protein organism = synthetic construct
SEQUENCE: 9 YTFSSYGIHW V	
SEQ ID NO: 10	11
FEATURE REGION	moltype = AA length = 11 Location/Qualifiers 1..11 note = Designed HVR-H1 sequence 10
source	1..11 mol_type = protein organism = synthetic construct
SEQUENCE: 10 YTFSGYWIHW V	
SEQ ID NO: 11	11
FEATURE REGION	moltype = AA length = 11 Location/Qualifiers 1..11 note = Designed HVR-H1 sequence 11
source	1..11 mol_type = protein organism = synthetic construct
SEQUENCE: 11 YTFSNYWIHW V	
SEQ ID NO: 12	11
FEATURE REGION	moltype = AA length = 11 Location/Qualifiers 1..11 note = Designed HVR-H1 sequence 12
source	1..11 mol_type = protein organism = synthetic construct
SEQUENCE: 12 FTFSGYWIHW V	
SEQ ID NO: 13	11
FEATURE REGION	moltype = AA length = 11 Location/Qualifiers 1..11 note = Designed HVR-H1 sequence 13
source	1..11 mol_type = protein organism = synthetic construct
SEQUENCE: 13 FTFSNYWIHW V	
SEQ ID NO: 14	11
FEATURE REGION	moltype = AA length = 11 Location/Qualifiers 1..11 note = Designed HVR-H1 sequence 14
source	1..11 mol_type = protein organism = synthetic construct
SEQUENCE: 14 YTFSDYWIHW V	

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SEQ ID NO: 15 FEATURE REGION source SEQUENCE: 15 YSISSLGHWA WI	moltype = AA length = 12 Location/Qualifiers 1..12 note = Designed HVR-H1 sequence 15 1..12 mol_type = protein organism = synthetic construct	12
SEQ ID NO: 16 FEATURE REGION source SEQUENCE: 16 YSISSLGHYWN WI	moltype = AA length = 12 Location/Qualifiers 1..12 note = Designed HVR-H1 sequence 16 1..12 mol_type = protein organism = synthetic construct	12
SEQ ID NO: 17 FEATURE REGION source SEQUENCE: 17 YSISSLGHYWS WI	moltype = AA length = 12 Location/Qualifiers 1..12 note = Designed HVR-H1 sequence 17 1..12 mol_type = protein organism = synthetic construct	12
SEQ ID NO: 18 FEATURE REGION source SEQUENCE: 18 YSISSLGHYWT WI	moltype = AA length = 12 Location/Qualifiers 1..12 note = Designed HVR-H1 sequence 18 1..12 mol_type = protein organism = synthetic construct	12
SEQ ID NO: 19 FEATURE REGION source SEQUENCE: 19 YSISSLGYHWA WI	moltype = AA length = 12 Location/Qualifiers 1..12 note = Designed HVR-H1 sequence 19 1..12 mol_type = protein organism = synthetic construct	12
SEQ ID NO: 20 FEATURE REGION source SEQUENCE: 20 YSISSLGYHWI WI	moltype = AA length = 12 Location/Qualifiers 1..12 note = Designed HVR-H1 sequence 20 1..12 mol_type = protein organism = synthetic construct	12
SEQ ID NO: 21 FEATURE REGION source SEQUENCE: 21 YSISSLGYHWG WI	moltype = AA length = 12 Location/Qualifiers 1..12 note = Designed HVR-H1 sequence 21 1..12 mol_type = protein organism = synthetic construct	12
SEQ ID NO: 22 FEATURE REGION source SEQUENCE: 22 YSISSLGYHWN WI	moltype = AA length = 12 Location/Qualifiers 1..12 note = Designed HVR-H1 sequence 22 1..12 mol_type = protein organism = synthetic construct	12

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SEQ ID NO: 23 FEATURE REGION source SEQUENCE: 23 YSISSLGYHWS WI	moltype = AA length = 12 Location/Qualifiers 1..12 note = Designed HVR-H1 sequence 23 1..12 mol_type = protein organism = synthetic construct	
		12
SEQ ID NO: 24 FEATURE REGION source SEQUENCE: 24 YSISSLGHHD WI	moltype = AA length = 12 Location/Qualifiers 1..12 note = Designed HVR-H1 sequence 24 1..12 mol_type = protein organism = synthetic construct	
		12
SEQ ID NO: 25 FEATURE REGION source SEQUENCE: 25 YSISSLGYWD WI	moltype = AA length = 12 Location/Qualifiers 1..12 note = Designed HVR-H1 sequence 25 1..12 mol_type = protein organism = synthetic construct	
		12
SEQ ID NO: 26 FEATURE REGION source SEQUENCE: 26 YSISSLGYWN WI	moltype = AA length = 12 Location/Qualifiers 1..12 note = Designed HVR-H1 sequence 26 1..12 mol_type = protein organism = synthetic construct	
		12
SEQ ID NO: 27 FEATURE REGION source SEQUENCE: 27 YSISSLGYWT WI	moltype = AA length = 12 Location/Qualifiers 1..12 note = Designed HVR-H1 sequence 27 1..12 mol_type = protein organism = synthetic construct	
		12
SEQ ID NO: 28 FEATURE REGION source SEQUENCE: 28 YSITSGHHWA WI	moltype = AA length = 12 Location/Qualifiers 1..12 note = Designed HVR-H1 sequence 28 1..12 mol_type = protein organism = synthetic construct	
		12
SEQ ID NO: 29 FEATURE REGION source SEQUENCE: 29 YSITSGHHWD WI	moltype = AA length = 12 Location/Qualifiers 1..12 note = Designed HVR-H1 sequence 29 1..12 mol_type = protein organism = synthetic construct	
		12
SEQ ID NO: 30 FEATURE REGION source SEQUENCE: 30	moltype = AA length = 12 Location/Qualifiers 1..12 note = Designed HVR-H1 sequence 30 1..12 mol_type = protein organism = synthetic construct	

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YSITSGHHWG WI	12
SEQ ID NO: 31	moltype = AA length = 12
FEATURE	Location/Qualifiers
REGION	1..12
source	note = Designed HVR-H1 sequence 31
SEQUENCE: 31	1..12
YSITSGHHWN WI	mol_type = protein
	organism = synthetic construct
SEQ ID NO: 32	12
FEATURE	moltype = AA length = 12
REGION	Location/Qualifiers
source	1..12
SEQUENCE: 32	note = Designed HVR-H1 sequence 32
YSITSGHHWS WI	1..12
SEQ ID NO: 33	mol_type = protein
FEATURE	organism = synthetic construct
REGION	1..12
source	note = Designed HVR-H1 sequence 33
SEQUENCE: 33	1..12
YSISSGHHWG WI	moltype = AA length = 12
	Location/Qualifiers
SEQ ID NO: 34	1..12
FEATURE	note = Designed HVR-H1 sequence 34
REGION	1..12
source	mol_type = protein
SEQUENCE: 34	organism = synthetic construct
YSITSGHYWA WI	12
SEQ ID NO: 35	moltype = AA length = 12
FEATURE	Location/Qualifiers
REGION	1..12
source	note = Designed HVR-H1 sequence 35
SEQUENCE: 35	1..12
YSITSGHYWD WI	mol_type = protein
	organism = synthetic construct
SEQ ID NO: 36	12
FEATURE	moltype = AA length = 12
REGION	Location/Qualifiers
source	1..12
SEQUENCE: 36	note = Designed HVR-H1 sequence 36
YSITSGHYWG WI	1..12
SEQ ID NO: 37	mol_type = protein
FEATURE	organism = synthetic construct
REGION	1..12
source	note = Designed HVR-H1 sequence 37
SEQUENCE: 37	1..12
YSITSGHYWN WI	moltype = AA length = 12
	Location/Qualifiers
SEQ ID NO: 38	1..12
FEATURE	note = Designed HVR-H1 sequence 38
REGION	1..12
source	mol_type = protein
	organism = synthetic construct

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SEQUENCE: 38 YSITSGHYWS WI	12
SEQ ID NO: 39 FEATURE REGION source	moltype = AA length = 12 Location/Qualifiers 1..12 note = Designed HVR-H1 sequence 39 1..12 mol_type = protein organism = synthetic construct
SEQUENCE: 39 YSITSGYHWA WI	12
SEQ ID NO: 40 FEATURE REGION source	moltype = AA length = 12 Location/Qualifiers 1..12 note = Designed HVR-H1 sequence 40 1..12 mol_type = protein organism = synthetic construct
SEQUENCE: 40 YSITSGYHWG WI	12
SEQ ID NO: 41 FEATURE REGION source	moltype = AA length = 12 Location/Qualifiers 1..12 note = Designed HVR-H1 sequence 41 1..12 mol_type = protein organism = synthetic construct
SEQUENCE: 41 YSISSGGHHWN WI	12
SEQ ID NO: 42 FEATURE REGION source	moltype = AA length = 12 Location/Qualifiers 1..12 note = Designed HVR-H1 sequence 42 1..12 mol_type = protein organism = synthetic construct
SEQUENCE: 42 YSITSGYHWN WI	12
SEQ ID NO: 43 FEATURE REGION source	moltype = AA length = 12 Location/Qualifiers 1..12 note = Designed HVR-H1 sequence 43 1..12 mol_type = protein organism = synthetic construct
SEQUENCE: 43 YSITSGYHWS WI	12
SEQ ID NO: 44 FEATURE REGION source	moltype = AA length = 12 Location/Qualifiers 1..12 note = Designed HVR-H1 sequence 44 1..12 mol_type = protein organism = synthetic construct
SEQUENCE: 44 YSITSGYYWD WI	12
SEQ ID NO: 45 FEATURE REGION source	moltype = AA length = 12 Location/Qualifiers 1..12 note = Designed HVR-H1 sequence 45 1..12 mol_type = protein organism = synthetic construct
SEQUENCE: 45 YSISSGGHHWT WI	12
SEQ ID NO: 46 FEATURE REGION source	moltype = AA length = 12 Location/Qualifiers 1..12 note = Designed HVR-H1 sequence 46 1..12 mol_type = protein

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SEQUENCE: 46 YSISSLGHYWD WI	organism = synthetic construct	
SEQ ID NO: 47 FEATURE REGION	moltype = AA length = 13 Location/Qualifiers 1..13	12
source	note = Designed HVR-H1 sequence 47 1..13 mol_type = protein organism = synthetic construct	
SEQUENCE: 47 FSLSTSGVAV SWI		13
SEQ ID NO: 48 FEATURE REGION	moltype = AA length = 13 Location/Qualifiers 1..13	
source	note = Designed HVR-H1 sequence 48 1..13 mol_type = protein organism = synthetic construct	
SEQUENCE: 48 FSLSTGGVAV GWI		13
SEQ ID NO: 49 FEATURE REGION	moltype = AA length = 13 Location/Qualifiers 1..13	
source	note = Designed HVR-H1 sequence 49 1..13 mol_type = protein organism = synthetic construct	
SEQUENCE: 49 FSLSTGGVAV SWI		13
SEQ ID NO: 50 FEATURE REGION	moltype = AA length = 13 Location/Qualifiers 1..13	
source	note = Designed HVR-H1 sequence 50 1..13 mol_type = protein organism = synthetic construct	
SEQUENCE: 50 FSLSTGGVGV AWI		13
SEQ ID NO: 51 FEATURE REGION	moltype = AA length = 13 Location/Qualifiers 1..13	
source	note = Designed HVR-H1 sequence 51 1..13 mol_type = protein organism = synthetic construct	
SEQUENCE: 51 FSLSTGGVGV SWI		13
SEQ ID NO: 52 FEATURE REGION	moltype = AA length = 13 Location/Qualifiers 1..13	
source	note = Designed HVR-H1 sequence 52 1..13 mol_type = protein organism = synthetic construct	
SEQUENCE: 52 FSLSTSGVAV AWI		13
SEQ ID NO: 53 FEATURE REGION	moltype = AA length = 20 Location/Qualifiers 1..20	
source	note = Designed HVR-H2 sequence 1 1..20 mol_type = protein organism = synthetic construct	
SEQUENCE: 53 LARIDWDDDK RYSPSLKSRL		20
SEQ ID NO: 54 FEATURE REGION	moltype = AA length = 20 Location/Qualifiers 1..20	
source	note = Designed HVR-H2 sequence 2 1..20	

