

COMPOSITIONS OF MULTISPECIFIC ANTIGEN BINDING POLYPEPTIDES AND METHODS OF USE

CROSS REFERENCE

[0001] This application claims the benefit of U.S. Provisional Application No. 63/587,623, filed October 3, 2023, U.S. Provisional Application No. 63/608,015, filed December 8, 2023, U.S. Provisional Application No. 63/642,534, filed May 3, 2024, and U.S. Provisional Application No. 63/667,432, filed July 3, 2024, which applications are incorporated herein by reference in their entireties.

SUMMARY

[0002] Described herein are bispecific, trispecific and tetraspecific binding polypeptides. The binding polypeptides described herein possess certain advantages. Due to their compact size and leveraging of surrogate light chain technology the polypeptides simplify screening, and possess advantages in production and delivery. The purity of the binding polypeptides described herein is high as there are no mispaired by-products, addressing a significant limitation with previous bispecific and trispecific binding molecules. As surrogate light chains can form productive binding units with any heavy chain screening and development are significantly streamlined. Also their compact size allows these bispecific and trispecific binding polypeptides to be encoded by smaller nucleic acids making them amenable for gene therapy applications. Their small molecular size also reduces the amount of antigen available to elicit anti-drug antibodies.

[0003] Described herein in one aspect is a multispecific antigen binding polypeptide comprising: (a) a first antigen binding moiety, comprising a first heavy chain variable region; (b) a second antigen binding moiety, comprising a second heavy chain variable region; and (c) a third antigen binding moiety, comprising a third heavy chain variable region; wherein the first antigen binding moiety binds to a first target, the second antigen binding moiety binds to a second target, and the third antigen binding moiety binds to a third target, wherein the first antigen binding moiety, the second antigen binding moiety and the third antigen binding moiety are paired to a light chain polypeptide. In certain embodiments, the first antigen binding moiety, the second antigen binding moiety, and the third antigen binding moiety are directly connected without a linker. In certain embodiments, a C-terminus of the first heavy chain variable region is directly connected to an N-terminus of the second heavy chain variable region. In certain embodiments, a C-terminus of the second heavy chain variable region is directly connected to an N-terminus of the third heavy chain variable region. In certain embodiments, a C-terminus of the first heavy chain variable region is directly connected to an N-terminus of the second heavy chain variable region, and

wherein a C-terminus of the second heavy chain variable region is directly connected to an N-terminus of the third heavy chain variable region. In certain embodiments, the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety are linked via a linker. In certain embodiments, the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety are covalently linked via the linker. In certain embodiments, the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety are non-covalently linked via the linker. In certain embodiments, the linker couples the C-terminus of the first antigen binding moiety to the N-terminus of the second antigen binding moiety. In certain embodiments, the linker couples the C-terminus of the second antigen binding moiety to the N-terminus of the third antigen binding moiety. In certain embodiments, the multispecific antigen binding polypeptide further comprises a fourth antigen binding moiety, wherein the fourth antigen binding moiety comprises a fourth heavy chain variable region, wherein the fourth antigen binding moiety binds to a fourth target, wherein the fourth antigen binding moiety is paired to a light chain polypeptide. In certain embodiments, the first antigen binding moiety, the second antigen binding moiety, the third antigen binding moiety, and the fourth antigen binding moiety are directly connected without a linker. In certain embodiments, a C-terminus of the third heavy chain variable region is directly connected to an N-terminus of the fourth heavy chain variable region. In certain embodiments, the first antigen binding moiety, the second antigen binding moiety, the third antigen binding moiety, and/or the fourth antigen binding moiety are linked via a linker. In certain embodiments, the linker couples the C-terminus of the third antigen binding moiety to the N-terminus of the fourth antigen binding moiety. In certain embodiments, the linker comprises an amino acid sequence with at least 90%, at least 95%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to SEQ ID NO: 151. In certain embodiments, the first antigen binding moiety, the second antigen binding moiety, the third antigen binding moiety, and/or the fourth antigen binding moiety comprises a crossed domain. In certain embodiments, the first antigen binding moiety, the second antigen binding moiety, the third antigen binding moiety, and/or the fourth antigen binding moiety comprises at least two crossed domains, wherein the at least two crossed domains are comprised in at least two different antigen binding moieties. In certain embodiments, the first antigen binding moiety, the second antigen binding moiety, the third antigen binding moiety, and/or the fourth antigen binding moiety comprises at least three crossed domains wherein the at least three crossed domains are comprised in at least three different antigen binding moieties. In certain embodiments, the light chain polypeptide paired to the first antigen binding moiety, the second antigen binding moiety, and the third antigen binding moiety comprise the same amino acid sequence. In certain embodiments, the light chain polypeptide paired to the first antigen

binding moiety, the second antigen binding moiety, and the third antigen binding moiety comprise different amino acid sequences. In certain embodiments, the light chain polypeptide paired to the first antigen binding moiety, the second antigen binding moiety, the third antigen binding moiety, and the fourth antigen binding moiety comprise different amino acid sequences. In certain embodiments, the light chain polypeptide comprises a light chain constant region comprising one or more amino acid substitutions from a heavy chain first constant region (CH1). In certain embodiments, the light chain polypeptide comprises a light chain constant region comprising one or more amino acid substitutions from a heavy chain first constant region (CH1) and the light chain comprises an amino acid sequence comprising at least 90%, at least 95%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to the amino acid sequence set forth in SEQ ID NO: 111 or 112. In certain embodiments, the light chain polypeptide comprises a light chain constant region comprising one or more amino acid substitutions from a heavy chain first constant region (CH1) and the light chain comprises an amino acid sequence comprising at least 90%, at least 95%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to the amino acid sequence set forth in SEQ ID NO: 121 or 122. In certain embodiments, the light chain polypeptide comprises a light chain constant region comprising one or more amino acid substitutions from a heavy chain first constant region (CH1) and the light chain comprises an amino acid sequence comprising at least 90%, at least 95%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to the amino acid sequence set forth in SEQ ID NO: 131 or 132. In certain embodiments, the light chain polypeptide is a universal light chain polypeptide. In certain embodiments, the universal light chain polypeptide is a common light chain polypeptide. In certain embodiments, the universal light chain polypeptide is a surrogate light chain polypeptide. In certain embodiments, the surrogate light chain polypeptide comprises a VpreB sequence fused to a $\lambda 5$ sequence. In certain embodiments, the VpreB sequence comprises an amino acid sequence comprising at least 90%, at least 95%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to the amino acid sequence set forth in SEQ ID NO: 101. In certain embodiments, the $\lambda 5$ sequence comprises an amino acid sequence comprising at least 90%, at least 95%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to the amino acid sequence set forth in SEQ ID NO: 106. In certain embodiments, the surrogate light chain polypeptide comprises: (a) a light chain complementarity determining region 1 (LCDR1) comprising the amino acid sequence set forth in SEQ ID NO: 103; (b) a light chain complementarity determining region 2 (LCDR2) comprising the amino acid sequence set forth in SEQ ID NO: 104; and/or(c) a light chain complementarity determining region 3 (LCDR3) comprising the amino acid sequence set forth in SEQ ID NO: 105. In certain embodiments, the surrogate light chain polypeptide comprises an

amino acid sequence comprising at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 102. In certain embodiments, the common light chain polypeptide comprises an amino acid sequence comprising at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 303. In certain embodiments, the first target, the second target and/or the third target is VEGF-A or a fragment thereof. In certain embodiments, the multispecific antigen binding polypeptide binds to VEGF-A or a fragment thereof with an EC₅₀ of about 5 picomolar or less. In certain embodiments, the multispecific antigen binding polypeptide binds with an affinity to VEGF-A or a fragment thereof at least 8-fold stronger than faricimab. In certain embodiments, the multispecific antigen binding polypeptide inhibits the interaction of VEGF-A and the VEGF-A receptor. In certain embodiments, the multispecific antigen binding polypeptide inhibits the interaction of VEGF-A and the VEGF-A receptor with an IC₅₀ of about 18 nanomolar or less. In certain embodiments, the multispecific antigen binding polypeptide inhibits the interaction of VEGF-A and the VEGF-A receptor at least 1.3-fold stronger than faricimab. In certain embodiments, the first target, the second target and/or the third target is ANG-2 or a fragment thereof. In certain embodiments, the multispecific antigen binding polypeptide binds to ANG-2 or a fragment thereof with an EC₅₀ of about 11 picomolar or less. In certain embodiments, the multispecific antigen binding polypeptide with an affinity binds to ANG-2 or a fragment thereof at least 300 fold stronger than faricimab. In certain embodiments, the multispecific antigen binding polypeptide inhibits the interaction of ANG-2 and the ANG-2 receptor. In certain embodiments, the multispecific antigen binding polypeptide inhibits the interaction of ANG-2 and the ANG-2 receptor with an IC₅₀ of about 3.1 nanomolar or less. In certain embodiments, the multispecific antigen binding polypeptide inhibits the interaction of ANG-2 and the ANG-2 receptor at least 12-fold stronger than faricimab. In certain embodiments, the first target, the second target and/or the third target is VEGF-C or a fragment thereof. In certain embodiments, the multispecific antigen binding polypeptide binds to VEGF-C or a fragment thereof with an EC₅₀ of about 19 picomolar or less. In certain embodiments, the multispecific antigen binding polypeptide inhibits the interaction of VEGF-C and the VEGF-C receptor. In certain embodiments, the multispecific antigen binding polypeptide inhibits the interaction of VEGF-C and the VEGF-C receptor with an IC₅₀ of about 3.8 nanomolar or less. In certain embodiments, the first target is VEGF-A or fragment thereof, the second target is ANG-2 or a fragment thereof, and the third target is VEGF-C or a fragment. In certain embodiments, the first, second, and third antigen binding moiety bind different polypeptide antigens. In certain embodiments, the first, second, and third antigen binding moiety bind the same polypeptide antigens. In certain embodiments, the first antigen binding moiety, the second

antigen binding moiety, and/or the third antigen binding moiety binds to VEGF-A. In certain embodiments, the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety binds to VEGF-A and comprises an immunoglobulin heavy chain variable region comprising: (a) a heavy chain complementarity determining region 1 (HCDR1) comprising the amino acid sequence set forth in SEQ ID NO: 3; (b) a heavy chain complementarity determining region 2 (HCDR2) comprising the amino acid sequence set forth in SEQ ID NO: 4; and/or (c) a heavy chain complementarity determining region 3 (HCDR3) comprising the amino acid sequence set forth in SEQ ID NO: 5; wherein the heavy chain variable region binds to VEGF-A upon pairing with the light chain polypeptide. In certain embodiments, the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety comprises an immunoglobulin heavy chain variable region comprising an amino acid sequence comprising at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 1. In certain embodiments, the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety comprises an amino acid sequence comprising at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 2. In certain embodiments, the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety binds to ANG-2. In certain embodiments, the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety binds to ANG-2 and comprises an immunoglobulin heavy chain variable region comprising: (a) a heavy chain complementarity determining region 1 (HCDR1) comprising the amino acid sequence set forth in SEQ ID NO: 13; (b) a heavy chain complementarity determining region 2 (HCDR2) comprising the amino acid sequence set forth in SEQ ID NO: 14; and/or (c) a heavy chain complementarity determining region 3 (HCDR3) comprising the amino acid sequence set forth in SEQ ID NO: 15; wherein the heavy chain variable region binds to ANG-2 upon pairing with the light chain polypeptide. In certain embodiments, the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety comprises an immunoglobulin heavy chain variable region comprising an amino acid sequence comprising at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 11. In certain embodiments, the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety comprises an amino acid sequence comprising at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 12. In certain embodiments, the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety binds to VEGF-C. In certain embodiments, the first antigen binding moiety, the second antigen binding moiety, or the third antigen binding

moiety binds to VEGF-C and comprises an immunoglobulin heavy chain variable region comprising: (a) a heavy chain complementarity determining region 1 (HCDR1) comprising the amino acid sequence set forth in SEQ ID NO: 23; (b) a heavy chain complementarity determining region 2 (HCDR2) comprising the amino acid sequence set forth in SEQ ID NO: 24; and/or (c) a heavy chain complementarity determining region 3 (HCDR3) comprising the amino acid sequence set forth in SEQ ID NO: 25; wherein the heavy chain variable region binds to VEGF-A upon pairing with the light chain polypeptide. In certain embodiments, the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety comprises an immunoglobulin heavy chain variable region comprising an amino acid sequence comprising at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 21. In certain embodiments, the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety comprises an amino acid sequence comprising at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 22. In certain embodiments, each of the first antigen binding moiety, the second antigen binding moiety and the third antigen binding moiety is non-covalently paired to the surrogate light chain polypeptide. In certain embodiments, each of the first antigen binding moiety, the second antigen binding moiety and the third antigen binding moiety is covalently paired to the surrogate light chain polypeptide. In certain embodiments, the first, second, or third antigen binding moiety comprise a heavy chain first constant region (CH1) comprising one or more amino acid substitutions from a light chain constant region. In certain embodiments, the first antigen binding moiety comprises a first heavy chain variable region (VH) and a heavy chain first constant region (CH1). In certain embodiments, the second antigen binding moiety comprises a second heavy chain variable region (VH) and a heavy chain first constant region (CH1). In certain embodiments, the third antigen binding moiety comprises a third heavy chain variable region (VH) and a heavy chain first constant region (CH1). In certain embodiments, the multispecific antigen binding polypeptide comprises an amino acid sequence comprising at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in any one of SEQ ID NOs: 201 to 205. In certain embodiments, the multispecific antigen binding polypeptide comprises an amino acid sequence comprising at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 201. In certain embodiments, the multispecific antigen binding polypeptide comprises an amino acid sequence comprising at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 202. In certain embodiments, the multispecific antigen binding polypeptide comprises an amino acid sequence comprising at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set

forth in SEQ ID NO: 203. In certain embodiments, the heavy chain first constant region comprises an amino acid sequence with at least 80%, at least 90%, at least 95%, at least 97%, at least 98%, at least 99%, or at least 100% identity to the amino acid sequence set forth in SEQ ID NO: 141. In certain embodiments, the first antigen binding moiety comprises a first heavy chain variable region (VH), a heavy chain first constant region (CH1), a heavy chain second constant region (CH2), and/or a heavy chain third constant region (CH3). In certain embodiments, the second antigen binding moiety comprises a second heavy chain variable region (VH), a heavy chain first constant region (CH1), a heavy chain second constant region (CH2), and/or a heavy chain third constant region (CH3). In certain embodiments, the third antigen binding moiety comprises a third heavy chain variable region (VH), a heavy chain first constant region (CH1), a heavy chain second constant region (CH2), and/or a heavy chain third constant region (CH3). In certain embodiments, the first target, the second target, the third target, and/or the fourth target is ErbB3 or a fragment thereof. In certain embodiments, the multispecific antigen binding polypeptide binds to ErbB3 or a fragment thereof with an EC₅₀ of about 0.57 nanomolar or less. In certain embodiments, the first target, the second target, the third target, and/or the fourth target is VEGF-A or a fragment thereof. In certain embodiments, the multispecific antigen binding polypeptide binds to VEGF-A or a fragment thereof with an EC₅₀ of about 24 picomolar or less. In certain embodiments, the first target, the second target, the third target, and/or the fourth target is ANG-2 or a fragment thereof. In certain embodiments, In certain embodiments, In certain embodiments, In certain embodiments, the multispecific antigen binding polypeptide binds to ANG-2 or a fragment thereof with an EC₅₀ of about 32 picomolar or less. In certain embodiments, the first target, the second target, the third target, and/or the fourth target is VEGF-C or a fragment thereof. In certain embodiments, the multispecific antigen binding polypeptide binds to VEGF-C or a fragment thereof with an EC₅₀ of about 4.3 nanomolar or less. In certain embodiments, the first target is ErbB3 or fragment thereof, the second target is VEGF-A or a fragment thereof, the third target is ANG-2 or a fragment thereof, and the fourth target is VEGF-C or a fragment thereof. In certain embodiments, the multispecific antigen binding polypeptide comprises an amino acid sequence comprising at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 301. In certain embodiments, each of the first antigen binding moiety, the second antigen binding moiety, the third antigen binding moiety, and/or the fourth antigen binding moiety is paired to the surrogate light chain polypeptide. In certain embodiments, the surrogate light chain polypeptide comprises an amino acid sequence at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 102. In certain embodiments, the first target, the second target, and/or the third target, is EGFr or a fragment thereof. In certain embodiments, the multispecific

antigen binding polypeptide binds to EGFR or a fragment thereof with an EC₅₀ of about 0.36 nanomolar or less. In certain embodiments, the first target, the second target, and/or the third target is ErbB2 or a fragment thereof. In certain embodiments, the multispecific antigen binding polypeptide binds to ErbB2 or a fragment thereof with an EC₅₀ of about 52 picomolar or less. In certain embodiments, the first target, the second target, and/or the third target is ErbB3 or a fragment thereof. In certain embodiments, the multispecific antigen binding polypeptide binds to ErbB3 or a fragment thereof with an EC₅₀ of about 3 nanomolar or less. In certain embodiments, the first target is EGFR or fragment thereof, the second target is ErbB2 or a fragment thereof, and the third target is ErbB3 or a fragment thereof. In certain embodiments, the multispecific antigen binding polypeptide comprises an amino acid sequence comprising at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 302. In certain embodiments, each of the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety is paired to the common light chain polypeptide. In certain embodiments, the common light chain polypeptide comprises an amino acid sequence at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 303. In certain embodiments, the first target, the second target, the third target, and/or the fourth target is c-Met or a fragment thereof. In certain embodiments, the multispecific antigen binding polypeptide binds to c-Met or a fragment thereof with an EC₅₀ of about 0.21 nanomolar or less. In certain embodiments, the first target, the second target, the third target, and/or the fourth target is EGFR or a fragment thereof. In certain embodiments, the multispecific antigen binding polypeptide binds to EGFR or a fragment thereof with an EC₅₀ of about 0.33 nanomolar or less. In certain embodiments, the first target, the second target, the third target, and/or the fourth target is ErbB2 or a fragment thereof. In certain embodiments, the multispecific antigen binding polypeptide binds to ErbB2 or a fragment thereof with an EC₅₀ of about 51 picomolar or less. In certain embodiments, the first target, the second target, the third target, and/or the fourth target is ErbB3 or a fragment thereof. In certain embodiments, the multispecific antigen binding polypeptide binds to ErbB3 or a fragment thereof with an EC₅₀ of about 2.8 nanomolar or less. In certain embodiments, the first target is EGFR or fragment thereof, the second target is ErbB2 or a fragment thereof, and the third target is ErbB3 or a fragment thereof. In certain embodiments, the multispecific antigen binding polypeptide comprises an amino acid sequence comprising at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 302. In certain embodiments, each of the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety is paired to the common light chain polypeptide. In certain embodiments, the common light chain polypeptide comprises an amino acid sequence at least 85%, 90%, 95%,

96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 303. In certain embodiments, the first target, the second target, the third target, and/or the fourth target is c-Met or a fragment thereof. In certain embodiments, the multispecific antigen binding polypeptide binds to c-Met or a fragment thereof with an EC₅₀ of about 0.21 nanomolar or less. In certain embodiments, the first target, the second target, the third target, and/or the fourth target is EGFR or a fragment thereof. In certain embodiments, the multispecific antigen binding polypeptide binds to EGFR or a fragment thereof with an EC₅₀ of about 0.33 nanomolar or less. In certain embodiments, the first target, the second target, the third target, and/or the fourth target is ErbB2 or a fragment thereof. In certain embodiments, the multispecific antigen binding polypeptide binds to ErbB2 or a fragment thereof with an EC₅₀ of about 51 picomolar or less. In certain embodiments, the first target, the second target, the third target, and/or the fourth target is ErbB3 or a fragment thereof. In certain embodiments, the multispecific antigen binding polypeptide binds to ErbB3 or a fragment thereof with an EC₅₀ of about 2.8 nanomolar or less. In certain embodiments, the first target is cMet or fragment thereof, the second target is EGFR or a fragment thereof, the third target is ErbB2 or a fragment thereof, and the fourth target is ErbB3 or a fragment thereof. In certain embodiments, the multispecific antigen binding polypeptide comprises an amino acid sequence comprising at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 304. In certain embodiments, each of the first antigen binding moiety, the second antigen binding moiety, the third antigen binding moiety, and/or the fourth antigen binding moiety is paired to the common light chain polypeptide. In certain embodiments, the common light chain polypeptide comprises an amino acid sequence at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 303. In certain embodiments, wherein the first antigen binding moiety, the second antigen binding moiety, the third antigen binding moiety, and/or the fourth antigen binding moiety comprises a crossed domain. In certain embodiments, the second antigen binding moiety comprises a crossed domain. In certain embodiments, the multispecific antigen binding polypeptide comprises an amino acid sequence comprising at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 308. In certain embodiments, each of the first antigen binding moiety, the second antigen binding moiety, the third antigen binding moiety, and/or the fourth antigen binding moiety is paired to the common light chain polypeptide. In certain embodiments, the common light chain polypeptide comprises an amino acid sequence at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 309. In certain embodiments, the first antigen binding moiety, the second antigen binding moiety, the third antigen binding moiety, and/or the fourth antigen binding moiety is paired to a domain swapped surrogate light chain