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mol_type = protein
organism = synthetic construct
SEQUENCE: 54
LALIDWDDDK RYSPSLKSRL                                20

SEQ ID NO: 55      moltype = AA length = 20
FEATURE          Location/Qualifiers
REGION           1..20
source            note = Designed HVR-H2 sequence 3
                  1..20
                  mol_type = protein
                  organism = synthetic construct
SEQUENCE: 55
LALIDWDDDK YYSTSLKSRL                                20

SEQ ID NO: 56      moltype = AA length = 20
FEATURE          Location/Qualifiers
REGION           1..20
source            note = Designed HVR-H2 sequence 4
                  1..20
                  mol_type = protein
                  organism = synthetic construct
SEQUENCE: 56
LALIDWDDDK YYSPSLKSRL                                20

SEQ ID NO: 57      moltype = AA length = 20
FEATURE          Location/Qualifiers
REGION           1..20
source            note = Designed HVR-H2 sequence 5
                  1..20
                  mol_type = protein
                  organism = synthetic construct
SEQUENCE: 57
LALIDWAGDK YYSTSLKSRL                                20

SEQ ID NO: 58      moltype = AA length = 20
FEATURE          Location/Qualifiers
REGION           1..20
source            note = Designed HVR-H2 sequence 6
                  1..20
                  mol_type = protein
                  organism = synthetic construct
SEQUENCE: 58
LALIDWAGDK YYSPSLKSRL                                20

SEQ ID NO: 59      moltype = AA length = 20
FEATURE          Location/Qualifiers
REGION           1..20
source            note = Designed HVR-H2 sequence 7
                  1..20
                  mol_type = protein
                  organism = synthetic construct
SEQUENCE: 59
LARIDWDDDK YYSTSLKSRL                                20

SEQ ID NO: 60      moltype = AA length = 20
FEATURE          Location/Qualifiers
REGION           1..20
source            note = Designed HVR-H2 sequence 8
                  1..20
                  mol_type = protein
                  organism = synthetic construct
SEQUENCE: 60
LARIDWDDDK YYSTSLKSRL                                20

SEQ ID NO: 61      moltype = AA length = 20
FEATURE          Location/Qualifiers
REGION           1..20
source            note = Designed HVR-H2 sequence 9
                  1..20
                  mol_type = protein
                  organism = synthetic construct
SEQUENCE: 61
LARIDWDGDK YYSTSLKSRL                                20

SEQ ID NO: 62      moltype = AA length = 20
FEATURE          Location/Qualifiers
REGION           1..20
source            note = Designed HVR-H2 sequence 10

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source          1..20
               mol_type = protein
               organism = synthetic construct
SEQUENCE: 62
IGDIYHSGST YYSPSLKSRV                                20

SEQ ID NO: 63      moltype = AA  length = 20
FEATURE          Location/Qualifiers
REGION           1..20
note = Designed HVR-H2 sequence 11
source          1..20
               mol_type = protein
               organism = synthetic construct
SEQUENCE: 63
IGEIYHSGST YYSPSLKSRV                                20

SEQ ID NO: 64      moltype = AA  length = 20
FEATURE          Location/Qualifiers
REGION           1..20
note = Designed HVR-H2 sequence 12
source          1..20
               mol_type = protein
               organism = synthetic construct
SEQUENCE: 64
IGEIYYSGST YYSPSLKSRV                                20

SEQ ID NO: 65      moltype = AA  length = 20
FEATURE          Location/Qualifiers
REGION           1..20
note = Designed HVR-H2 sequence 13
source          1..20
               mol_type = protein
               organism = synthetic construct
SEQUENCE: 65
IGSIYHSGNT YYNPSLKSRV                                20

SEQ ID NO: 66      moltype = AA  length = 20
FEATURE          Location/Qualifiers
REGION           1..20
note = Designed HVR-H2 sequence 14
source          1..20
               mol_type = protein
               organism = synthetic construct
SEQUENCE: 66
IGEIYHSGNT YYNPSLKSRV                                20

SEQ ID NO: 67      moltype = AA  length = 20
FEATURE          Location/Qualifiers
REGION           1..20
note = Designed HVR-H2 sequence 15
source          1..20
               mol_type = protein
               organism = synthetic construct
SEQUENCE: 67
IGEIYHSGST YYNPSLKSRV                                20

SEQ ID NO: 68      moltype = AA  length = 20
FEATURE          Location/Qualifiers
REGION           1..20
note = Designed HVR-H2 sequence 16
source          1..20
               mol_type = protein
               organism = synthetic construct
SEQUENCE: 68
IGEIYYSGST YYNPSLKSRV                                20

SEQ ID NO: 69      moltype = AA  length = 20
FEATURE          Location/Qualifiers
REGION           1..20
note = Designed HVR-H2 sequence 17
source          1..20
               mol_type = protein
               organism = synthetic construct
SEQUENCE: 69
IGDIYHSGNT YYNPSLKSRV                                20

SEQ ID NO: 70      moltype = AA  length = 20
FEATURE          Location/Qualifiers
REGION           1..20

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source          note = Designed HVR-H2 sequence 18
               1..20
               mol_type = protein
               organism = synthetic construct
SEQUENCE: 70
IGDIYHSGST YYNPSLKSRY                                         20

SEQ ID NO: 71      moltype = AA  length = 21
FEATURE          Location/Qualifiers
REGION           1..21
note = Designed HVR-H2 sequence 19
source          1..21
mol_type = protein
organism = synthetic construct
SEQUENCE: 71
VSAISGYGDT TYYADSVKGR F                                         21

SEQ ID NO: 72      moltype = AA  length = 21
FEATURE          Location/Qualifiers
REGION           1..21
note = Designed HVR-H2 sequence 20
source          1..21
mol_type = protein
organism = synthetic construct
SEQUENCE: 72
VSAISGYGGS TYYADSVKGR F                                         21

SEQ ID NO: 73      moltype = AA  length = 21
FEATURE          Location/Qualifiers
REGION           1..21
note = Designed HVR-H2 sequence 21
source          1..21
mol_type = protein
organism = synthetic construct
SEQUENCE: 73
VSAISGYGGT TYYADSVKGR F                                         21

SEQ ID NO: 74      moltype = AA  length = 21
FEATURE          Location/Qualifiers
REGION           1..21
note = Designed HVR-H2 sequence 22
source          1..21
mol_type = protein
organism = synthetic construct
SEQUENCE: 74
VSGISGAGDT TYYADSVKGR F                                         21

SEQ ID NO: 75      moltype = AA  length = 21
FEATURE          Location/Qualifiers
REGION           1..21
note = Designed HVR-H2 sequence 23
source          1..21
mol_type = protein
organism = synthetic construct
SEQUENCE: 75
VSGISGDGDT TYYADSVKGR F                                         21

SEQ ID NO: 76      moltype = AA  length = 21
FEATURE          Location/Qualifiers
REGION           1..21
note = Designed HVR-H2 sequence 24
source          1..21
mol_type = protein
organism = synthetic construct
SEQUENCE: 76
VSGISGDDGS TYYADSVKGR F                                         21

SEQ ID NO: 77      moltype = AA  length = 21
FEATURE          Location/Qualifiers
REGION           1..21
note = Designed HVR-H2 sequence 25
source          1..21
mol_type = protein
organism = synthetic construct
SEQUENCE: 77
VSGISGYGDT TYYADSVKGR F                                         21

SEQ ID NO: 78      moltype = AA  length = 21
FEATURE          Location/Qualifiers

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REGION          1..21
source          note = Designed HVR-H2 sequence 26
                1..21
                mol_type = protein
                organism = synthetic construct
SEQUENCE: 78
VSGISGYGGT TYYADSVKGR F                                21

SEQ ID NO: 79      moltype = AA length = 21
FEATURE          Location/Qualifiers
REGION           1..21
                note = Designed HVR-H2 sequence 27
source            1..21
                mol_type = protein
                organism = synthetic construct
SEQUENCE: 79
VSVISGDDGT TYYADSVKGR F                                21

SEQ ID NO: 80      moltype = AA length = 21
FEATURE          Location/Qualifiers
REGION           1..21
                note = Designed HVR-H2 sequence 28
source            1..21
                mol_type = protein
                organism = synthetic construct
SEQUENCE: 80
VSVISGYGGS TYYADSVKGR F                                21

SEQ ID NO: 81      moltype = AA length = 21
FEATURE          Location/Qualifiers
REGION           1..21
                note = Designed HVR-H2 sequence 29
source            1..21
                mol_type = protein
                organism = synthetic construct
SEQUENCE: 81
VSGISGDGST TYYADSVKGR F                                21

SEQ ID NO: 82      moltype = AA length = 21
FEATURE          Location/Qualifiers
REGION           1..21
                note = Designed HVR-H2 sequence 30
source            1..21
                mol_type = protein
                organism = synthetic construct
SEQUENCE: 82
VSGISGYGST TYYADSVKGR F                                21

SEQ ID NO: 83      moltype = AA length = 21
FEATURE          Location/Qualifiers
REGION           1..21
                note = Designed HVR-H2 sequence 31
source            1..21
                mol_type = protein
                organism = synthetic construct
SEQUENCE: 83
VSVISGSGST TYYADSVKGR F                                21

SEQ ID NO: 84      moltype = AA length = 21
FEATURE          Location/Qualifiers
REGION           1..21
                note = Designed HVR-H2 sequence 32
source            1..21
                mol_type = protein
                organism = synthetic construct
SEQUENCE: 84
VSVISGYGSS TYYADSVKGR F                                21

SEQ ID NO: 85      moltype = AA length = 21
FEATURE          Location/Qualifiers
REGION           1..21
                note = Designed HVR-H2 sequence 33
source            1..21
                mol_type = protein
                organism = synthetic construct
SEQUENCE: 85
VSVISGYGST TYYADSVKGR F                                21

SEQ ID NO: 86      moltype = AA length = 21

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FEATURE Location/Qualifiers
 REGION 1..21
 note = Designed HVR-H2 sequence 34
 source 1..21
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 86
 VSAISGYGST TYYADSVKGR F 21

SEQ ID NO: 87 moltype = AA length = 21
 FEATURE Location/Qualifiers
 REGION 1..21
 note = Designed HVR-H2 sequence 35
 source 1..21
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 87
 VSSISGYGDT TYYADSVKGR F 21

SEQ ID NO: 88 moltype = AA length = 21
 FEATURE Location/Qualifiers
 REGION 1..21
 note = Designed HVR-H2 sequence 36
 source 1..21
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 88
 VSSISGYGGS TYYADSVKGR F 21

SEQ ID NO: 89 moltype = AA length = 21
 FEATURE Location/Qualifiers
 REGION 1..21
 note = Designed HVR-H2 sequence 37
 source 1..21
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 89
 VSSISGYGGT TYYADSVKGR F 21

SEQ ID NO: 90 moltype = AA length = 21
 FEATURE Location/Qualifiers
 REGION 1..21
 note = Designed HVR-H2 sequence 38
 source 1..21
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 90
 VSYISGAGDT TYYADSVKGR F 21