polypeptide, wherein the domain swapped surrogate light chain comprises a VpreB sequence fused to a heavy chain first constant region (CH1). In certain embodiments, the domain swapped surrogate light chain polypeptide comprises an amino acid sequence at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 132. In certain embodiments, the first antigen binding moiety, the second antigen binding moiety, the third antigen binding moiety, and/or the fourth antigen binding moiety comprises at least two crossed domain. In certain embodiments, the first antigen binding moiety, the second antigen binding moiety, the third antigen binding moiety, and/or the fourth antigen binding moiety comprises at least three crossed domain. In certain embodiments, the first antigen binding moiety, the second antigen binding moiety, the third antigen binding moiety, and/or the fourth antigen binding moiety comprises at least four crossed domain. In certain embodiments, each of the first antigen binding moiety, the third antigen binding moiety, and the fourth antigen binding moiety comprises a crossed domain. In certain embodiments, the multispecific antigen binding polypeptide comprises an amino acid sequence comprising at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 310. In certain embodiments, each of the first antigen binding moiety, the second antigen binding moiety, the third antigen binding moiety, and/or the fourth antigen binding moiety is paired to a domain swapped common light chain polypeptide, wherein the domain swapped common light chain comprises a light chain variable region (VL) fused to a heavy chain first constant region (CH1). In certain embodiments, the domain swapped surrogate light chain polypeptide comprises an amino acid sequence at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 311. In certain embodiments, each of the first antigen binding moiety, the second antigen binding moiety, the third antigen binding moiety, and/or the fourth antigen binding moiety is paired to the surrogate light chain polypeptide. In certain embodiments, the surrogate light chain polypeptide comprises an amino acid sequence at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 102. In certain embodiments, the first target, the second target, and the third target are the same. In certain embodiments, the first target, the second target, and the third target are PD-1 or a fragment thereof. In certain embodiments, the multispecific antigen binding polypeptide binds to PD-1 or a fragment thereof. In certain embodiments, the multispecific antigen binding polypeptide binds to PD-1 or a fragment thereof with an EC₅₀ of about 90 picomolar or less. In certain embodiments, the multispecific antigen binding polypeptide comprises an amino acid sequence comprising at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 305. In certain embodiments, each of the first antigen binding moiety, the second antigen binding

moiety, and/or the third antigen binding moiety is paired to the common light chain polypeptide. In certain embodiments, the common light chain polypeptide comprises an amino acid sequence at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 307. In certain embodiments, the first target, the second target, the third target, and the fourth target are the same. In certain embodiments, the first target, the second target, the third target, and the fourth target are PD-1 or a fragment thereof. In certain embodiments, the multispecific antigen binding polypeptide binds to PD-1 or a fragment thereof. In certain embodiments, the multispecific antigen binding polypeptide binds to PD-1 or a fragment thereof with an EC₅₀ of about 60 picomolar or less. In certain embodiments, the first, second, third, or fourth antigen binding moiety comprises a first heavy chain variable region (VH), a heavy chain first constant region (CH1), a heavy chain second constant region (CH2), and/or a heavy chain third constant region (CH3). In certain embodiments, the multispecific antigen binding polypeptide comprises an amino acid sequence comprising at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 306. In certain embodiments, each of the first antigen binding moiety, the second antigen binding moiety, the third antigen binding moiety is paired to the common light chain polypeptide. In certain embodiments, the common light chain polypeptide comprises an amino acid sequence at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 307. Also described is a pharmaceutical composition comprising the multispecific antigen binding polypeptide and a pharmaceutically acceptable carrier, excipient, or diluent. In certain embodiments, the pharmaceutical composition is formulated for intravenous administration. In certain embodiments, the pharmaceutical composition is formulated for intravitreal administration. Also described is a nucleic acid or plurality of nucleic acids encoding the multispecific antigen binding polypeptide. Also described is an expression vector comprising the nucleic acid. In certain embodiments the expression vector is RNA. In certain embodiments the expression vector is plasmid or linearized DNA. In certain embodiments the expression vector is a viral vector. In certain embodiments the viral vector is an adenovirus. In certain embodiments the viral vector is an adeno-associated virus. In certain embodiments the viral vector is a lentivirus virus. Also described is a pharmaceutical composition comprising the nucleic acid or plurality of nucleic acids encoding the multispecific antigen binding polypeptide and a pharmaceutically acceptable carrier, excipient, or diluent. In certain embodiments, the pharmaceutical composition is formulated for intravenous administration. In certain embodiments, the pharmaceutical composition is formulated for intravitreal administration. Also described herein is a method of treating a disease in an individual comprising administering to the individual the multispecific antigen binding polypeptide, the nucleic acid or plurality of

nucleic acids encoding the multispecific antigen binding polypeptide, or pharmaceutical composition thereby treating the disease. In certain embodiments, the disease is an ocular disease. In certain embodiments, the ocular disease comprises macular degeneration. In certain embodiments, the macular degeneration is neovascular age-related macular degeneration. In certain embodiments, the ocular disease comprises diabetic macular edema. In certain embodiments, the ocular disease comprises retinal vein occlusion. In certain embodiments, the disease is a cancer.

[0004] Described herein in another aspect is a multispecific antigen binding polypeptide comprising: (a) a first antigen binding moiety, comprising a first heavy chain variable region and a first heavy chain first constant region (CH1) paired with a first light chain; and (b) a second antigen binding moiety, comprising a second heavy chain variable region and a second heavy chain first constant region (CH1) paired with a second light chain; wherein a C to terminus of the first CH1 is coupled to an N-terminus of the second heavy chain variable region wherein the first antigen binding moiety binds to a first target, the second antigen binding moiety binds to a second target. In certain embodiments, the first light chain and the second light chain are a common light chain. In certain embodiments, the first light chain and the second light chain are a surrogate light chain. In certain embodiments, the first antigen binding moiety and the second antigen binding moiety are directly coupled without a linker. In certain embodiments, the surrogate light chain polypeptide comprises a VpreB sequence conjugated to a $\lambda 5$ sequence. In certain embodiments, the VpreB sequence comprises an amino acid sequence with at least 90%, at least 95%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to the amino acid sequence set forth in SEQ ID NO101. In certain embodiments, the $\lambda 5$ sequence comprises an amino acid sequence with at least 90%, at least 95%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to the amino acid sequence set forth in SEQ ID NO: 106. In certain embodiments, the surrogate light chain polypeptide comprises: (a) a light chain complementarity determining region 1 (LCDR1) comprising the amino acid sequence set forth in SEQ ID NO: 103; (b) a light chain complementarity determining region 2 (LCDR2) comprising the amino acid sequence set forth in SEQ ID NO: 104; and/or (c) a light chain complementarity determining region 3 (LCDR3) comprising the amino acid sequence set forth in SEQ ID NO: 105. In certain embodiments, the surrogate light chain polypeptide comprises an amino acid sequence at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 102. In certain embodiments, each of the first antigen binding moiety and/or the second antigen binding moiety is non covalently paired to the surrogate light chain polypeptide. In certain embodiments, each of the first antigen binding moiety and/or the second antigen binding moiety is covalently paired to the surrogate light chain

polypeptide. In certain embodiments, the first and second antigen binding moiety bind antigens on different polypeptides. In certain embodiments, the first and second antigen binding moiety bind antigens on the same polypeptide. In certain embodiments, the first target, and or the second target is VEGF-A or a fragment thereof. In certain embodiments, the multispecific antigen binding polypeptide binds to VEGF-A or a fragment thereof with an EC50 of about 5 picomolar or less. In certain embodiments, the multispecific antigen binding polypeptide binds to VEGF-A or a fragment thereof at least 8-fold stronger than faricimab. In certain embodiments, the first target, and or the second target is ANG-2 or a fragment thereof. In certain embodiments, the multispecific antigen binding polypeptide binds to ANG-2 or a fragment thereof with an EC50 of about 11 picomolar or less. In certain embodiments, the multispecific antigen binding polypeptide binds to ANG-2 or a fragment thereof at least 300 fold stronger than faricimab. In certain embodiments, the first target, and or the second target is VEGF-C or a fragment thereof. In certain embodiments, the multispecific antigen binding polypeptide binds to VEGF-C or a fragment thereof with an EC50 of about 19 picomolar or less. In certain embodiments, the first target and the second target are independently selected from VEGF-A or fragment thereof, ANG-2 or a fragment thereof, and VEGF-C or a fragment thereof. In certain embodiments, the first and/or second antigen binding moiety bind antigens on different polypeptides. In certain embodiments, the first and/or second antigen binding moiety bind antigens on the same polypeptide. In certain embodiments, the first antigen binding moiety and/or the second antigen binding moiety binds to VEGF-A. In certain embodiments, the first antigen binding moiety and/or the second antigen binding moiety binds to VEGF-A and comprises an immunoglobulin heavy chain variable region comprising: (a) a heavy chain complementarity determining region 1 (HCDR1) comprising the amino acid sequence set forth in SEQ ID NO: 3; (b) a heavy chain complementarity determining region 2 (HCDR2) comprising the amino acid sequence set forth in SEQ ID NO: 4; and/or (c) a heavy chain complementarity determining region 3 (HCDR3) comprising the amino acid sequence set forth in SEQ ID NO: 5; wherein the heavy chain variable region binds to VEGF-A upon pairing with the light chain polypeptide. In certain embodiments, the first antigen binding moiety and/or the second antigen binding moiety comprises an immunoglobulin heavy chain variable region comprises an amino acid sequence comprising at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 1. In certain embodiments, the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety comprises an amino acid sequence comprising at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 2. In certain embodiments, the first antigen binding moiety and/or the second antigen binding moiety binds to ANG-2. In certain embodiments, the

first antigen binding moiety and/or the second antigen binding moiety bind to ANG-2 and comprises an immunoglobulin heavy chain variable region comprising: (a) a heavy chain complementarity determining region 1 (HCDR1) comprising the amino acid sequence set forth in SEQ ID NO: 13; (b) a heavy chain complementarity determining region 2 (HCDR2) comprising the amino acid sequence set forth in SEQ ID NO: 14; and/or (c) a heavy chain complementarity determining region 3 (HCDR3) comprising the amino acid sequence set forth in SEQ ID NO: 15; wherein the heavy chain variable region binds to ANG-2 upon pairing with the light chain polypeptide. In certain embodiments, the first antigen binding moiety and/or the second antigen binding moiety comprises an immunoglobulin heavy chain variable region comprising an amino acid sequence comprising at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 11. In certain embodiments, the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety comprises an amino acid sequence comprising at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 12. In certain embodiments, the multispecific antigen binding polypeptide comprises a first polypeptide chain comprising an amino acid sequence at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 401. In certain embodiments, the multispecific antigen binding polypeptide comprises a second polypeptide chain comprising an amino acid sequence at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 102. In certain embodiments, the first or second antigen binding moiety comprises a first heavy chain variable region (VH), a heavy chain first constant region (CH1), a heavy chain second constant region (CH2), and/or a heavy chain third constant region (CH3). In certain embodiments, the multispecific antigen binding polypeptide comprises a first polypeptide chain comprising an amino acid sequence at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 406. In certain embodiments, the multispecific antigen binding polypeptide comprises a second polypeptide chain comprising an amino acid sequence at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 102. In certain embodiments, the first antigen binding moiety and/or the second antigen binding moiety binds to VEGF-C. In certain embodiments, the first antigen binding moiety and/or the second antigen binding moiety binds to VEGF-C and comprises an immunoglobulin heavy chain variable region comprising: (a) a heavy chain complementarity determining region 1 (HCDR1) comprising the amino acid sequence set forth in SEQ ID NO: 23; (b) a heavy chain complementarity determining region 2 (HCDR2) comprising the amino acid sequence set forth in SEQ ID NO: 24; and/or (c) a heavy chain complementarity determining region 3 (HCDR3) comprising the amino acid sequence set

forth in SEQ ID NO: 25; wherein the heavy chain variable region binds to VEGF-C upon pairing with the light chain polypeptide. In certain embodiments, the first antigen binding moiety and/or the second antigen binding moiety comprises an immunoglobulin heavy chain variable region comprising an amino acid sequence comprising at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 21. In certain embodiments, the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety comprises an amino acid sequence comprising at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 22. In certain embodiments, each of the first antigen binding moiety, and/or the second antigen binding moiety is non-covalently paired to the surrogate light chain polypeptide. In certain embodiments, each of the first antigen binding moiety, and/or the second antigen binding moiety is covalently paired to the surrogate light chain polypeptide. In certain embodiments, the first antigen binding moiety comprises a first heavy chain variable region (VH) and a heavy chain first constant region (CH1). In certain embodiments, the second antigen binding moiety comprises a second heavy chain variable region (VH) and a heavy chain first constant region (CH1). In certain embodiments, the heavy chain first constant region comprises an amino acid sequence with at least 80%, at least 90%, at least 95%, at least 97%, at least 98%, at least 99%, or at least 100% identity to the amino acid sequence set forth in SEQ ID NO: 141. In certain embodiments, the first antigen binding moiety comprises a first heavy chain variable region (VH), a heavy chain first constant region (CH1), a heavy chain second constant region (CH2), and/or a heavy chain third constant region (CH3). In certain embodiments, the second antigen binding moiety comprises a second heavy chain variable region (VH), a heavy chain first constant region (CH1), a heavy chain second constant region (CH2), and/or a heavy chain third constant region (CH3). Also described is a pharmaceutical composition comprising the multispecific antigen binding polypeptide and a pharmaceutically acceptable carrier, excipient, or diluent. In certain embodiments, the pharmaceutical composition is formulated for intravenous administration. In certain embodiments, the pharmaceutical composition is formulated for intravitreal administration. Also described is a nucleic acid or plurality of nucleic acids encoding the multispecific antigen binding polypeptide. In certain embodiments is an expression vector comprising the nucleic acid. In certain embodiments the expression vector is RNA. In certain embodiments the expression vector is plasmid or linearized DNA. In certain embodiments the expression vector is a viral vector. In certain embodiments the viral vector is an adenovirus. In certain embodiments the viral vector is an adeno-associated virus. In certain embodiments the viral vector is a lentivirus virus. Also described is a pharmaceutical composition comprising the nucleic acid or plurality of nucleic acids encoding the multispecific antigen binding polypeptide

and a pharmaceutically acceptable carrier, excipient, or diluent. In certain embodiments, the pharmaceutical composition is formulated for intravenous administration. In certain embodiments, the pharmaceutical composition is formulated for intravitreal administration. Also described herein is a method of treating a disease in an individual comprising administering to the individual the multispecific antigen binding polypeptide, the nucleic acid or plurality of nucleic acids encoding the multispecific antigen binding polypeptide, or pharmaceutical composition thereby treating the disease. In certain embodiments, the disease is an ocular disease. In certain embodiments, the ocular disease comprises macular degeneration. In certain embodiments, the macular degeneration is neovascular age-related macular degeneration. In certain embodiments, the ocular disease comprises diabetic macular edema. In certain embodiments, the ocular disease comprises retinal vein occlusion. In certain embodiments, the disease is a cancer.

[0005] Described herein in one aspect is a vascular endothelial growth factor A (VEGF-A) antigen binding polypeptide or antigen binding fragment thereof comprising: (a) a heavy chain complementarity determining region 1 (HCDR1) comprising the amino acid sequence set forth in SEQ ID NO: 3; (b) a heavy chain complementarity determining region 2 (HCDR2) comprising the amino acid sequence set forth in SEQ ID NO: 4; and/or (c) a heavy chain complementarity determining region 3 (HCDR3) comprising the amino acid sequence set forth in SEQ ID NO: 5; wherein the antigen binding polypeptide binds to VEGF-A. In certain embodiments, the antigen binding or antigen binding fragment thereof comprises a heavy chain variable region comprising an amino acid sequence comprising at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 1. In certain embodiments, the antigen binding or antigen binding fragment thereof comprises a heavy chain region comprising an amino acid sequence comprising at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 2. In certain embodiments, the antigen binding or antigen binding fragment thereof comprises a surrogate light chain. Also described is a pharmaceutical composition comprising the antigen binding polypeptide and a pharmaceutically acceptable carrier, excipient, or diluent. In certain embodiments, the pharmaceutical composition is formulated for intravenous administration. In certain embodiments, the pharmaceutical composition is formulated for intravitreal administration. Also described is a nucleic acid or plurality of nucleic acids encoding the antigen binding polypeptide. In certain embodiments is an expression vector comprising the nucleic acid. In certain embodiments the expression vector is RNA. In certain embodiments the expression vector is plasmid or linearized DNA. In certain embodiments the expression vector is a viral vector. In certain embodiments the viral vector is an adenovirus. In certain embodiments the viral vector is

an adeno-associated virus. In certain embodiments the viral vector is a lentivirus virus. Also described is a pharmaceutical composition comprising the nucleic acid or plurality of nucleic acids encoding the antigen binding polypeptide and a pharmaceutically acceptable carrier, excipient, or diluent. In certain embodiments, the pharmaceutical composition is formulated for intravenous administration. In certain embodiments, the pharmaceutical composition is formulated for intravitreal administration. Also described herein is a method of treating a disease in an individual comprising administering to the individual the antigen binding polypeptide, the nucleic acid or plurality of nucleic acids encoding the antigen binding polypeptide, or pharmaceutical composition thereby treating the disease. In certain embodiments, the disease is an ocular disease. In certain embodiments, the ocular disease comprises macular degeneration. In certain embodiments, the macular degeneration is neovascular age-related macular degeneration. In certain embodiments, the ocular disease comprises diabetic macular edema. In certain embodiments, the ocular disease comprises retinal vein occlusion. In certain embodiments, the disease is a cancer.

[0006] Described herein in another aspect is an angiopoietin 2 (ANG-2) antigen binding polypeptide or antigen binding fragment thereof comprising: (a) a heavy chain complementarity determining region 1 (HCDR1) comprising the amino acid sequence set forth in SEQ ID NO: 13; (b) a heavy chain complementarity determining region 2 (HCDR2) comprising the amino acid sequence set forth in SEQ ID NO: 14; and/or (c) a heavy chain complementarity determining region 3 (HCDR3) comprising the amino acid sequence set forth in SEQ ID NO: 15, wherein the polypeptide binds to ANG-2. In certain embodiments, the antigen binding or antigen binding fragment thereof comprises a heavy chain variable region comprising an amino acid sequence comprising at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 11. In certain embodiments, the antigen binding or antigen binding fragment thereof comprises a heavy chain region comprising an amino acid sequence comprising at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 12. In certain embodiments, the antigen binding or antigen binding fragment thereof comprises a surrogate light chain. Also described is a pharmaceutical composition comprising the antigen binding polypeptide and a pharmaceutically acceptable carrier, excipient, or diluent. In certain embodiments, the pharmaceutical composition is formulated for intravenous administration. In certain embodiments, the pharmaceutical composition is formulated for intravitreal administration. Also described is a nucleic acid or plurality of nucleic acids encoding the antigen binding polypeptide. In certain embodiments is an expression vector comprising the nucleic acid. In certain embodiments the expression vector is RNA. In certain embodiments the expression vector is plasmid or linearized DNA. In certain

embodiments the expression vector is a viral vector. In certain embodiments the viral vector is an adenovirus. In certain embodiments the viral vector is an adeno-associated virus. In certain embodiments the viral vector is a lentivirus virus. Also described is a pharmaceutical composition comprising the nucleic acid or plurality of nucleic acids encoding the antigen binding polypeptide and a pharmaceutically acceptable carrier, excipient, or diluent. In certain embodiments, the pharmaceutical composition is formulated for intravenous administration. In certain embodiments, the pharmaceutical composition is formulated for intravitreal administration. Also described herein is a method of treating a disease in an individual comprising administering to the individual the antigen binding polypeptide, the nucleic acid or plurality of nucleic acids encoding the antigen binding polypeptide, or pharmaceutical composition thereby treating the disease. In certain embodiments, the disease is an ocular disease. In certain embodiments, the ocular disease comprises macular degeneration. In certain embodiments, the macular degeneration is neovascular age-related macular degeneration. In certain embodiments, the ocular disease comprises diabetic macular edema. In certain embodiments, the ocular disease comprises retinal vein occlusion. In certain embodiments, the disease is a cancer.

[0007] Described herein in one aspect is a vascular endothelial growth factor C (VEGF-C) antigen binding polypeptide or antigen binding fragment thereof comprising: (a) a heavy chain complementarity determining region 1 (HCDR1) comprising the amino acid sequence set forth in SEQ ID NO: 23; (b) a heavy chain complementarity determining region 2 (HCDR2) comprising the amino acid sequence set forth in SEQ ID NO: 24; and (c) a heavy chain complementarity determining region 3 (HCDR3) comprising the amino acid sequence set forth in SEQ ID NO: 25; wherein the antigen binding polypeptide binds to VEGF-C. In certain embodiments, the antigen binding or antigen binding fragment thereof comprises a heavy chain variable region comprising an amino acid sequence comprising at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 21. In certain embodiments, the antigen binding or antigen binding fragment thereof comprises a heavy chain region comprising an amino acid sequence comprising at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 22. In certain embodiments, the antigen binding or antigen binding fragment thereof comprises a surrogate light chain. Also described is a pharmaceutical composition comprising the antigen binding polypeptide and a pharmaceutically acceptable carrier, excipient, or diluent. In certain embodiments, the pharmaceutical composition is formulated for intravenous administration. In certain embodiments, the pharmaceutical composition is formulated for intravitreal administration. Also described is a nucleic acid or plurality of nucleic acids encoding the antigen binding polypeptide.