SEQ ID NO: 91 moltype = AA length = 21
 FEATURE Location/Qualifiers
 REGION 1..21
 note = Designed HVR-H2 sequence 39
 source 1..21
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 91
 VSSISGAGDT TYYADSVKGR F 21

SEQ ID NO: 92 moltype = AA length = 21
 FEATURE Location/Qualifiers
 REGION 1..21
 note = Designed HVR-H2 sequence 40
 source 1..21
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 92
 VSYISGAGGT TYYADSVKGR F 21

SEQ ID NO: 93 moltype = AA length = 21
 FEATURE Location/Qualifiers
 REGION 1..21
 note = Designed HVR-H2 sequence 41
 source 1..21
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 93
 VSYISGDGDT TYYADSVKGR F 21

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SEQ ID NO: 94      moltype = AA  length = 21
FEATURE          Location/Qualifiers
REGION           1..21
source            note = Designed HVR-H2 sequence 42
                  1..21
                  mol_type = protein
                  organism = synthetic construct
SEQUENCE: 94      VSYISGDDGS TYYADSVKGR F               21

SEQ ID NO: 95      moltype = AA  length = 21
FEATURE          Location/Qualifiers
REGION           1..21
source            note = Designed HVR-H2 sequence 43
                  1..21
                  mol_type = protein
                  organism = synthetic construct
SEQUENCE: 95      VSYISGDDGT TYYADSVKGR F              21

SEQ ID NO: 96      moltype = AA  length = 21
FEATURE          Location/Qualifiers
REGION           1..21
source            note = Designed HVR-H2 sequence 44
                  1..21
                  mol_type = protein
                  organism = synthetic construct
SEQUENCE: 96      VSYISGSGDT TYYADSVKGR F              21

SEQ ID NO: 97      moltype = AA  length = 21
FEATURE          Location/Qualifiers
REGION           1..21
source            note = Designed HVR-H2 sequence 45
                  1..21
                  mol_type = protein
                  organism = synthetic construct
SEQUENCE: 97      VSSISGAGGS TYYADSVKGR F               21

SEQ ID NO: 98      moltype = AA  length = 21
FEATURE          Location/Qualifiers
REGION           1..21
source            note = Designed HVR-H2 sequence 46
                  1..21
                  mol_type = protein
                  organism = synthetic construct
SEQUENCE: 98      VSYISGYGDT TYYADSVKGR F               21

SEQ ID NO: 99      moltype = AA  length = 21
FEATURE          Location/Qualifiers
REGION           1..21
source            note = Designed HVR-H2 sequence 47
                  1..21
                  mol_type = protein
                  organism = synthetic construct
SEQUENCE: 99      VSYISGYGGT TYYADSVKGR F               21

SEQ ID NO: 100     moltype = AA  length = 21
FEATURE          Location/Qualifiers
REGION           1..21
source            note = Designed HVR-H2 sequence 48
                  1..21
                  mol_type = protein
                  organism = synthetic construct
SEQUENCE: 100     VSSISGAGGT TYYADSVKGR F               21

SEQ ID NO: 101     moltype = AA  length = 21
FEATURE          Location/Qualifiers
REGION           1..21
source            note = Designed HVR-H2 sequence 49
                  1..21
                  mol_type = protein
                  organism = synthetic construct
SEQUENCE: 101     VSSISGDDGT TYYADSVKGR F              21

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SEQ ID NO: 102      moltype = AA length = 21
FEATURE          Location/Qualifiers
REGION           1..21
source            note = Designed HVR-H2 sequence 50
                  1..21
                  mol_type = protein
                  organism = synthetic construct
SEQUENCE: 102
VSSISGDGGT TYYADSVKGR F                                21

SEQ ID NO: 103      moltype = AA length = 21
FEATURE          Location/Qualifiers
REGION           1..21
source            note = Designed HVR-H2 sequence 51
                  1..21
                  mol_type = protein
                  organism = synthetic construct
SEQUENCE: 103
VSSISGAGSS TYYADSVKGR F                                21

SEQ ID NO: 104      moltype = AA length = 21
FEATURE          Location/Qualifiers
REGION           1..21
source            note = Designed HVR-H2 sequence 52
                  1..21
                  mol_type = protein
                  organism = synthetic construct
SEQUENCE: 104
VSSISGAGST TYYADSVKGR F                                21

SEQ ID NO: 105      moltype = AA length = 21
FEATURE          Location/Qualifiers
REGION           1..21
source            note = Designed HVR-H2 sequence 53
                  1..21
                  mol_type = protein
                  organism = synthetic construct
SEQUENCE: 105
VSSISGDGSS TYYADSVKGR F                                21

SEQ ID NO: 106      moltype = AA length = 21
FEATURE          Location/Qualifiers
REGION           1..21
source            note = Designed HVR-H2 sequence 54
                  1..21
                  mol_type = protein
                  organism = synthetic construct
SEQUENCE: 106
VSSISGDGST TYYADSVKGR F                                21

SEQ ID NO: 107      moltype = AA length = 21
FEATURE          Location/Qualifiers
REGION           1..21
source            note = Designed HVR-H2 sequence 55
                  1..21
                  mol_type = protein
                  organism = synthetic construct
SEQUENCE: 107
VSSISGYGSS TYYADSVKGR F                                21

SEQ ID NO: 108      moltype = AA length = 21
FEATURE          Location/Qualifiers
REGION           1..21
source            note = Designed HVR-H2 sequence 56
                  1..21
                  mol_type = protein
                  organism = synthetic construct
SEQUENCE: 108
VSSISGYGST TYYADSVKGR F                                21

SEQ ID NO: 109      moltype = AA length = 21
FEATURE          Location/Qualifiers
REGION           1..21
source            note = Designed HVR-H2 sequence 57
                  1..21
                  mol_type = protein
                  organism = synthetic construct
SEQUENCE: 109

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IGWINPNRGD TKYAQKFQGR V

21

SEQ ID NO: 110 moltype = AA length = 21
 FEATURE Location/Qualifiers
 REGION 1..21
 note = Designed HVR-H2 sequence 58
 source 1..21
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 110
 IGWINPNRGD TNYAQKFQGR V

21

SEQ ID NO: 111 moltype = AA length = 21
 FEATURE Location/Qualifiers
 REGION 1..21
 note = Designed HVR-H2 sequence 59
 source 1..21
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 111
 IGWINPNRGG TKYAQKFQGR V

21

SEQ ID NO: 112 moltype = AA length = 21
 FEATURE Location/Qualifiers
 REGION 1..21
 note = Designed HVR-H2 sequence 60
 source 1..21
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 112
 IGWINPNRGG TNYAQKFQGR V

21

SEQ ID NO: 113 moltype = AA length = 21
 FEATURE Location/Qualifiers
 REGION 1..21
 note = Designed HVR-H2 sequence 61
 source 1..21
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 113
 IGWINPNRGS TKYAQKFQGR V

21

SEQ ID NO: 114 moltype = AA length = 21
 FEATURE Location/Qualifiers
 REGION 1..21
 note = Designed HVR-H2 sequence 62
 source 1..21
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 114
 IGWINPNRGS TNYAQKFQGR V

21

SEQ ID NO: 115 moltype = AA length = 21
 FEATURE Location/Qualifiers
 REGION 1..21
 note = Designed HVR-H2 sequence 63
 source 1..21
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 115
 IGRINPNFGD TNYAQKFQGR V

21

SEQ ID NO: 116 moltype = AA length = 21
 FEATURE Location/Qualifiers
 REGION 1..21
 note = Designed HVR-H2 sequence 64
 source 1..21
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 116
 IGWINPNFGD TNYAQKFQGR V

21

SEQ ID NO: 117 moltype = AA length = 21
 FEATURE Location/Qualifiers
 REGION 1..21
 note = Designed HVR-H2 sequence 65
 source 1..21
 mol_type = protein
 organism = synthetic construct

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SEQUENCE: 117
IGWINPNFGS TKYAQKFQGR V 21

SEQ ID NO: 118 moltype = AA length = 21
FEATURE Location/Qualifiers
REGION 1..21
note = Designed HVR-H2 sequence 66
source 1..21
mol_type = protein
organism = synthetic construct

SEQUENCE: 118
IGWINPNFGS TNYAQKFQGR V 21

SEQ ID NO: 119 moltype = AA length = 21
FEATURE Location/Qualifiers
REGION 1..21
note = Designed HVR-H2 sequence 67
source 1..21
mol_type = protein
organism = synthetic construct

SEQUENCE: 119
IGIINPNRGD TKYAQKFQGR V 21

SEQ ID NO: 120 moltype = AA length = 21
FEATURE Location/Qualifiers
REGION 1..21
note = Designed HVR-H2 sequence 68
source 1..21
mol_type = protein
organism = synthetic construct

SEQUENCE: 120
IGIINPNRGD TNYAQKFQGR V 21

SEQ ID NO: 121 moltype = AA length = 21
FEATURE Location/Qualifiers
REGION 1..21
note = Designed HVR-H2 sequence 69
source 1..21
mol_type = protein
organism = synthetic construct

SEQUENCE: 121
IGIINPNFGD TNYAQKFQGR V 21

SEQ ID NO: 122 moltype = AA length = 21
FEATURE Location/Qualifiers
REGION 1..21
note = Designed HVR-H2 sequence 70
source 1..21
mol_type = protein
organism = synthetic construct

SEQUENCE: 122
IGWISPSGGG TKYAQKFQGR V 21

SEQ ID NO: 123 moltype = AA length = 21
FEATURE Location/Qualifiers
REGION 1..21
note = Designed HVR-H2 sequence 71
source 1..21
mol_type = protein
organism = synthetic construct

SEQUENCE: 123
IGWISPSGGG TNYAQKFQGR V 21

SEQ ID NO: 124 moltype = AA length = 21
FEATURE Location/Qualifiers
REGION 1..21
note = Designed HVR-H2 sequence 72
source 1..21
mol_type = protein
organism = synthetic construct

SEQUENCE: 124
IGWISPSGGG TKYAQKFQGR V 21

SEQ ID NO: 125 moltype = AA length = 21
FEATURE Location/Qualifiers
REGION 1..21
note = Designed HVR-H2 sequence 73
source 1..21
mol_type = protein

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organism = synthetic construct
SEQUENCE: 125
IGWISPSSGG TNYAQKFQGR V 21

SEQ ID NO: 126      moltype = AA length = 21
FEATURE          Location/Qualifiers
REGION           1..21
source            note = Designed HVR-H2 sequence 74
                 1..21
                 mol_type = protein
                 organism = synthetic construct

SEQUENCE: 126
IGWIYPSGGG TKYAQKFQGR V 21

SEQ ID NO: 127      moltype = AA length = 21
FEATURE          Location/Qualifiers
REGION           1..21
source            note = Designed HVR-H2 sequence 75
                 1..21
                 mol_type = protein
                 organism = synthetic construct

SEQUENCE: 127
IGWIYPSGGG TNYAQKFQGR V 21

SEQ ID NO: 128      moltype = AA length = 21
FEATURE          Location/Qualifiers
REGION           1..21
source            note = Designed HVR-H2 sequence 76
                 1..21
                 mol_type = protein
                 organism = synthetic construct

SEQUENCE: 128
IGWISPSSGS TNYAQKFQGR V 21

SEQ ID NO: 129      moltype = AA length = 21
FEATURE          Location/Qualifiers
REGION           1..21
source            note = Designed HVR-H2 sequence 77
                 1..21
                 mol_type = protein
                 organism = synthetic construct