In certain embodiments is an expression vector comprising the nucleic acid. In certain embodiments the expression vector is RNA. In certain embodiments the expression vector is plasmid or linearized DNA. In certain embodiments the expression vector is a viral vector. In certain embodiments the viral vector is an adenovirus. In certain embodiments the viral vector is an adeno-associated virus. In certain embodiments the viral vector is a lentivirus virus. Also described is a pharmaceutical composition comprising the nucleic acid or plurality of nucleic acids encoding the antigen binding polypeptide and a pharmaceutically acceptable carrier, excipient, or diluent. In certain embodiments, the pharmaceutical composition is formulated for intravenous administration. In certain embodiments, the pharmaceutical composition is formulated for intravitreal administration. Also described herein is a method of treating a disease in an individual comprising administering to the individual the antigen binding polypeptide, the nucleic acid or plurality of nucleic acids encoding the antigen binding polypeptide, or pharmaceutical composition thereby treating the disease. In certain embodiments, the disease is an ocular disease. In certain embodiments, the ocular disease comprises macular degeneration. In certain embodiments, the macular degeneration is neovascular age-related macular degeneration. In certain embodiments, the ocular disease comprises diabetic macular edema. In certain embodiments, the ocular disease comprises retinal vein occlusion. In certain embodiments, the disease is a cancer.

[0008] Described herein in one aspect is a multispecific antigen binding polypeptide comprising: (a) a first antigen binding moiety, comprising a first heavy chain variable region (VH) and a heavy chain first constant region (CH1); (b) a second antigen binding moiety, comprising a second heavy chain variable region (VH) and a second heavy chain first constant region (CH1); and (c) a third antigen binding moiety, comprising a third heavy chain variable region (VH) and a third heavy chain first constant region (CH1); wherein the first antigen binding moiety binds to a first target, the second antigen binding moiety binds to a second target, and the third antigen binding moiety binds to a third target, wherein the first antigen binding moiety, the second antigen binding moiety, and the third antigen binding moiety are non-covalently paired to a light chain polypeptide. In certain embodiments, the light chain polypeptide is a surrogate light chain polypeptide. In certain embodiments, the surrogate light chain polypeptide comprises a VpreB sequence fused to a $\lambda 5$ sequence. In certain embodiments, the surrogate light chain polypeptide comprises an amino acid sequence comprising at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 102. In certain embodiments, the surrogate light chain polypeptide comprises the amino acid sequence set forth in SEQ ID NO: 102. In certain embodiments, the first antigen binding moiety, the second antigen binding moiety, and the third antigen binding moiety are independently selected from the list consisting of

VEGF-A, VEGF-C, and ANG-2. In certain embodiments, a C-terminus of the first heavy chain variable region or the first antigen binding moiety is directly connected to an N-terminus of the second heavy chain variable region. In certain embodiments, a C-terminus of the second heavy chain variable region or the second antigen binding moiety is directly connected to an N-terminus of the third heavy chain variable region. In certain embodiments, a C-terminus of the first heavy chain variable region or the first antigen binding moiety is directly connected to an N-terminus of the second heavy chain variable region, and wherein a C-terminus of the second heavy chain variable region or the second antigen binding moiety is directly connected to an N-terminus of the third heavy chain variable region. In certain embodiments, the multispecific antigen binding polypeptide comprises an amino acid sequence comprising at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 201. In certain embodiments, the multispecific antigen binding polypeptide comprises an amino acid sequence comprising at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 202. In certain embodiments, the multispecific antigen binding polypeptide comprises at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 203. In certain embodiments, the first, second, and third antigen binding moiety comprise or consist of the amino acid sequence set forth in SEQ ID NO: 201. In certain embodiments, the first, second, and third antigen binding moiety comprise or consist of the amino acid sequence set forth in SEQ ID NO: 202. In certain embodiments, the first, second, and third antigen binding moiety comprise or consist of the amino acid sequence set forth in SEQ ID NO: 203. In certain embodiments, the multispecific antigen binding polypeptide is encoded by a nucleic acid. In certain embodiments, described is a method of treating a disease in an individual comprising administering to the individual the multispecific antigen binding polypeptide, the nucleic acid or plurality of nucleic acids encoding the multispecific antigen binding polypeptide, or pharmaceutical composition, thereby treating the disease. In certain embodiments, the disease is an ocular disease. In certain embodiments, the ocular disease comprises macular degeneration. In certain embodiments, the macular degeneration is neovascular age-related macular degeneration. In certain embodiments, wherein the ocular disease comprises diabetic macular edema. In certain embodiments, the ocular disease comprises retinal vein occlusion. In certain embodiments, the disease is a cancer.

BRIEF DESCRIPTION OF THE DRAWINGS

[0009] The novel features described herein are set forth with particularity in the appended claims. A better understanding of the features and advantages of the features described herein will be obtained by reference to the following detailed description that sets forth illustrative

examples, in which the principles of the features described herein are utilized, and the accompanying drawings of which:

[0010] FIG. 1 is an exemplary trispecific antigen binding polypeptide comprising three binding moieties that bind to three different targets. Each of the three binding moieties comprises a variable heavy chain region (V_H) linked to a heavy chain first constant region ($CH1$). Each of the three binding moieties also comprises a VpreB domain linked to a $\lambda 5$ domain.

[0011] FIG. 2 is an exemplary trispecific antigen binding polypeptide comprising three binding moieties that bind to three different targets. One of the binding moieties that binds to target 3 comprises a crossed domain. Each of the three binding moieties comprises a variable heavy chain region (V_H) linked to a heavy chain first constant region ($CH1$). Each of the three binding moieties also comprises a VpreB domain linked to a $\lambda 5$ domain or a variable light chain region (V_L) linked to a constant light chain region (CL).

[0012] FIG. 3 is an exemplary trispecific antigen binding polypeptide comprising three binding moieties that bind to three different targets. Two of the binding moieties comprise a crossed domain. Each of the three binding moieties comprises a variable heavy chain region (V_H) linked to a heavy chain first constant region ($CH1$). Each of the three binding moieties also comprises a VpreB domain linked to a $\lambda 5$ domain or a variable light chain region (V_L) linked to a constant light chain region (CL).

[0013] FIG. 4 is an exemplary trispecific antigen binding polypeptide comprising three binding moieties that bind to three different targets. Each of the three binding moieties comprises a variable heavy chain region (V_H) linked to a heavy chain first constant region ($CH1$). Each of the three binding moieties also comprises a variable light chain region (V_L) linked to a constant light chain region (CL).

[0014] FIGs. 5A-5C illustrate SDS-PAGE and SE-HPLC analysis of RO-104 a trispecific antigen binding polypeptide that binds to VEGF-A, ANG-2 and VEGF-C. **FIG. 5A** illustrates SDS-PAGE results for reduced and non-reduced samples. **FIG. 5B** illustrates an SE-HPLC graph of the trispecific antigen binding polypeptide. **FIG. 5C** shows SE-HPLC results of the trispecific antigen binding polypeptide produced in small and large scales.

[0015] FIGs. 6A-6E illustrate trispecific RO-104's binding affinity to VEGF-A, ANG-2, and VEGF-C in comparison with Faricimab, which binds to VEGF-A and ANG-2. **FIG. 6A** illustrates ELISA-binding results for Faricimab's binding to VEGF-A. **FIG. 6B** illustrates ELISA-binding results for Faricimab's binding to ANG-2. **FIG. 6C** illustrates ELISA-binding results for RO-104 trispecific antigen binding polypeptide's binding to VEGF-A. **FIG. 6D** illustrates ELISA-binding results for RO-104 trispecific antigen binding polypeptide's binding to

ANG-2. **FIG. 6E** illustrates ELISA-binding results for RO-104 trispecific antigen binding polypeptide's binding to VEGF-C.

[0016] FIGs. 6F-6I illustrate trispecific RO-104's binding affinity to VEGF-A, ANG-2, and VEGF-C in comparison with Aflibercept, which binds to VEGF-A. **FIG. 6F** illustrates ELISA-binding results for Aflibercept's binding to VEGF-A. **FIG. 6G** illustrates ELISA-binding results for RO-104 trispecific antigen binding polypeptide's binding to VEGF-A. **FIG. 6H** illustrates ELISA-binding results for RO-104 trispecific antigen binding polypeptide's binding to ANG-2. **FIG. 6I** illustrates ELISA-binding results for RO-104 trispecific antigen binding polypeptide's binding to VEGF-C.

[0017] FIGs. 7A-7C illustrate the binding affinity of three different constructs of VEGF-A/ANG-2/VEGF-C trispecific antigen binding polypeptide to VEGF-A, ANG-2, and VEGF-C. **FIG. 7A** illustrates ELISA-binding results for trispecific antigen binding polypeptides binding to VEGF-A. **FIG. 7B** illustrates ELISA-binding results for trispecific antigen binding polypeptides binding to ANG-2. **FIG. 7C** illustrates ELISA-binding results for trispecific antigen binding polypeptides binding to VEGF-C.

[0018] FIGs. 8A-8C illustrate trispecific RO-104's anti-angiogenic efficacy in comparison with Faricimab in a rat model. **FIG. 8A** illustrates retinal vascular images 8 days after treatment with RO-104 or Faricimab. **FIG. 8B** shows the results of lesion size on day 8 after treating with RO-104 or Faricimab. **FIG. 8C** shows the comparison of the area of choroidal neovascularization lesions in each eye on day 8 in arbitrary units (a.u.), after being treated with the control, Faricimab, or RO-104.

[0019] FIG. 8D illustrates trispecific RO-104's anti-angiogenic efficacy in comparison with both Faricimab and Aflibercept in a rat model. The graph shows the corrected total lesion fluorescence in each eye on day 8 in arbitrary units (a.u.), after being treated with the control, Faricimab, Aflibercept, or RO-104.

[0020] FIGs. 9A-9D illustrate the IC_{50} of RO-104 and Faricimab. **FIG. 9A** shows IC_{50} of RO-104 and Faricimab for VEGF-A. **FIG. 9B** shows IC_{50} of RO-104 and Faricimab for ANG-2. **FIG. 9C** shows IC_{50} of RO-104 and Faricimab for VEGF-C. **FIG. 9D** shows IC_{50} of RO-104 and Faricimab in VEGF-A/ANG-2/VEGF-C tri-specific target receptor interaction.

[0021] FIGs. 10A-10C illustrate inhibition of endothelial cell migration by RO-104. **FIG. 10A** shows the HUVEC cells treated with VEGF, Aflibercept, and RO-104. **FIG. 10B** shows the HUVEC wound density of VEGF-A induced in vitro wound closure of HUVEC cells in the presence of either RO-104 or aflibercept. **FIG. 10C** shows the HUVEC wound confluence of VEGF-A induced in vitro wound closure of HUVEC cells in the presence of either RO-104 or aflibercept.

[0022] **FIG. 11** shows the OD450nm ratio over background of anti-drug antibody (ADA) titer in pooled human serum against three different constructs of VEGF-A /ANG-2/VEGF-C trispecific antigen binding polypeptides, Brolucizumab, and Ranibizumab.

[0023] **FIG. 12** shows the concentration of RO-104 bound to VEGF-A, ANG-2, and VEGF-C in vitreous humor across 29-day study.

[0024] **FIG. 13** illustrates ErbB3/VEGF-A/ANG-2/VEGF-C tetraspecific surrobody binding affinity to ErbB3, VEGF-A, ANG-2, VEGF-C, and PD-1.

[0025] **FIG. 14** illustrates EGFR/ErbB2/ErbB3 trispecific antibody binding affinity to EGFR, ErbB2, and ErbB3.

[0026] **FIG. 15** illustrates c-Met/EGFR/ErbB2/ErbB3 tetraspecific antibody binding affinity to c-Met, EGFR, ErbB2, and ErbB3.

[0027] **FIGs. 16A-16B** are exemplary monospecific antibodies with multiple antigen binding units. **FIG. 16A** is an exemplary monospecific anti-PD1 trivalent antibody. Each of the three PD-1 binding moieties comprises a variable heavy chain region (V_H) linked to a heavy chain first constant region (CH1) and a variable light chain region (V_L) linked to a light chain constant region (CL). **FIG. 16B** is an exemplary monospecific anti-PD1 tetravalent antibody. Each of the four PD-1 binding moieties comprises a variable heavy chain region (V_H) linked to a heavy chain first constant region (CH1) and a variable light chain region (V_L) linked to a light chain constant region (CL). The tetravalent antibody also comprises a heavy chain second constant region (CH2) and a heavy chain third constant region (CH3).

[0028] **FIG. 17** illustrates anti-PD-1 trivalent and tetravalent antibody binding affinity to PD-1.

[0029] **FIGs. 18A-18D** illustrate SDS-PAGE and SE-HPLC analysis of RP-010 and RP-015 trispecific antigen binding polypeptides that bind to VEGF-A, ANG-2 and VEGF-C. **FIG. 18A** illustrates SDS-PAGE results for reduced and non-reduced samples of RP-010. **FIG. 18B** illustrates SE-HPLC graph of the RP-010 trispecific antigen binding polypeptide. **FIG. 18C** illustrates SDS-PAGE results for reduced and non-reduced samples of RP-015. **FIG. 18D** illustrates SE-HPLC graph of the RP-015 trispecific antigen binding polypeptide.

[0030] **FIGs. 19A-19C** illustrate trispecific RP-015's binding affinity to VEGF-A, ANG-2, and VEGF-C in comparison with RO-104. **FIG. 19A** illustrates ELISA-binding results for RP-015 trispecific antigen binding polypeptide's binding to VEGF-A. **FIG. 19B** illustrates ELISA-binding results for RP-015 trispecific antigen binding polypeptide's binding to ANG-2. **FIG. 19C** illustrates ELISA-binding results for RP-015 trispecific antigen binding polypeptide's binding to VEGF-C.

[0031] **FIGs. 20A-20D** illustrate SDS-PAGE and SE-HPLC analysis of RP-028 and RP-029 bispecific antigen binding polypeptides that bind to VEGF-A and ANG-2. **FIG. 20A** illustrates

SDS-PAGE results for reduced and non-reduced samples of RP-028. **FIG. 20B** illustrates SE-HPLC graph of the RP-028 bispecific antigen binding polypeptide. **FIG. 20C** illustrates SDS-PAGE results for reduced and non-reduced samples of RP-029. **FIG. 20D** illustrates SE-HPLC graph of the RP-029 bispecific antigen binding polypeptide.

[0032] FIGs. 21A-21B illustrate bispecific RP-028 and RP-029's binding affinity to VEGF-A and ANG-2. **FIG. 21A** illustrates ELISA-binding results for RP-028 and RP-029 bispecific antigen binding polypeptides' binding to VEGF-A. **FIG. 21B** illustrates ELISA-binding results for RP-028 and RP-029 bispecific antigen binding polypeptides' binding to ANG-2.

[0033] FIGs. 22A-22D illustrate inhibition of RP-028, RP-029 and Faricimab to the binding of the target receptor. **FIG. 22A** shows IC_{50} of RP-028 and Faricimab for VEGF-A and VEGF R2/KDR. **FIG. 22B** shows IC_{50} of RP-028 and Faricimab for ANG-2 and Tie2. **FIG. 22C** shows IC_{50} of RP-029 and Faricimab for VEGF-A and VEGF R2/KDR. **FIG. 22D** shows IC_{50} of RP-029 and Faricimab for ANG-2 and Tie2.

DETAILED DESCRIPTION

[0034] Described herein in one aspect, is multispecific antigen binding polypeptide comprising: a first antigen binding moiety, comprising a first heavy chain variable region; a second antigen binding moiety, comprising a second heavy chain variable region; and a third antigen binding moiety, comprising a third heavy chain variable region; wherein the first antigen binding moiety binds to a first target, the second antigen binding moiety binds to a second target, and the third antigen binding moiety binds to a third target, wherein the first antigen binding moiety, the second antigen binding moiety and the third antigen binding moiety are paired to a light chain polypeptide. In some embodiments, the multispecific antigen binding polypeptide further comprises a fourth heavy chain variable region, wherein the fourth antigen binding moiety binds to a fourth target, wherein the fourth antigen binding moiety is paired to the light chain polypeptide.

[0035] Described herein in one aspect is a multispecific antigen binding polypeptide comprising: (a) a first antigen binding moiety, comprising a first heavy chain variable region (VH) and a heavy chain first constant region (CH1); (b) a second antigen binding moiety, comprising a second heavy chain variable region (VH) and a second heavy chain first constant region (CH1); and (c) a third antigen binding moiety, comprising a third heavy chain variable region (VH) and a third heavy chain first constant region (CH1); wherein the first antigen binding moiety binds to a first target, the second antigen binding moiety binds to a second target, and the third antigen binding moiety binds to a third target, wherein the first antigen binding moiety, the second

antigen binding moiety, and the third antigen binding moiety are non-covalently paired to a light chain polypeptide.

[0036] Described herein in another aspect is a multispecific antigen binding polypeptide comprising: a first antigen binding moiety, comprising a first heavy chain variable region and a first heavy chain first constant region (CH1) paired with a first light chain; and a second antigen binding moiety, comprising a second heavy chain variable region and a second heavy chain first constant region (CH1) paired with a second light chain; wherein a C to terminus of the first CH1 is coupled to an N-terminus of the second heavy chain variable region wherein the first antigen binding moiety binds to a first target, the second antigen binding moiety binds to a second target.

[0037] In the following description, certain specific details are set forth in order to provide a thorough understanding of various embodiments. However, one skilled in the art will understand that the embodiments provided may be practiced without these details. Unless the context requires otherwise, throughout the specification and claims which follow, the word “comprise” and variations thereof, such as, “comprises” and “comprising” are to be construed in an open, inclusive sense, that is, as “including, but not limited to.” 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. It should also be noted that the term “or” is generally employed in its sense including “and/or” unless the content clearly dictates otherwise. Further, headings provided herein are for convenience only and do not interpret the scope or meaning of the claimed embodiments.

[0038] As used herein the term “about” refers to an amount that is near the stated amount by 10% or less.

[0039] As used herein “vascular endothelial growth factor A” or “VEGF-A” refers to the polypeptide encoded by the *VEGFA* gene, which amino acid sequence is available at www.uniprot.org/uniprot/P15692. Such sequence includes post-translational modifications, naturally occurring amino acid variants, and naturally occurring splice variants that do not affect the binding of the antigen binding polypeptides and bispecific antigen binding polypeptides described herein.

[0040] As used herein “Angiopoietin 2” or “ANG-2” refers to the polypeptide encoded by the *ANGPT2* gene, which amino acid sequence is available at www.uniprot.org/uniprot/O15123. Such sequence includes post-translational modifications, naturally occurring amino acid variants, and naturally occurring splice variants that do not affect the binding of the antigen binding polypeptides and bispecific antigen binding polypeptides described herein.

[0041] As used herein “vascular endothelial growth factor C” or “VEGF-C” refers to the polypeptide encoded by the *VEGFA* gene, which amino acid sequence is available at

www.uniprot.org/uniprot/P49767. Such sequence includes post-translational modifications, naturally occurring amino acid variants, and naturally occurring splice variants that do not affect the binding of the antigen binding polypeptides and bispecific antigen binding polypeptides described herein.

[0042] As used herein “receptor tyrosine-protein kinase erbB-3” or “ErbB3” refers to the polypeptide encoded by the *ERBB3* gene, which amino acid sequence is available at <https://www.uniprot.org/uniprotkb/P21860/entry>. Such sequence includes post-translational modifications, naturally occurring amino acid variants, and naturally occurring splice variants that do not affect the binding of the antigen binding polypeptides and bispecific antigen binding polypeptides described herein.

[0043] As used herein “receptor tyrosine-protein kinase erbB-2” or “ErbB2” refers to the polypeptide encoded by the *ERBB2* gene, which amino acid sequence is available at <https://www.uniprot.org/uniprotkb/P04626/entry>. Such sequence includes post-translational modifications, naturally occurring amino acid variants, and naturally occurring splice variants that do not affect the binding of the antigen binding polypeptides and bispecific antigen binding polypeptides described herein.

[0044] As used herein “epidermal growth factor receptor” or “EGFR” refers to the polypeptide encoded by the *EGFR* gene, which amino acid sequence is available at <https://www.uniprot.org/uniprotkb/P00533/entry>. Such sequence includes post-translational modifications, naturally occurring amino acid variants, and naturally occurring splice variants that do not affect the binding of the antigen binding polypeptides and bispecific antigen binding polypeptides described herein.

[0045] As used herein “hepatocyte growth factor receptor” or “c-Met” refers to the polypeptide encoded by the *MET* gene, which amino acid sequence is available at <https://www.uniprot.org/uniprotkb/P08581/entry>. Such sequence includes post-translational modifications, naturally occurring amino acid variants, and naturally occurring splice variants that do not affect the binding of the antigen binding polypeptides and bispecific antigen binding polypeptides described herein.

[0046] As used herein “programmed cell death protein 1” or “PD-1” refers to the polypeptide encoded by the *PDCDI* gene, which amino acid sequence is available at <https://www.uniprot.org/uniprotkb/Q15116/entry>. Such sequence includes post-translational modifications, naturally occurring amino acid variants, and naturally occurring splice variants that do not affect the binding of the antigen binding polypeptides and bispecific antigen binding polypeptides described herein.

[0047] As used herein a “surrogate light chain” refers to a light chain that is expressed during early B cell development that can associate promiscuously with two or more different expressed heavy chains. A specific surrogate light chain can be formed by fusion of a VpreB polypeptide and $\lambda 5$ polypeptide, and can productively associate with two or more structurally distinct heavy chains. Such surrogate light chains are described in U.S. 8,114,967; U.S. 10,214,580; and 8,969,082, each of which are incorporated herein in their entirety.

[0048] As used herein a “common light chain” or “universal light chain” refers to a single light chain that can productively associate with two or more structurally distinct heavy chains.