SEQUENCE: 129
IGWISPSSGS TKYAQKFQGR V 21

SEQ ID NO: 130      moltype = AA length = 21
FEATURE          Location/Qualifiers
REGION           1..21
source            note = Designed HVR-H2 sequence 78
                 1..21
                 mol_type = protein
                 organism = synthetic construct

SEQUENCE: 130
IGWISPSSGS TNYAQKFQGR V 21

SEQ ID NO: 131      moltype = AA length = 21
FEATURE          Location/Qualifiers
REGION           1..21
source            note = Designed HVR-H2 sequence 79
                 1..21
                 mol_type = protein
                 organism = synthetic construct

SEQUENCE: 131
IGWISPSSGS TKYAQKFQGR V 21

SEQ ID NO: 132      moltype = AA length = 21
FEATURE          Location/Qualifiers
REGION           1..21
source            note = Designed HVR-H2 sequence 80
                 1..21
                 mol_type = protein
                 organism = synthetic construct

SEQUENCE: 132
IGIIYPSGGG TNYAQKFQGR V 21

SEQ ID NO: 133      moltype = AA length = 21
FEATURE          Location/Qualifiers
REGION           1..21
source            note = Designed HVR-H2 sequence 81
                 1..21

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mol_type = protein
organism = synthetic construct
SEQUENCE: 133
IGIIISPSSGG TKYAQKFQGR V                                21

SEQ ID NO: 134      moltype = AA length = 21
FEATURE          Location/Qualifiers
REGION           1..21
note = Designed HVR-H2 sequence 82
source            1..21
mol_type = protein
organism = synthetic construct

SEQUENCE: 134
IGIIISPSSGG TNYAQKFQGR V                                21

SEQ ID NO: 135      moltype = AA length = 21
FEATURE          Location/Qualifiers
REGION           1..21
note = Designed HVR-H2 sequence 83
source            1..21
mol_type = protein
organism = synthetic construct

SEQUENCE: 135
IGIIYPSGGS TNYAQKFQGR V                                21

SEQ ID NO: 136      moltype = AA length = 23
FEATURE          Location/Qualifiers
REGION           1..23
note = Designed HVR-H2 sequence 84
source            1..23
mol_type = protein
organism = synthetic construct

SEQUENCE: 136
VGRIKSKTDG YTTEYAAPVK GRF                                23

SEQ ID NO: 137      moltype = AA length = 11
FEATURE          Location/Qualifiers
REGION           1..11
note = Designed HVR-H1 sequence 53
source            1..11
mol_type = protein
organism = synthetic construct

SEQUENCE: 137
FTFSDYIAHW V                                              11

SEQ ID NO: 138      moltype = AA length = 11
FEATURE          Location/Qualifiers
REGION           1..11
note = Designed HVR-H1 sequence 54
source            1..11
mol_type = protein
organism = synthetic construct

SEQUENCE: 138
FTFSDYGIHW V                                              11

SEQ ID NO: 139      moltype = AA length = 11
FEATURE          Location/Qualifiers
REGION           1..11
note = Designed HVR-H1 sequence 55
source            1..11
mol_type = protein
organism = synthetic construct

SEQUENCE: 139
YTFSNYAIHW V                                              11

SEQ ID NO: 140      moltype = AA length = 11
FEATURE          Location/Qualifiers
REGION           1..11
note = Designed HVR-H1 sequence 56
source            1..11
mol_type = protein
organism = synthetic construct

SEQUENCE: 140
YTFSSYAIHW V                                              11

SEQ ID NO: 141      moltype = AA length = 11
FEATURE          Location/Qualifiers
REGION           1..11
note = Designed HVR-H1 sequence 57

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source          1..11
               mol_type = protein
               organism = synthetic construct
SEQUENCE: 141
YTFTDYAIHW V                                         11

SEQ ID NO: 142          moltype = AA  length = 11
FEATURE          Location/Qualifiers
REGION           1..11
note = Designed HVR-H1 sequence 58
source          1..11
               mol_type = protein
               organism = synthetic construct
SEQUENCE: 142
YTFTDYGIHW V                                         11

SEQ ID NO: 143          moltype = AA  length = 11
FEATURE          Location/Qualifiers
REGION           1..11
note = Designed HVR-H1 sequence 60
source          1..11
               mol_type = protein
               organism = synthetic construct
SEQUENCE: 143
YTFTNYGIHW V                                         11

SEQ ID NO: 144          moltype = AA  length = 11
FEATURE          Location/Qualifiers
REGION           1..11
note = Designed HVR-H1 sequence 61
source          1..11
               mol_type = protein
               organism = synthetic construct
SEQUENCE: 144
FTPSGYGIHW V                                         11

SEQ ID NO: 145          moltype = AA  length = 11
FEATURE          Location/Qualifiers
REGION           1..11
note = Designed HVR-H1 sequence 62
source          1..11
               mol_type = protein
               organism = synthetic construct
SEQUENCE: 145
FTFSNYAIHW V                                         11

SEQ ID NO: 146          moltype = AA  length = 11
FEATURE          Location/Qualifiers
REGION           1..11
note = Designed HVR-H1 sequence 63
source          1..11
               mol_type = protein
               organism = synthetic construct
SEQUENCE: 146
FTFSSYGIHW V                                         11

SEQ ID NO: 147          moltype = AA  length = 11
FEATURE          Location/Qualifiers
REGION           1..11
note = Designed HVR-H1 sequence 64
source          1..11
               mol_type = protein
               organism = synthetic construct
SEQUENCE: 147
FTFSDYWIHW V                                         11

SEQ ID NO: 148          moltype = AA  length = 11
FEATURE          Location/Qualifiers
REGION           1..11
note = Designed HVR-H1 sequence 65
source          1..11
               mol_type = protein
               organism = synthetic construct
SEQUENCE: 148
FTFTSYWIHW V                                         11

SEQ ID NO: 149          moltype = AA  length = 12
FEATURE          Location/Qualifiers
REGION           1..12

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source	note = Designed HVR-H1 sequence 66 1..12 mol_type = protein organism = synthetic construct	
SEQUENCE: 149 YSISSLGGYYWG WI		12
SEQ ID NO: 150 FEATURE REGION	moltype = AA length = 12 Location/Qualifiers 1..12 note = Designed HVR-H1 sequence 67	
source	1..12 mol_type = protein organism = synthetic construct	
SEQUENCE: 150 YSITSGYYWN WI		12
SEQ ID NO: 151 FEATURE REGION	moltype = AA length = 12 Location/Qualifiers 1..12 note = Designed HVR-H1 sequence 68	
source	1..12 mol_type = protein organism = synthetic construct	
SEQUENCE: 151 YSITSGYYWS WI		12
SEQ ID NO: 152 FEATURE REGION	moltype = AA length = 12 Location/Qualifiers 1..12 note = Designed HVR-H1 sequence 69	
source	1..12 mol_type = protein organism = synthetic construct	
SEQUENCE: 152 YSISSLGHYWA WI		12
SEQ ID NO: 153 FEATURE REGION	moltype = AA length = 12 Location/Qualifiers 1..12 note = Designed HVR-H1 sequence 70	
source	1..12 mol_type = protein organism = synthetic construct	
SEQUENCE: 153 YSISSLGHYWG WI		12
SEQ ID NO: 154 FEATURE REGION	moltype = AA length = 13 Location/Qualifiers 1..13 note = Designed HVR-H1 sequence 71	
source	1..13 mol_type = protein organism = synthetic construct	
SEQUENCE: 154 FSLSTSTGVAV GWI		13
SEQ ID NO: 155 FEATURE REGION	moltype = AA length = 13 Location/Qualifiers 1..13 note = Designed HVR-H1 sequence 72	
source	1..13 mol_type = protein organism = synthetic construct	
SEQUENCE: 155 FSLSTSTGVGV AWI		13
SEQ ID NO: 156 FEATURE REGION	moltype = AA length = 13 Location/Qualifiers 1..13 note = Designed HVR-H1 sequence 73	
source	1..13 mol_type = protein organism = synthetic construct	
SEQUENCE: 156 FSLSTSTGVGV GWI		13
SEQ ID NO: 157 FEATURE	moltype = AA length = 13 Location/Qualifiers	

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REGION	1..13 note = Designed HVR-H1 sequence 74	
source	1..13 mol_type = protein organism = synthetic construct	
SEQUENCE: 157	FSLSTGGVGV GWI	13
SEQ ID NO: 158	moltype = AA length = 21	
FEATURE	Location/Qualifiers	
REGION	1..21	
source	note = Designed HVR-H2 sequence 85 1..21 mol_type = protein organism = synthetic construct	
SEQUENCE: 158	VSAISGSGST TYYADSVKGR F	21
SEQ ID NO: 159	moltype = AA length = 21	
FEATURE	Location/Qualifiers	
REGION	1..21	
source	note = Designed HVR-H2 sequence 86 1..21 mol_type = protein organism = synthetic construct	
SEQUENCE: 159	VSSISGSGDT TYYADSVKGR F	21
SEQ ID NO: 160	moltype = AA length = 21	
FEATURE	Location/Qualifiers	
REGION	1..21	
source	note = Designed HVR-H2 sequence 87 1..21 mol_type = protein organism = synthetic construct	
SEQUENCE: 160	VSSISGSGGS TYYADSVKGR F	21
SEQ ID NO: 161	moltype = AA length = 21	
FEATURE	Location/Qualifiers	
REGION	1..21	
source	note = Designed HVR-H2 sequence 88 1..21 mol_type = protein organism = synthetic construct	
SEQUENCE: 161	VSSISGSGGT TYYADSVKGR F	21
SEQ ID NO: 162	moltype = AA length = 21	
FEATURE	Location/Qualifiers	
REGION	1..21	
source	note = Designed HVR-H2 sequence 89 1..21 mol_type = protein organism = synthetic construct	
SEQUENCE: 162	VSSISGDGGS TYYADSVKGR F	21
SEQ ID NO: 163	moltype = AA length = 21	
FEATURE	Location/Qualifiers	
REGION	1..21	
source	note = Designed HVR-H2 sequence 90 1..21 mol_type = protein organism = synthetic construct	
SEQUENCE: 163	VSSISGSGST TYYADSVKGR F	21
SEQ ID NO: 164	moltype = AA length = 26	
FEATURE	Location/Qualifiers	
REGION	1..26	
source	note = Framework FW-H1 sequence 1..26 mol_type = protein organism = synthetic construct	
SEQUENCE: 164	EVQLVESGGG LVQPGGSLRL SCAASG	26
SEQ ID NO: 165	moltype = AA length = 10	

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FEATURE Location/Qualifiers
REGION 1..10
note = Framework FW-H2 sequence
source 1..10
mol_type = protein
organism = synthetic construct

SEQUENCE: 165
RQAPGKGLEW 10

SEQ ID NO: 166 moltype = AA length = 29
FEATURE Location/Qualifiers
REGION 1..29
note = Framework FW-H3 sequence
source 1..29
mol_type = protein
organism = synthetic construct

SEQUENCE: 166
TISSRDNSKN TLYLQLNSLR AEDTAVYYC 29

SEQ ID NO: 167 moltype = AA length = 11
FEATURE Location/Qualifiers
REGION 1..11
note = Framework FW-H4 sequence
source 1..11
mol_type = protein
organism = synthetic construct

SEQUENCE: 167
WGQGTLTVS S 11

SEQ ID NO: 168 moltype = AA length = 120
FEATURE Location/Qualifiers
REGION 1..120
note = Hit ID 4029 - VH
source 1..120
mol_type = protein
organism = synthetic construct

SEQUENCE: 168
EVQLVESGGG LVQPGGSLRL SCAASGYSIT SGYHWGWIRO APGKGLEWVS YISGAGDTTY 60
YADSVKGRFT ISRDNSKNTL YLQLNLSLRAE DTAVYYCARD YGDYYGFDYW GQGTLTVSS 120

SEQ ID NO: 169 moltype = AA length = 112
FEATURE Location/Qualifiers
REGION 1..112
note = HIT ID 4029 - VL
source 1..112
mol_type = protein
organism = synthetic construct

SEQUENCE: 169
DIQLTQSPSS LSASVGDRVT ITCRASQSVD FYGISFLAWY QQKPGKAPKL LIYDASNLET 60
GVPSRFSGSG SGTDFTLTIS SLQPEDFATY YCQQSYRTPF TFGQGTLVKEI KR 112

SEQ ID NO: 170 moltype = AA length = 11
FEATURE Location/Qualifiers
REGION 1..11
note = Designed HVR-H1 sequence 59
source 1..11
mol_type = protein
organism = synthetic construct

SEQUENCE: 170
YTFTNYAIHW V 11

SEQ ID NO: 171 moltype = AA length = 123
FEATURE Location/Qualifiers
REGION 1..123
note = Hit ID 7097 - VH
source 1..123
mol_type = protein
organism = synthetic construct

SEQUENCE: 171
EVQLVESGGG LVQPGGSLRL SCAASGYSIS SGHHWDWIRO APGKGLEWVS YISGAGDTTY 60
YADSVKGRFT ISRDNSKNTL YLQLNLSLRAE DTAVYYCARE GSDAVLGDFW AYWQQGTLVT 120
VSS 123

SEQ ID NO: 172 moltype = AA length = 108
FEATURE Location/Qualifiers
REGION 1..108
note = HIT ID 7097 - VL
source 1..108
mol_type = protein

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organism = synthetic construct

SEQUENCE: 172
DIQLTQSPSS LSASVGDRVT ITCRASQGIS SYLAWYQQKP GKAPKLLIYD ASNLETGVPS 60
RFSGSGSGTD FTLTISSSLQP EDFATYYCQQ YYSTPLTFGQ GTKVEIKR 108

SEQ ID NO: 173 moltype = AA length = 124
FEATURE Location/Qualifiers
REGION 1..124
note = Hit ID 5906 - VH
source 1..124
mol_type = protein
organism = synthetic construct

SEQUENCE: 173
EVQLVESGGG LVQPGGSLRL SCAASGYSIS SGYHWNWIRQ APGKGLEWWS YISGDGDTTY 60
YADSVKGRFT ISRDNSKNTL YLQLNLSLRAE DTAVYYCARD LGGYYGWGRY FDYWGQGTLV 120
TVSS 124

SEQ ID NO: 174 moltype = AA length = 108
FEATURE Location/Qualifiers
REGION 1..108
note = HIT ID 5906 - VL
source 1..108
mol_type = protein
organism = synthetic construct

SEQUENCE: 174
DIQLTQSPSS LSASVGDRVT ITCRASQSVS SYLAWYQQKP GKAPKLLIYD ASNLETGVPS 60
RFSGSGSGTD FTLTISSSLQP EDFATYYCQQ SYSTPLTFGQ GTKVEIKR 108

SEQ ID NO: 175 moltype = AA length = 119
FEATURE Location/Qualifiers
REGION 1..119
note = Hit ID 7040 - VH
source 1..119
mol_type = protein
organism = synthetic construct

SEQUENCE: 175
EVQLVESGGG LVQPGGSLRL SCAASGYSIS SGYYWNWIRQ APGKGLEWIG WISPSGGSTN 60
YAQKFQGRVT ISRDNSKNTL YLQLNLSLRAE DTAVYYCARD LTAGGFWDYWG QGTLTVSS 119

SEQ ID NO: 176 moltype = AA length = 108
FEATURE Location/Qualifiers
REGION 1..108
note = HIT ID 7040 - VL
source 1..108
mol_type = protein
organism = synthetic construct

SEQUENCE: 176
DIQLTQSPSS LSASVGDRVT ITCRASQGIS SYLAWYQQKP GKAPKLLIYD ASNLETGVPS 60
RFSGSGSGTD FTLTISSSLQP EDFATYYCQQ YYSTPLTFGQ GTKVEIKR 108

SEQ ID NO: 177 moltype = AA length = 120
FEATURE Location/Qualifiers
REGION 1..120
note = Hit ID 5924 - VH
source 1..120
mol_type = protein
organism = synthetic construct

SEQUENCE: 177
EVQLVESGGG LVQPGGSLRL SCAASGYSIS SGYHWGWIRO APGKGLEWIG IISPSSGSTK 60
YAQKFQGRVT ISRDNSKNTL YLQLNLSLRAE DTAVYYCARG AGVHYALDYW GQGTLTVSS 120

SEQ ID NO: 178 moltype = AA length = 108
FEATURE Location/Qualifiers
REGION 1..108
note = HIT ID 5924 - VL
source 1..108
mol_type = protein
organism = synthetic construct

SEQUENCE: 178
DIQLTQSPSS LSASVGDRVT ITCRASQSVS SYLAWYQQKP GKAPKLLIYD ASNLETGVPS 60
RFSGSGSGTD FTLTISSSLQP EDFATYYCQQ SYSTPLTFGQ GTKVEIKR 108

SEQ ID NO: 179 moltype = AA length = 123
FEATURE Location/Qualifiers
REGION 1..123
note = Hit ID 4034 - VH
source 1..123
mol_type = protein
organism = synthetic construct

-continued

SEQUENCE: 179
 EVQLVESGGG LVQPGGSLRL SCAASGYSIS SGHYWNWIRQ APGKGLEWVS SISGYGSTTY 60
 YADSVKGRFT ISRDNSKNTL YLQLNSLRAE DTAVYYCARE RYYGSTDYAF DYWGQGTLVT 120
 VSS 123

SEQ ID NO: 180 moltype = AA length = 107
 FEATURE Location/Qualifiers
 REGION 1..107
 note = HIT ID 4034 - VL
 source 1..107
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 180
 DIQLTQSPSS LSASVGDRVT ITCSASSRVS HVFWYQQKPG KAPKLLIYAA STLQSGVPSR 60
 RFSGSGSGTDF TLTIISSLQPE DFATYFCLQG THFPWTFCQG TKVEIKR 107

SEQ ID NO: 181 moltype = AA length = 118
 FEATURE Location/Qualifiers
 REGION 1..118
 note = Hit ID 6010 - VH
 source 1..118
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 181
 EVQLVESGGG LVQPGGSLRL SCAASGYSIS SGHYWNWIRQ APGKGLEWIG WINPNRGDTN 60
 YAQKFQGRVT ISRDNSKNTL YLQLNSLRAE DTAVYYCARD YYGDFDYWGQ GTLTVSS 118

SEQ ID NO: 182 moltype = AA length = 108
 FEATURE Location/Qualifiers
 REGION 1..108
 note = HIT ID 6010 - VL
 source 1..108
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 182
 DIQLTQSPSS LSASVGDRVT ITCRASQSIS SYLNWYQQKP GKAPKLLIYD ASNLETGVPS 60
 RFSGSGSGTDF FTLTIISSLQP EDFATYYCQH HYGTPLTFQG GTKVEIKR 108

SEQ ID NO: 183 moltype = AA length = 123
 FEATURE Location/Qualifiers
 REGION 1..123
 note = Hit ID 7183 - VH
 source 1..123
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 183
 EVQLVESGGG LVQPGGSLRL SCAASGYSIS SGHYWNWIRQ APGKGLEWVS SISGYGDTTY 60
 YADSVKGRFT ISRDNSKNTL YLQLNSLRAE DTAVYYCARE GSDTVLGDFW AYWGQGTLVT 120
 VSS 123

SEQ ID NO: 184 moltype = AA length = 108
 FEATURE Location/Qualifiers
 REGION 1..108
 note = HIT ID 7183 - VL
 source 1..108
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 184
 DIQLTQSPSS LSASVGDRVT ITCRASQSIS SYLNWYQQKP GKAPKLLIYD ASN RATGIPS 60
 RFSGSGSGTDF FTLTIISSLQP EDFATYYCQH SYSTPPPTFGQ GTKVEIKR 108

SEQ ID NO: 185 moltype = AA length = 120
 FEATURE Location/Qualifiers
 REGION 1..120
 note = Hit ID 4036 - VH
 source 1..120
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 185
 EVQLVESGGG LVQPGGSLRL SCAASGFSLS TSGVGVGWIR QAPGKGLEWI GEIYHSGSTY 60
 YSPSLKSRVT ISRDNSKNTL YLQLNSLRAE DTAVYYCARE RYGSYYFDYW GQGTLTVSS 120

SEQ ID NO: 186 moltype = AA length = 112
 FEATURE Location/Qualifiers
 REGION 1..112
 note = HIT ID 4036 - VL
 source 1..112
 mol_type = protein
 organism = synthetic construct

-continued

SEQUENCE: 186
DIQLTQSPSS LSASVGDRVT ITCRASQSVF FYGKSFQDWY QQKPGKAPKL LIYDASSLES 60
GVPSRFSGGG SGTDFTLTIS SLQPEDFATY YCQQYYRIPP TFGQGTKEI KR 112

SEQ ID NO: 187 moltype = AA length = 117
FEATURE Location/Qualifiers
REGION 1..117
note = Hit ID 5115 - VH
source 1..117
mol_type = protein
organism = synthetic construct

SEQUENCE: 187
EVQLVESGGG LVQPGGSLRL SCAASGYSIS SGHYWGWIRQ APGKGLEWIG EIYHSGSTYY 60
SPSLKSRVTI SRDNSKNTLY LQLNSLRAED TAVYYCARES YYAFDYWGQG TLTVSS 117

SEQ ID NO: 188 moltype = AA length = 108
FEATURE Location/Qualifiers
REGION 1..108
note = HIT ID 5115 - VL
source 1..108
mol_type = protein
organism = synthetic construct

SEQUENCE: 188
DIQLTQSPSS LSASVGDRVT ITCRASQSVS SYLAQYQQKP GKAPKLLIYA ASTLQSGVPS 60
RFGSGSGTDF FTLSISSLQP EDFATYYCQQ YYTTPLTFGQ GTKVEIKR 108

SEQ ID NO: 189 moltype = AA length = 119
FEATURE Location/Qualifiers
REGION 1..119
note = Hit ID 5404 - VH
source 1..119
mol_type = protein
organism = synthetic construct

SEQUENCE: 189
EVQLVESGGG LVQPGGSLRL SCAASGYSIS SGYHWAWIRQ APGKGLEWIG EIYHSGSTYY 60
SPSLKSRVTI SRDNSKNTLY LQLNSLRAED TAVYYCARSP YYGVFDYWG QGTLTVSS 119

SEQ ID NO: 190 moltype = AA length = 107
FEATURE Location/Qualifiers
REGION 1..107
note = HIT ID 5404 - VL
source 1..107
mol_type = protein
organism = synthetic construct

SEQUENCE: 190
DIQLTQSPSS LSASVGDRVT ITCASSSRVG SVVWYQQKPG KAPKLLIYDA SNLETGVPSR 60
FSGSGSGTDF TLTSSLQPE DFATYYCQQY THDPVTFGQG TKVEIKR 107

SEQ ID NO: 191 moltype = AA length = 120
FEATURE Location/Qualifiers
REGION 1..120
note = Hit ID 3757 - VH
source 1..120
mol_type = protein
organism = synthetic construct