[0049] As used herein the term “individual,” “patient,” or “subject” refers to individuals diagnosed with, suspected of being afflicted with, or at-risk of developing at least one disease for which the described compositions and method are useful for treating. In certain embodiments the individual is a mammal. In certain embodiments, the mammal is a mouse, rat, rabbit, dog, cat, horse, cow, sheep, pig, goat, llama, alpaca, or yak. In certain embodiments, the individual is a human.

[0050] Among the provided antigen binding polypeptides are monoclonal antibodies, multispecific antibodies (for example, bispecific antibodies, trispecific antibodies, and polyreactive antibodies), and antibody fragments. The antibodies include antibody-conjugates and molecules comprising the antibodies, such as chimeric molecules. Thus, an antibody includes, but is not limited to, full-length and native antibodies, as well as fragments and portion thereof retaining the binding specificities thereof, such as any specific binding portion thereof including those having any number of, immunoglobulin classes and/or isotypes (e.g., IgG1, IgG2, IgG3, IgG4, IgM, IgA, IgD, IgE and IgM); and biologically relevant (antigen-binding) fragments or specific binding portions thereof, including but not limited to Fab, F(ab')₂, Fv, and scFv (single chain or related entity). A monoclonal antibody is generally one within a composition of substantially homogeneous antibodies; thus, any individual antibodies comprised within the monoclonal antibody composition are identical except for possible naturally occurring mutations that may be present in minor amounts. The monoclonal antibody can comprise a human IgG1 constant region. The monoclonal antibody can comprise a human IgG4 constant region.

[0051] The term “antibody” herein is used in the broadest sense and includes monoclonal antibodies, bispecific antibodies, and includes intact antibodies and functional (antigen-binding) antibody fragments thereof, including fragment antigen binding (Fab) fragments, F(ab')₂ fragments, Fab' fragments, Fv fragments, recombinant IgG (rIgG) fragments, single chain antibody fragments, including single chain variable fragments (sFv or scFv), and single domain antibodies (e.g., sdAb, sdFv, nanobody) fragments. The term encompasses genetically engineered and/or otherwise modified forms of immunoglobulins, such as intrabodies, peptibodies, chimeric

antibodies, fully human antibodies, humanized antibodies, and heteroconjugate antibodies, multispecific, e.g., bispecific, antibodies, diabodies, triabodies, and tandem di-scFv, tandem tri-scFv. Unless otherwise stated, the term “antibody” should be understood to encompass functional antibody fragments thereof. The term also encompasses intact or full-length antibodies, including antibodies of any class or sub-class, including IgG and sub-classes thereof, IgM, IgE, IgA, and IgD. The antibody can comprise a human IgG1 constant region. The antibody can comprise a human IgG4 constant region.

[0052] The term “antigen binding polypeptide” or “antigen binding moiety” herein is used in the broadest sense and includes polypeptides that bind to an antigen. The term may include monoclonal antibodies, bispecific antibodies, and includes intact antibodies and functional (antigen-binding) antibody fragments thereof, including fragment antigen binding (Fab) fragments, F(ab')₂ fragments, Fab' fragments, Fv fragments, recombinant IgG (rIgG) fragments, single chain antibody fragments, including single chain variable fragments (sFv or scFv), and single domain antibodies (e.g., sdAb, sdFv, nanobody) fragments. The term encompasses genetically engineered and/or otherwise modified forms of immunoglobulins, such as intrabodies, peptibodies, chimeric antibodies, surrobodies, fully human antibodies, humanized antibodies, and heteroconjugate antibodies, multispecific, e.g., bispecific, antibodies, diabodies, triabodies, and tandem di-scFv, tandem tri-scFv. Unless otherwise stated, the term “antigen binding polypeptide” should be understood to encompass functional antigen binding polypeptide and fragments thereof. The term also encompasses intact or full-length antibodies, including antibodies of any class or sub-class, including IgG and sub-classes thereof, IgM, IgE, IgA, and IgD.

[0053] As used herein the terms “heavy chain” or “light chain” relate to polypeptides derived from or similar to heavy chains or light chains of antibodies or antibody like molecules. The light chains and heavy chains of such antibodies or antibody like molecules may consist of several domains. In a whole antibody, each heavy chain comprises a heavy chain variable region (abbreviated herein as VH) and a heavy chain constant region. The heavy chain constant region comprises the heavy chain constant domains CH1, hinge, CH2 and CH3 (antibody classes IgA, IgD, and IgG) and optionally the heavy chain constant domain CH4 (antibody classes IgE and IgM). Each light chain comprises a light chain variable domain (abbreviated herein as VL) and a light chain constant domain CL.

[0054] Herein a molecule, peptide, polypeptide, antibody, or antibody fragment can be referred to as “bispecific” or “dual-specific” including grammatical equivalents. A bispecific molecule possesses the ability to specifically bind to at least two structurally distinct targets. The specific binding may be the result of two distinct binding moieties that are structurally distinct at the

molecular level, including but not limited to distinct non-identical amino acid sequences; or a single binding moiety that is able to specifically bind to two structurally distinct targets with high affinity (e.g., with a KD less than about 1×10^{-6}). A molecule, peptide, polypeptide, antibody, or antibody fragment referred to as “multi-specific” refers to a molecule that possesses the ability to specifically bind to at least three structurally distinct targets. A “bispecific antibody” including grammatical equivalents refers to a bispecific molecule that preserves at least one fragment of an antibody able to specifically bind a target, for example, a variable region, heavy or light chain, or one or more complementarity determining regions from an antibody molecule.

[0055] Herein a molecule, peptide, polypeptide, antibody, or antibody fragment can be referred to as “trispecific” including grammatical equivalents. A trispecific molecule possesses the ability to specifically bind to at least three structurally distinct targets. The specific binding may be the result of three distinct binding moieties that are structurally distinct at the molecular level, including but not limited to distinct non-identical amino acid sequences; or a single binding moiety that is able to specifically bind to three structurally distinct targets with high affinity (e.g., with a KD less than about 1×10^{-6}). Herein a molecule, peptide, polypeptide, antibody, or antibody fragment can be referred to as “tetraspecific” including grammatical equivalents. A tetraspecific molecule possesses the ability to specifically bind to at least four structurally distinct targets. The specific binding may be the result of four distinct binding moieties that are structurally distinct at the molecular level, including but not limited to distinct non-identical amino acid sequences; or a single binding moiety that is able to specifically bind to four structurally distinct targets with high affinity (e.g., with a KD less than about 1×10^{-6}). A molecule, peptide, polypeptide, antibody, or antibody fragment referred to as “multi-specific” refers to a molecule that possesses the ability to specifically bind to at least three structurally distinct targets. A “multi-specific antibody” including grammatical equivalents refers to a multi-specific molecule that preserves at least one fragment of an antibody able to specifically bind with a target, for example, a variable region, heavy or light chain, or complementarity determining region from an antibody molecule.

[0056] The terms “complementarity determining region,” and “CDR,” which are synonymous with “hypervariable region” or “HVR,” are known in the art to refer to non-contiguous sequences of amino acids within antibody variable regions, which confer antigen specificity and/or binding affinity. In general, there are three CDRs in each heavy chain variable region (CDR-H1, CDR-H2, CDR-H3) and three CDRs in each light chain variable region (CDR-L1, CDR-L2, CDR-L3). “Framework regions” and “FR” are known in the art to refer to the non-CDR portions of the variable regions of the heavy and light chains. In general, there are four FRs in each full-length heavy chain variable region (FR-H1, FR-H2, FR-H3, and FR-H4), and four FRs in each full-length light chain variable region (FR-L1, FR-L2, FR-L3, and FR-L4). The precise amino acid

sequence boundaries of a given CDR or FR can be readily determined using any of a number of well-known schemes, including those described by Kabat et al. (1991), "Sequences of Proteins of Immunological Interest," 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD ("Kabat" numbering scheme); Al-Lazikani et al., (1997) *JMB* 273,927-948 ("Chothia" numbering scheme); MacCallum et al., *J. Mol. Biol.* 262:732-745 (1996), "Antibody-antigen interactions: Contact analysis and binding site topography," *J. Mol. Biol.* 262, 732-745." ("Contact" numbering scheme); Lefranc MP et al., "IMGT unique numbering for immunoglobulin and T cell receptor variable domains and Ig superfamily V-like domains," *Dev Comp Immunol*, 2003 Jan;27(1):55-77 ("IMGT" numbering scheme); Honegger A and Plückthun A, "Yet another numbering scheme for immunoglobulin variable domains: an automatic modeling and analysis tool," *J Mol Biol*, 2001 Jun 8;309(3):657-70, ("Aho" numbering scheme); and Whitelegg NR and Rees AR, "WAM: an improved algorithm for modelling antibodies on the WEB," *Protein Eng.* 2000 Dec;13(12):819-24 ("AbM" numbering scheme. In certain embodiments, the CDRs of the antigen binding polypeptides described herein can be defined by a method selected from Kabat, Chothia, IMGT, Aho, AbM, or combinations thereof.

[0057] The boundaries of a given CDR or FR may vary depending on the scheme used for identification. For example, the Kabat scheme is based on structural alignments, while the Chothia scheme is based on structural information. Numbering for both the Kabat and Chothia schemes is based upon the most common antibody region sequence lengths, with insertions accommodated by insertion letters, for example, "30a," and deletions appearing in some antibodies. The two schemes place certain insertions and deletions ("indels") at different positions, resulting in differential numbering. The Contact scheme is based on analysis of complex crystal structures and is similar in many respects to the Chothia numbering scheme.

[0058] The term "variable region" or "variable domain" refers to the domain of an antibody heavy or light chain that is involved in binding the antibody to antigen. The variable domains of the heavy chain and light chain (V_H and V_L , respectively) of a native antibody generally have similar structures, with each domain comprising four conserved framework regions (FRs) and three CDRs (*See e.g.*, Kindt et al. *Kuby Immunology*, 6th ed., W.H. Freeman and Co., page 91(2007)). A single V_H or V_L domain may be sufficient to confer antigen-binding specificity. Furthermore, antigen binding polypeptides that bind a particular antigen may be isolated using a V_H or V_L domain from an antibody that binds the antigen to screen a library of complementary V_L or V_H domains, respectively (*See e.g.*, Portolano et al., *J. Immunol.* 150:880-887 (1993); Clarkson et al., *Nature* 352:624-628 (1991)).

[0059] The terms "crossed domain" or "CrossMab" refers to the light chain constant and heavy chain constant domains of an antibody or an antigen binding moiety being crossed over. A

crossed domain comprises one or more amino acid substitutions to a light chain constant domain corresponding to one or more amino acids from an immunoglobulin CH1 domain and vice versa. The crossed domain enforces correct light chain association in the multispecific antigen binding polypeptides (*See e.g.*, Surowka et al., *MABS*. 13(1): E1967714 (2021)).