SEQUENCE: 191
EVQLVESGGG LVQPGGSLRL SCAASGFTFT DYGIHWVRQA PGKGLEWIGW ISPSGGTKY 60
AQKFQGRVTI SRDNSKNTLY LQLNSLRAED TAVYYCARHS YYGVGDFDYW GQGTLTVSS 120

SEQ ID NO: 192 moltype = AA length = 108
FEATURE Location/Qualifiers
REGION 1..108
note = HIT ID 3757 - VL
source 1..108
mol_type = protein
organism = synthetic construct

SEQUENCE: 192
DIQLTQSPSS LSASVGDRVT ITCRASQSVS SYLAQYQQKP GKAPKLLIYD ASNLETGVPS 60
RFGSGSGTDF FTLSISSLQP EDFATYYCQQ SYSTPLTFGQ GTKVEIKR 108

SEQ ID NO: 193 moltype = AA length = 120
FEATURE Location/Qualifiers
REGION 1..120
note = Hit ID 5103 - VH
source 1..120
mol_type = protein
organism = synthetic construct

SEQUENCE: 193
EVQLVESGGG LVQPGGSLRL SCAASGFTFT DYGIHWVRQA PGKGLEWIGW ISPSGGTKY 60

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AQKFQGRVTI SRDNSKNTLY LQLNSLRAED TAVYYCARHS YYGVGDFDYW GQGTLTVSS 120

SEQ ID NO: 194 moltype = AA length = 108
 FEATURE Location/Qualifiers
 REGION 1..108
 note = HIT ID 5103 - VL
 source 1..108
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 194 DIQLTQSPSS LSASVGDRVT ITCRASQSVS SYLAWSQQKP GKAPKLLIYD ASNLETGVPS 60
 RFSGSQSGTD FTLTISLQP EDFATYYCQQ SYSTPLTFGQ GTKVEIKR 108

SEQ ID NO: 195 moltype = AA length = 117
 FEATURE Location/Qualifiers
 REGION 1..117
 note = Hit ID 4027 - VH
 source 1..117
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 195 EVQLVESGGG LVQPGGSLRL SCAASGYSIT SGHHWNWIRQ APGKGLEWIG WISPSSGGTK 60
 YAQKFQGRVT ISRDNSKNTL YLQLNSLRAE DTAVYYCARG FDGFHYWGQG TLTVSS 117

SEQ ID NO: 196 moltype = AA length = 112
 FEATURE Location/Qualifiers
 REGION 1..112
 note = HIT ID 4027 - VL
 source 1..112
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 196 DIQLTQSPSS LSASVGDRVT ITCRASESVD FYGISFLPWY QQKPGKAPKL LIYDASN RAT 60
 GIPSRFSGSG SGTDFTLTIS SLQPEDFATY YCQQSYSWPW TFGQGKTVEI KR 112

SEQ ID NO: 197 moltype = AA length = 117
 FEATURE Location/Qualifiers
 REGION 1..117
 note = VH in FIG. 1B
 source 1..117
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 197 EVQLVESGGG LVQPGGSLRL SCAASGFTFT SYGIHWVRQA PGKGLEWVSG ISGAGDTYY 60
 ADSVKGRFTI SRDNSKNTLY LQLNSLRAED TAVYYCARER DYDFDYWGQG TLTVSS 117

SEQ ID NO: 198 moltype = AA length = 11
 FEATURE Location/Qualifiers
 REGION 1..11
 note = Formula (I)
 SITE 1
 note = misc_feature - Xaa can be any naturally occurring amino acid
 REGION 4..5
 note = misc_feature - Xaa can be any naturally occurring amino acid
 SITE 7
 note = misc_feature - Xaa can be any naturally occurring amino acid
 source 1..11
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 198 XTFXXYXIH V 11

SEQ ID NO: 199 moltype = AA length = 12
 FEATURE Location/Qualifiers
 REGION 1..12
 note = Formula (II)
 SITE 4
 note = misc_feature - Xaa can be any naturally occurring amino acid
 REGION 7..8
 note = misc_feature - Xaa can be any naturally occurring amino acid
 SITE 10
 note = misc_feature - Xaa can be any naturally occurring amino acid
 source 1..12

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mol_type = protein
organism = synthetic construct

SEQUENCE: 199
YSIXSGXXWX WI

SEQ ID NO: 200      moltype = AA length = 13
FEATURE
REGION
1..13
note = Formula (III)
SITE
6
note = misc_feature - Xaa can be any naturally occurring
amino acid
SITE
9
note = misc_feature - Xaa can be any naturally occurring
amino acid
SITE
11
note = misc_feature - Xaa can be any naturally occurring
amino acid
source
1..13
mol_type = protein
organism = synthetic construct

SEQUENCE: 200
FSLSTXGVXV XWI

SEQ ID NO: 201      moltype = AA length = 20
FEATURE
REGION
1..20
note = Formula (IV)
SITE
3
note = misc_feature - Xaa can be any naturally occurring
amino acid
SITE
5
note = misc_feature - Xaa can be any naturally occurring
amino acid
REGION
7..8
note = misc_feature - Xaa can be any naturally occurring
amino acid
SITE
11
note = misc_feature - Xaa can be any naturally occurring
amino acid
SITE
14
note = misc_feature - Xaa can be any naturally occurring
amino acid
source
1..20
mol_type = protein
organism = synthetic construct

SEQUENCE: 201
LAXIXWXXDK YYSXSLKSRL

SEQ ID NO: 202      moltype = AA length = 20
FEATURE
REGION
1..20
note = Formula (V)
SITE
3
note = misc_feature - Xaa can be any naturally occurring
amino acid
REGION
5..6
note = misc_feature - Xaa can be any naturally occurring
amino acid
source
1..20
mol_type = protein
organism = synthetic construct

SEQUENCE: 202
IGXIXXSGST YYSPSLKSRV

SEQ ID NO: 203      moltype = AA length = 20
FEATURE
REGION
1..20
note = Formula (VI)
SITE
3
note = misc_feature - Xaa can be any naturally occurring
amino acid
SITE
6
note = misc_feature - Xaa can be any naturally occurring
amino acid
SITE
9
note = misc_feature - Xaa can be any naturally occurring
amino acid
SITE
11

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source          note = misc_feature - Xaa can be any naturally occurring
                amino acid
1..20
mol_type = protein
organism = synthetic construct

SEQUENCE: 203
IGXIYXSGXT XYNPSLKSrv                                         20

SEQ ID NO: 204      moltype = AA length = 21
FEATURE          Location/Qualifiers
REGION           1..21
note = Formula (VII)
SITE             3
note = misc_feature - Xaa can be any naturally occurring
                amino acid
SITE             7
note = misc_feature - Xaa can be any naturally occurring
                amino acid
REGION          9..10
note = misc_feature - Xaa can be any naturally occurring
                amino acid
source          1..21
mol_type = protein
organism = synthetic construct

SEQUENCE: 204
VSXISGXGXX TYYADSVKGR F                                         21

SEQ ID NO: 205      moltype = AA length = 21
FEATURE          Location/Qualifiers
REGION           1..21
note = Formula (VIII)
SITE             3
note = misc_feature - Xaa can be any naturally occurring
                amino acid
SITE             8
note = misc_feature - Xaa can be any naturally occurring
                amino acid
SITE             10
note = misc_feature - Xaa can be any naturally occurring
                amino acid
SITE             12
note = misc_feature - Xaa can be any naturally occurring
                amino acid
source          1..21
mol_type = protein
organism = synthetic construct

SEQUENCE: 205
IGXINPNXGX TXYAQKFQGR V                                         21

SEQ ID NO: 206      moltype = AA length = 21
FEATURE          Location/Qualifiers
REGION           1..21
note = Formula (IX)
SITE             3
note = misc_feature - Xaa can be any naturally occurring
                amino acid
SITE             5
note = misc_feature - Xaa can be any naturally occurring
                amino acid
SITE             8
note = misc_feature - Xaa can be any naturally occurring
                amino acid
SITE             10
note = misc_feature - Xaa can be any naturally occurring
                amino acid
SITE             12
note = misc_feature - Xaa can be any naturally occurring
                amino acid
source          1..21
mol_type = protein
organism = synthetic construct

SEQUENCE: 206
IGXIXPSXGX TXYAQKFQGR V                                         21

SEQ ID NO: 207      moltype = AA length = 23
FEATURE          Location/Qualifiers
REGION           1..23
note = Formula (X)
SITE             5

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note = misc_feature - Xaa can be any naturally occurring
amino acid
REGION 8..9
note = misc_feature - Xaa can be any naturally occurring
amino acid
SITE 11
note = misc_feature - Xaa can be any naturally occurring
amino acid
SITE 14
note = misc_feature - Xaa can be any naturally occurring
amino acid
SITE 18
note = misc_feature - Xaa can be any naturally occurring
amino acid
source 1..23
mol_type = protein
organism = synthetic construct

SEQUENCE: 207
VGRIKSXXG XTTXYAAXVK GRF 23

SEQ ID NO: 208      moltype = AA length = 20
FEATURE Location/Qualifiers
REGION 1..20
note = Formula (XI)
SITE 3
note = misc_feature - Xaa can be any naturally occurring
amino acid
REGION 5..6
note = misc_feature - Xaa can be any naturally occurring
amino acid
source 1..20
mol_type = protein
organism = synthetic construct

SEQUENCE: 208
IGIXXSGST YYSPSLKSRV 20

SEQ ID NO: 209      moltype = AA length = 20
FEATURE Location/Qualifiers
REGION 1..20
note = Formula (XII)
SITE 3
note = misc_feature - Xaa can be any naturally occurring
amino acid
SITE 6
note = misc_feature - Xaa can be any naturally occurring
amino acid
SITE 9
note = misc_feature - Xaa can be any naturally occurring
amino acid
SITE 11
note = misc_feature - Xaa can be any naturally occurring
amino acid
source 1..20
mol_type = protein
organism = synthetic construct

SEQUENCE: 209
IGXIYXSGXT XYNPSLKSRV 20

SEQ ID NO: 210      moltype = AA length = 23
FEATURE Location/Qualifiers
REGION 1..23
note = Formula (XIII)
SITE 5
note = misc_feature - Xaa can be any naturally occurring
amino acid
REGION 8..9
note = misc_feature - Xaa can be any naturally occurring
amino acid
SITE 11
note = misc_feature - Xaa can be any naturally occurring
amino acid
SITE 18
note = misc_feature - Xaa can be any naturally occurring
amino acid
source 1..23
mol_type = protein
organism = synthetic construct

SEQUENCE: 210
VGRIKSXXG XTTEYAAXVK GRF 23

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SEQ ID NO: 211      moltype = DNA  length = 23
FEATURE
misc_feature        Location/Qualifiers
1..23
note = Primer F_1999
source
1..23
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 211
cgtttgtcct gtgcagcttc cggt                                23

SEQ ID NO: 212      moltype = DNA  length = 25
FEATURE
misc_feature        Location/Qualifiers
1..25
note = Primer R_1999
source
1..25
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 212
cgaggccctt acccgggggcc tgacg                                25

SEQ ID NO: 213      moltype = DNA  length = 21
FEATURE
misc_feature        Location/Qualifiers
1..21
note = Primer F_2003
source
1..21
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 213
ccgggttaagg gcctcgagtgt g                                21

SEQ ID NO: 214      moltype = DNA  length = 33
FEATURE
misc_feature        Location/Qualifiers
1..33
note = Primer R_2003
source
1..33
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 214
gagcacgtcc gttcgaattt tcgcgactta tag                                33

SEQ ID NO: 215      moltype = DNA  length = 45
FEATURE
misc_feature        Location/Qualifiers
1..45
note = Primer S1089
source
1..45
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 215
acaactgaac agcttaagag ctgaggacac tgccgtctat tattg                                45

SEQ ID NO: 216      moltype = DNA  length = 32
FEATURE
misc_feature        Location/Qualifiers
1..32
note = Primer S1090
source
1..32
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 216
gaggagacgg tgactagtgt tccttgacc  ca                                32

SEQ ID NO: 217      moltype = DNA  length = 34
FEATURE
misc_feature        Location/Qualifiers
1..34
note = Primer F_2898
source
1..34
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 217
tacttatgtt ggccatcgccc tcaccatca  ctgc                                34

SEQ ID NO: 218      moltype = DNA  length = 28
FEATURE
misc_feature        Location/Qualifiers
1..28
note = Primer R_2898
source
1..28
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 218

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cgagactttt cctggtttct gttgatac	28
SEQ ID NO: 219 moltype = DNA length = 22 FEATURE Location/Qualifiers misc_feature 1..22 note = Primer F_2013 source 1..22 mol_type = other DNA organism = synthetic construct	
SEQUENCE: 219 gaaaccaggaa aaagctccga ag	22
SEQ ID NO: 220 moltype = DNA length = 29 FEATURE Location/Qualifiers misc_feature 1..29 note = Primer R_2013 source 1..29 mol_type = other DNA organism = synthetic construct	
SEQUENCE: 220 cgtcccgaa ccggatccag agaagc gag	29
SEQ ID NO: 221 moltype = DNA length = 35 FEATURE Location/Qualifiers misc_feature 1..35 note = Primer F2929 source 1..35 mol_type = other DNA organism = synthetic construct	
SEQUENCE: 221 acccatcagca gtctgcagcc ggaagacttc gcaac	35
SEQ ID NO: 222 moltype = DNA length = 27 FEATURE Location/Qualifiers misc_feature 1..27 note = Primer R2929 source 1..27 mol_type = other DNA organism = synthetic construct	
SEQUENCE: 222 gatctccacc ttggtagccct gtccgaa	27
SEQ ID NO: 223 moltype = AA length = 16 FEATURE Location/Qualifiers REGION 1..16 note = HVR-H3 sequence 1 source 1..16 mol_type = protein organism = synthetic construct	
SEQUENCE: 223 ARDLGGYYGW GRYFDY	16
SEQ ID NO: 224 moltype = AA length = 11 FEATURE Location/Qualifiers REGION 1..11 note = HVR-H3 sequence 2 source 1..11 mol_type = protein organism = synthetic construct	
SEQUENCE: 224 ARDLTAGGFD Y	11
SEQ ID NO: 225 moltype = AA length = 11 FEATURE Location/Qualifiers REGION 1..11 note = HVR-H3 sequence 3 source 1..11 mol_type = protein organism = synthetic construct	
SEQUENCE: 225 ARDPGVGFFD V	11
SEQ ID NO: 226 moltype = AA length = 12 FEATURE Location/Qualifiers REGION 1..12 note = HVR-H3 sequence 4 source 1..12 mol_type = protein organism = synthetic construct	

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SEQUENCE: 226	
ARDPGYTWYF DV	12
SEQ ID NO: 227	moltype = AA length = 12
FEATURE	Location/Qualifiers
REGION	1..12
source	note = HVR-H3 sequence 5
	1..12
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 227	
ARDYGDYYGF DY	12
SEQ ID NO: 228	moltype = AA length = 12
FEATURE	Location/Qualifiers
REGION	1..12
source	note = HVR-H3 sequence 6
	1..12
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 228	
ARDYGYTWYF DV	12
SEQ ID NO: 229	moltype = AA length = 10
FEATURE	Location/Qualifiers
REGION	1..10
source	note = HVR-H3 sequence 7
	1..10
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 229	
ARDYYGDFDY	10
SEQ ID NO: 230	moltype = AA length = 15
FEATURE	Location/Qualifiers
REGION	1..15
source	note = HVR-H3 sequence 8
	1..15
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 230	
AREGSDAVLG DWFAY	15
SEQ ID NO: 231	moltype = AA length = 15
FEATURE	Location/Qualifiers
REGION	1..15
source	note = HVR-H3 sequence 9
	1..15
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 231	
AREGSDTVLG DWFAY	15
SEQ ID NO: 232	moltype = AA length = 12
FEATURE	Location/Qualifiers
REGION	1..12
source	note = HVR-H3 sequence 10
	1..12
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 232	
ARERYGSYYF DY	12
SEQ ID NO: 233	moltype = AA length = 15
FEATURE	Location/Qualifiers
REGION	1..15
source	note = HVR-H3 sequence 11
	1..15
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 233	
ARERYYGSTD YAFDY	15
SEQ ID NO: 234	moltype = AA length = 10
FEATURE	Location/Qualifiers
REGION	1..10
source	note = HVR-H3 sequence 12
	1..10
	mol_type = protein

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	organism = synthetic construct	
SEQUENCE: 234 ARESYYAFDY		10
SEQ ID NO: 235 FEATURE REGION	moltype = AA length = 12 Location/Qualifiers 1..12	
source	note = HVR-H3 sequence 13 1..12 mol_type = protein organism = synthetic construct	
SEQUENCE: 235 ARGAGGVHYAL DY		12
SEQ ID NO: 236 FEATURE REGION	moltype = AA length = 9 Location/Qualifiers 1..9	
source	note = HVR-H3 sequence 14 1..9 mol_type = protein organism = synthetic construct	
SEQUENCE: 236 ARGFDGPHY		9
SEQ ID NO: 237 FEATURE REGION	moltype = AA length = 11 Location/Qualifiers 1..11	
source	note = HVR-H3 sequence 15 1..11 mol_type = protein organism = synthetic construct	
SEQUENCE: 237 ARGFYGGALD V		11
SEQ ID NO: 238 FEATURE REGION	moltype = AA length = 11 Location/Qualifiers 1..11	
source	note = HVR-H3 sequence 16 1..11 mol_type = protein organism = synthetic construct	
SEQUENCE: 238 ARGGGGYYFD V		11
SEQ ID NO: 239 FEATURE REGION	moltype = AA length = 10 Location/Qualifiers 1..10	
source	note = HVR-H3 sequence 17 1..10 mol_type = protein organism = synthetic construct	
SEQUENCE: 239 ARGGGLGFDY		10
SEQ ID NO: 240 FEATURE REGION	moltype = AA length = 10 Location/Qualifiers 1..10	
source	note = HVR-H3 sequence 18 1..10 mol_type = protein organism = synthetic construct	
SEQUENCE: 240 ARGLGLGPFDI		10
SEQ ID NO: 241 FEATURE REGION	moltype = AA length = 15 Location/Qualifiers 1..15	
source	note = HVR-H3 sequence 19 1..15 mol_type = protein organism = synthetic construct	
SEQUENCE: 241 ARGGSDTVIG DWFAY		15
SEQ ID NO: 242 FEATURE REGION	moltype = AA length = 10 Location/Qualifiers 1..10	
source	note = HVR-H3 sequence 20 1..10	

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SEQUENCE: 242 ARGGVGPFDI	mol_type = protein organism = synthetic construct	
		10
SEQ ID NO: 243 FEATURE REGION source	moltype = AA length = 11 Location/Qualifiers 1..11 note = HVR-H3 sequence 21 1..11 mol_type = protein organism = synthetic construct	
SEQUENCE: 243 ARGGYGGYLD V		11
SEQ ID NO: 244 FEATURE REGION source	moltype = AA length = 11 Location/Qualifiers 1..11 note = HVR-H3 sequence 22 1..11 mol_type = protein organism = synthetic construct	
SEQUENCE: 244 ARGLSSGYFD Y		11
SEQ ID NO: 245 FEATURE REGION source	moltype = AA length = 9 Location/Qualifiers 1..9 note = HVR-H3 sequence 23 1..9 mol_type = protein organism = synthetic construct	
SEQUENCE: 245 ARGSWYFDV		9
SEQ ID NO: 246 FEATURE REGION source	moltype = AA length = 9 Location/Qualifiers 1..9 note = HVR-H3 sequence 24 1..9 mol_type = protein organism = synthetic construct	
SEQUENCE: 246 ARGTRGLDY		9
SEQ ID NO: 247 FEATURE REGION source	moltype = AA length = 10 Location/Qualifiers 1..10 note = HVR-H3 sequence 25 1..10 mol_type = protein organism = synthetic construct	
SEQUENCE: 247 ARGYSDYFDY		10
SEQ ID NO: 248 FEATURE REGION source	moltype = AA length = 12 Location/Qualifiers 1..12 note = HVR-H3 sequence 26 1..12 mol_type = protein organism = synthetic construct	
SEQUENCE: 248 ARGYYYGRAF DY		12
SEQ ID NO: 249 FEATURE REGION source	moltype = AA length = 13 Location/Qualifiers 1..13 note = HVR-H3 sequence 27 1..13 mol_type = protein organism = synthetic construct	
SEQUENCE: 249 ARHSYYGVGD FDY		13
SEQ ID NO: 250 FEATURE REGION	moltype = AA length = 9 Location/Qualifiers 1..9 note = HVR-H3 sequence 28	

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source	1..9 mol_type = protein organism = synthetic construct	
SEQUENCE: 250		9
ARLFEGFPY		
SEQ ID NO: 251	moltype = AA length = 9	
FEATURE	Location/Qualifiers	
REGION	1..9	
	note = HVR-H3 sequence 29	
source	1..9 mol_type = protein organism = synthetic construct	
SEQUENCE: 251		9
ARLYDYFAY		
SEQ ID NO: 252	moltype = AA length = 10	
FEATURE	Location/Qualifiers	
REGION	1..10	
	note = HVR-H3 sequence 30	
source	1..10 mol_type = protein organism = synthetic construct	
SEQUENCE: 252		10
ARSGYYALDY		
SEQ ID NO: 253	moltype = AA length = 12	
FEATURE	Location/Qualifiers	
REGION	1..12	
	note = HVR-H3 sequence 31	
source	1..12 mol_type = protein organism = synthetic construct	
SEQUENCE: 253		12
ARSPYYYGVF DY		
SEQ ID NO: 254	moltype = AA length = 9	
FEATURE	Location/Qualifiers	
REGION	1..9	
	note = HVR-H3 sequence 32	
source	1..9 mol_type = protein organism = synthetic construct	
SEQUENCE: 254		
ARSYVYFDY		9
SEQ ID NO: 255	moltype = AA length = 19	
FEATURE	Location/Qualifiers	
REGION	1..19	
	note = HVR-H3 sequence 33	
source	1..19 mol_type = protein organism = synthetic construct	
SEQUENCE: 255		19
ARDGLGLRGV YYYYYGLDV		
SEQ ID NO: 256	moltype = AA length = 20	
FEATURE	Location/Qualifiers	
REGION	1..20	
	note = HVR-H3 sequence 34	
source	1..20 mol_type = protein organism = synthetic construct	
SEQUENCE: 256		
ARVGESGGIE SPYYYYGLDV		20
SEQ ID NO: 257	moltype = AA length = 15	
FEATURE	Location/Qualifiers	
REGION	1..15	
	note = HVR-L1 sequence 1	
source	1..15 mol_type = protein organism = synthetic construct	
SEQUENCE: 257		
RASESVDFYG ISFLP		15
SEQ ID NO: 258	moltype = AA length = 15	
FEATURE	Location/Qualifiers	
REGION	1..15	

-continued

source	note = HVR-L1 sequence 2 1..15 mol_type = protein organism = synthetic construct	
SEQUENCE: 258 RASQSVDFYG ISFLA		15
SEQ ID NO: 259 FEATURE REGION	moltype = AA length = 15 Location/Qualifiers 1..15 note = HVR-L1 sequence 3	
source	1..15 mol_type = protein organism = synthetic construct	
SEQUENCE: 259 RASQSVDFYG KSFLD		15
SEQ ID NO: 260 FEATURE REGION	moltype = AA length = 10 Location/Qualifiers 1..10 note = HVR-L1 sequence 4	
source	1..10 mol_type = protein organism = synthetic construct	
SEQUENCE: 260 SASSRVGGSVY		10
SEQ ID NO: 261 FEATURE REGION	moltype = AA length = 10 Location/Qualifiers 1..10 note = HVR-L1 sequence 5	
source	1..10 mol_type = protein organism = synthetic construct	
SEQUENCE: 261 SASSRVSHVF		10
SEQ ID NO: 262 FEATURE REGION	moltype = AA length = 11 Location/Qualifiers 1..11 note = HVR-L1 sequence 6	
source	1..11 mol_type = protein organism = synthetic construct	
SEQUENCE: 262 RASQGISSYL A		11
SEQ ID NO: 263 FEATURE REGION	moltype = AA length = 11 Location/Qualifiers 1..11 note = HVR-L1 sequence 7	
source	1..11 mol_type = protein organism = synthetic construct	
SEQUENCE: 263 RASQSVSSYL A		11
SEQ ID NO: 264 FEATURE REGION	moltype = AA length = 11 Location/Qualifiers 1..11 note = HVR-L1 sequence 8	
source	1..11 mol_type = protein organism = synthetic construct	
SEQUENCE: 264 RASQSISSYL N		11
SEQ ID NO: 265 FEATURE REGION	moltype = AA length = 11 Location/Qualifiers 1..11 note = HVR-L3 sequence 1	
source	1..11 mol_type = protein organism = synthetic construct	
SEQUENCE: 265 FCLQGTHFPW T		11
SEQ ID NO: 266 FEATURE	moltype = AA length = 11 Location/Qualifiers	

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REGION	1..11 note = HVR-L3 sequence 2	
source	1..11 mol_type = protein organism = synthetic construct	
SEQUENCE: 266		
YCQQSYRTPF T		11
SEQ ID NO: 267	moltype = AA length = 11	
FEATURE	Location/Qualifiers	
REGION	1..11	
source	note = HVR-L3 sequence 3	
1..11		
mol_type = protein		
organism = synthetic construct		
SEQUENCE: 267		
YCQQSYSWPW T		11
SEQ ID NO: 268	moltype = AA length = 11	
FEATURE	Location/Qualifiers	
REGION	1..11	
source	note = HVR-L3 sequence 4	
1..11		
mol_type = protein		
organism = synthetic construct		
SEQUENCE: 268		
YCQQYTHDPV T		11
SEQ ID NO: 269	moltype = AA length = 11	
FEATURE	Location/Qualifiers	
REGION	1..11	
source	note = HVR-L3 sequence 5	
1..11		
mol_type = protein		
organism = synthetic construct		
SEQUENCE: 269		
YCQQYYRIPP T		11
SEQ ID NO: 270	moltype = AA length = 11	
FEATURE	Location/Qualifiers	
REGION	1..11	
source	note = HVR-L3 sequence 6	
1..11		
mol_type = protein		
organism = synthetic construct		
SEQUENCE: 270		
YCQHHYGTPL T		11
SEQ ID NO: 271	moltype = AA length = 11	
FEATURE	Location/Qualifiers	
REGION	1..11	
source	note = HVR-L3 sequence 7	
1..11		
mol_type = protein		
organism = synthetic construct		
SEQUENCE: 271		
YCQQSYSTPL T		11
SEQ ID NO: 272	moltype = AA length = 11	
FEATURE	Location/Qualifiers	
REGION	1..11	
source	note = HVR-L3 sequence 8	
1..11		
mol_type = protein		
organism = synthetic construct		
SEQUENCE: 272		
YCQQSYSTPP T		11
SEQ ID NO: 273	moltype = AA length = 11	
FEATURE	Location/Qualifiers	
REGION	1..11	
source	note = HVR-L3 sequence 9	
1..11		
mol_type = protein		
organism = synthetic construct		
SEQUENCE: 273		
YCQQYYSTPL T		11
SEQ ID NO: 274	moltype = AA length = 11	

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FEATURE Location/Qualifiers
 REGION 1..11
 note = HVR-L3 sequence 10
 source 1..11
 mol_type = protein
 organism = synthetic construct
 SEQUENCE: 274
 YCQQYYTTPL T

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What is claimed is:

1. A non-human animal comprising polynucleotides that encode antibody heavy chain variable domains (V_H s), wherein each of the V_H s comprises a HVR-H1, a HVR-H2 and a HVR-H3, and wherein at least one V_H comprises an HVR-H1 that comprises an amino acid sequence according to a formula selected from the group consisting of:

(Formula I)

(SEQ ID NO: 198)

$X_1TFX_2X_3YX_4IHWV$,
 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;

(Formula II)

(SEQ ID NO: 199)

$YSIX_1SGX_2X_3WX_4WI$, 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; and

(Formula III)

(SEQ ID NO: 200)

$FSLSTX_1GVX_2VX_3WI$, wherein X_1 is G or S, X_2 is A or G, and X_3 is A, G, S, or T;

and

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

(Formula IV)

(SEQ ID NO: 201)

$LAX_1IX_2WX_3X_4DKX_5YSX_6SLKSRL$, 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)

(SEQ ID NO: 202)

$IGX_1IX_2X_3SGSTYYSPSLKSRV$, 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)

(SEQ ID NO: 203)

$IGX_1IYX_2SGX_3TX_4YNPSLKSRL$, 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)

(SEQ ID NO: 204)

$VSXIISGX_2GX_3X_4TYYADSVKGRF$, 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)

(SEQ ID NO: 205)

$IGX_1INPNX_2GX_3TX_4YAQKFQGRV$, 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;

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(Formula IX)

(SEQ ID NO: 206)

$IGX_1IX_2PSX_3GX_4TXYAQKFQGRV$, 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)

(SEQ ID NO: 207)

$VGRIX_1SKX_2X_3GX_4TTX_5YAAX_6VKGRF$, 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 non-human animal of claim 1, wherein at least two, at least three, at least four, at least five or at least ten of the V_H s comprise,

an HVR-H1 that comprises an amino acid sequence according to a formula selected from the group consisting of:

(Formula I)

(SEQ ID NO: 198)

$X_1TFX_2X_3YX_4IHWV$, 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;

(Formula II)

(SEQ ID NO: 199)

$YSIX_1SGX_2X_3WX_4WI$, 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; and

(Formula III)

(SEQ ID NO: 200)

$FSLSTX_1GVX_2VX_3WI$, wherein X_1 is G or S, X_2 is A or G, and X_3 is A, G, S, or T;

and

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

(Formula IV)

(SEQ ID NO: 201)

$LAX_1IX_2WX_3X_4DKX_5YSX_6SLKSRL$, 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)

(SEQ ID NO: 202)

$IGX_1IX_2X_3SGSTYYSPSLKSRV$, 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)

(SEQ ID NO: 203)

$IGX_1IYX_2SGX_3TX_4YNPSLKSRL$, 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;

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(Formula VII)

(SEQ ID NO: 204)

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;

(Formula VIII)

(SEQ ID NO: 205)

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;

(Formula IX)

(SEQ ID NO: 206)

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;

(Formula X)

(SEQ ID NO: 207)

VGRIX₁SKX₂X₃GX₄TTX₅VAAX₆VKGRF, 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.

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

(Formula XI)

(SEQ ID NO: 208)

IGX₁IX₂X₃SGSTYYSPSLKSRV, wherein X₁ is A, D, or E, X₂ is S or Y, and X₃ is H or Y;

(Formula XII)

(SEQ ID NO: 209)

IGX₁IYX₂SGX₃TX₄YNPSLKSrv, wherein X₁ is D, E, or S, X₂ is H or Y, X₃ is N or S, and X₄ is N or Y;

(Formula XIII)

(SEQ ID NO: 210)

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.

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

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

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

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

8. The non-human animal of claim 1, wherein the V_Hs contain fewer than about 6.5*10⁴ unique combinations of HVR-H1 and HVR-H2 sequences.

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

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

11. The non-human animal of claim 1, wherein each of the V_Hs comprises a HVR-H1 comprising an amino acid

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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.

5 12. The non-human animal of claim 1, wherein at least one of the V_Hs comprises a HVR-H1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOS:1-52, and a HVR-H2 of the antibody comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:53-136.

10 13. The non-human animal of claim 1, wherein the HVR-H1 and HVR-H2 of the at least one V_H are selected from the group consisting of:

a HVR-H1 comprising the amino acid sequence of Formula (II) and a HVR-H2 comprising the amino acid sequence of Formula (IX);

a HVR-H1 comprising the amino acid sequence of Formula (II) and a HVR-H2 comprising the amino acid sequence of Formula (VII);

a HVR-H1 comprising the amino acid sequence of Formula (I) and a HVR-H2 comprising the amino acid sequence of Formula (VII);

a HVR-H1 comprising the amino acid sequence of Formula (I) and a HVR-H2 comprising the amino acid sequence of Formula (IX);

a HVR-H1 comprising the amino acid sequence of Formula (II) and a HVR-H2 comprising the amino acid sequence of Formula (IV);

a HVR-H1 comprising the amino acid sequence of Formula (II) and a HVR-H2 comprising the amino acid sequence of Formula (V);

a HVR-H1 comprising the amino acid sequence of Formula (II) and a HVR-H2 comprising the amino acid sequence of Formula (VI);

a HVR-H1 comprising the amino acid sequence of Formula (I) and a HVR-H2 comprising the amino acid sequence of Formula (VI);

a HVR-H1 comprising the amino acid sequence of Formula (III) and a HVR-H2 comprising the amino acid sequence of Formula (VI);

a HVR-H1 comprising the amino acid sequence of Formula (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 (VII);

a HVR-H1 comprising the amino acid sequence of Formula (II) and a HVR-H2 comprising the amino acid sequence of Formula (VIII);

a HVR-H1 comprising the amino acid sequence of Formula (I) and a HVR-H2 comprising the amino acid sequence of Formula (V);

a HVR-H1 comprising the amino acid sequence of Formula (III) and a HVR-H2 comprising the amino acid sequence of Formula (V); and

a HVR-H1 comprising the amino acid sequence of Formula (I) and a HVR-H2 comprising the amino acid sequence of Formula (VIII).

14. The non-human animal of claim 1, wherein the HVR-H1 and HVR-H2 of the at least one V_H are selected from the group consisting of: a HVR-H1 comprising the amino acid sequence of SEQ ID NO:157, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:63; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:1, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:122; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:138, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:63; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:154, and a HVR-H2 comprising the amino acid sequence of SEQ ID

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NO:63; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:158, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:161; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:158, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:63; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:145, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:128; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:22, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:61; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:31, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:63; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:153, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:63; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:155, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:67; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:156, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:100; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:51, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:162; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:138, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:123; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:139, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:110; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:8, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:126; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:13, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:129; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:31, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:124; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:25, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:130; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:150, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:132; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:158, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:162; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:12, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:82; a HVR-H1 comprising the amino acid sequence of SEQ ID NO:149, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:117; and a HVR-H1 comprising the amino acid sequence of SEQ ID NO:7, and a HVR-H2 comprising the amino acid sequence of SEQ ID NO:134.

15. The non-human animal of claim 1, wherein the at least one V_H comprises a HVR-H3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 223-256.

16. The non-human animal of claim 1, wherein the at least one V_H 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.

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

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