[0060] Specific binding or binding of antigen binding polypeptide molecules described herein refers to binding mediated by one or more CDR portions of the antigen binding polypeptide. Not all CDRs may be required for specific binding. Specific binding can be demonstrated for example by an ELISA against a specific recited target or antigen that shows significant increase in binding compared to an isotype control antigen binding polypeptide.

[0061] As described herein an “epitope” refers to the binding determinant of an antigen binding polypeptide or fragment described herein minimally necessary for specific binding of the antigen binding polypeptide or fragment thereof to a target antigen. When the target antigen is a polypeptide the epitope will be a continuous or discontinuous epitope. A continuous epitope is formed by one region of the target antigen, while a discontinuous epitope may be formed from two or more separate regions. A discontinuous epitope, for example, may form when a target antigen adopts a tertiary structure that brings two amino acid sequences together and forms a three-dimensional structure bound by the antigen binding polypeptide. When the target antigen is a polypeptide the epitope will generally be a plurality of amino acids linked into a polypeptide chain. A continuous epitope may comprise 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 contiguous amino acids. While an epitope may comprise a contiguous polymer of amino acids, not every amino acid of the polymer may be contacted by an amino acid residue of the antigen binding polypeptide. Such non-contacted amino acids will still comprise part of the epitope as they may be important for the structure and linkage of the contacted amino acids. The skilled artisan may determine if any given antigen binding polypeptide binds an epitope of a reference antigen binding polypeptide, for example, by cross-blocking experiments with a reference antigen binding polypeptide. In certain embodiments, described herein, are antigen binding polypeptides that bind the same epitope of the described antigen binding polypeptides. In certain embodiments, described herein, are antigen binding polypeptides that are competitively blocked by the described antigen binding polypeptides. In certain embodiments, described herein, are antigen binding polypeptides that compete for binding with the described antigen binding polypeptides.

[0062] Among the provided antigen binding polypeptides are antibody fragments. An “antibody fragment” refers to a molecule other than an intact antibody that comprises a portion of an intact antibody that binds the antigen to which the intact antibody binds. Examples of antibody fragments include, but are not limited to, Fv, Fab, Fab’, Fab’-SH, F(ab’)₂; diabodies; linear

antibodies; single-chain antibody molecules (*e.g.* scFv or sFv); and multispecific antigen binding polypeptides formed from antibody fragments. In particular embodiments, the antigen binding polypeptides are single-chain antibody fragments comprising a variable heavy chain region and/or a variable light chain region, such as scFvs.

[0063] Antibody fragments can be made by various techniques, including but not limited to proteolytic digestion of an intact antibody as well as production by recombinant host cells. In some embodiments, the antigen binding polypeptides are recombinantly-produced fragments, such as fragments comprising arrangements that do not occur naturally, such as those with two or more antibody regions or chains joined by synthetic linkers, *e.g.*, polypeptide linkers, and/or those that are not produced by enzyme digestion of a naturally-occurring intact antibody. In some aspects, the antibody fragments are scFvs.

[0064] A “humanized” antibody is an antibody in which all or substantially all CDR amino acid residues are derived from non-human CDRs and all or substantially all FR amino acid residues are derived from human FRs. A humanized antibody optionally may include at least a portion of an antibody constant region derived from a human antibody. A “humanized form” of a non-human antibody refers to a variant of the non-human antibody that has undergone humanization, typically to reduce immunogenicity to humans, while retaining the specificity and affinity of the parental non-human antibody. In some embodiments, some FR residues in a humanized antibody are substituted with corresponding residues from a non-human antibody (*e.g.*, the antibody from which the CDR residues are derived), *e.g.*, to restore or improve antibody specificity or affinity.

[0065] Among the provided antigen binding polypeptides are human antibodies. A “human antibody” is an antibody with an amino acid sequence corresponding to that of an antibody produced by a human or a human cell, or non-human source that utilizes human antibody repertoires or other human antibody-encoding sequences, including human antibody libraries. The term excludes humanized forms of non-human antibodies comprising non-human antigen-binding regions, such as those in which all or substantially all CDRs are non-human.

[0066] Human antigen binding polypeptides may be prepared by administering an immunogen to a transgenic animal that has been modified to produce intact human antigen binding polypeptides or intact antigen binding polypeptides with human variable regions in response to antigenic challenge. Such animals typically contain all or a portion of the human immunoglobulin loci, which replace the endogenous immunoglobulin loci, or which are present extrachromosomally or integrated randomly into the animal’s chromosomes. In such transgenic animals, the endogenous immunoglobulin loci have generally been inactivated. Human antigen binding polypeptides also may be derived from human antibody libraries, including phage display and cell-free libraries, containing antibody-encoding sequences derived from a human repertoire.

[0067] The terms “polypeptide” and “protein” are used interchangeably to refer to a polymer of amino acid residues, and are not limited to a minimum length. Polypeptides, including the provided antigen binding polypeptides and antibody chains and other peptides, e.g., linkers and binding peptides, may include amino acid residues including natural and/or non-natural amino acid residues. The terms also include post-expression modifications of the polypeptide, for example, glycosylation, sialylation, acetylation, phosphorylation, and the like. In some aspects, the polypeptides may contain modifications with respect to a native or natural sequence, as long as the protein maintains the desired activity. These modifications may be deliberate, as through site-directed mutagenesis, or may be accidental, such as through mutations of hosts which produce the proteins or errors due to PCR amplification. In some embodiments, amino acid sequence variants of the antigen binding polypeptides provided herein are contemplated. A variant typically differs from a polypeptide specifically disclosed herein in one or more substitutions, deletions, additions and/or insertions. Such variants can be naturally occurring or can be synthetically generated, for example, by modifying one or more of the above polypeptide sequences of the invention and evaluating one or more biological activities of the polypeptide as described herein and/or using any of a number of known techniques. For example, it may be desirable to improve the binding affinity and/or other biological properties of the antibody. Amino acid sequence variants of an antibody may be prepared by introducing appropriate modifications into the nucleotide sequence encoding the antibody, or by peptide synthesis. Such modifications include, for example, deletions from, and/or insertions into and/or substitutions of residues within the amino acid sequences of the antibody. Any combination of deletion, insertion, and substitution can be made to arrive at the final construct, provided that the final construct possesses the desired characteristics, *e.g.*, antigen-binding.

[0068] Percent (%) sequence identity with respect to a reference polypeptide sequence is the percentage of amino acid residues in a candidate sequence that are identical with the amino acid residues in the reference polypeptide sequence, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity, and not considering any conservative substitutions as part of the sequence identity. Alignment for purposes of determining percent amino acid sequence identity can be achieved in various ways that are known for instance, using publicly available computer software such as BLAST, BLAST-2, ALIGN or Megalign (DNASTAR) software. Appropriate parameters for aligning sequences are able to be determined, including algorithms needed to achieve maximal alignment over the full length of the sequences being compared. For purposes herein, however, % amino acid sequence identity values are generated using the sequence comparison computer program ALIGN-2. The ALIGN-2 sequence comparison computer program was authored by Genentech, Inc., and the

source code has been filed with user documentation in the U.S. Copyright Office, Washington D.C., 20559, where it is registered under U.S. Copyright Registration No. TXU510087. The ALIGN-2 program is publicly available from Genentech, Inc., South San Francisco, Calif., or may be compiled from the source code. The ALIGN-2 program should be compiled for use on a UNIX operating system, including digital UNIX V4.0D. All sequence comparison parameters are set by the ALIGN-2 program and do not vary.

[0069] In situations where ALIGN-2 is employed for amino acid sequence comparisons, the % amino acid sequence identity of a given amino acid sequence A to, with, or against a given amino acid sequence B (which can alternatively be phrased as a given amino acid sequence A that has or comprises a certain % amino acid sequence identity to, with, or against a given amino acid sequence B) is calculated as follows: 100 times the fraction X/Y , where X is the number of amino acid residues scored as identical matches by the sequence alignment program ALIGN-2 in that program's alignment of A and B, and where Y is the total number of amino acid residues in B. It will be appreciated that where the length of amino acid sequence A is not equal to the length of amino acid sequence B, the % amino acid sequence identity of A to B will not equal the % amino acid sequence identity of B to A. Unless specifically stated otherwise, all % amino acid sequence identity values used herein are obtained as described in the immediately preceding paragraph using the ALIGN-2 computer program.

[0070] Amino acid sequence insertions and deletions include amino- and/or carboxyl-terminal fusions ranging in length from one residue to polypeptides containing a hundred or more residues, as well as intrasequence insertions and deletions of single or multiple amino acid residues. Examples of terminal insertions include an antibody with an N-terminal methionyl residue. Other insertional variants of the antibody molecule include the fusion to the N- or C-terminus of the antibody to an enzyme (e.g., for ADEPT) or a polypeptide which increases the serum half-life of the antibody. Examples of intrasequence insertion variants of the antibody molecules include an insertion of 3 amino acids in the light chain. Examples of terminal deletions include an antibody with a deletion of 7 or less amino acids at an end of the light chain.

[0071] In some embodiments, an antigen binding polypeptide or antigen binding moiety provided herein has a dissociation constant (K_D) of about 1 μ M, 100 nM, 50 nM, 40 nM, 30 nM, 20 nM, 10 nM, 5 nM, 2 nM, 1 nM, 0.5 nM, 0.1 nM, 0.05 nM, 0.01 nM or less (e.g., 10^{-8} M or less, e.g., from 10^{-8} M to 10^{-13} M, e.g., from 10^{-9} M to 10^{-13} M) for the antigen binding polypeptide target. In some embodiments, an antigen binding polypeptide provided herein has a dissociation constant (K_D) of about 100 nM, 50 nM, 40 nM, 30 nM, 20 nM, 10 nM, 5 nM, 2 nM, 1 nM, 0.5 nM, 0.1 nM, 0.05 nM, 0.01 nM, or 0.001 nM or greater (e.g., 10^{-8} M or less, e.g., from 10^{-8} M to 10^{-13} M, e.g., from 10^{-9} M to 10^{-13} M) for the antigen binding polypeptide target. The

antigen binding polypeptide target can be an anti-VEGF or anti-ANG-2 antigen binding polypeptide. K_D can be measured by any suitable assay. In certain embodiments, K_D can be measured using surface plasmon resonance assays (e.g., using a BIACORE®-2000, a BIACORE®-3000 or Octet).

[0072] In certain embodiments, the antigen binding polypeptides disclosed herein bind to VEGF-A. VEGF-A may have several different splice sites thus may have various isoforms depending on splice sites. Accordingly, in certain embodiments, the antigen binding polypeptides disclosed herein bind to VEGF₁₆₅. In certain embodiments, the antigen binding polypeptides disclosed herein bind to VEGF₁₂₁. In certain embodiments, the antigen binding polypeptides' binding affinity to VEGF₁₂₁ is predicative of the antigen binding polypeptides' efficacy in treating a disease of an eye. In certain embodiments, the antigen binding polypeptides disclosed herein bind to a peptide comprising a platelet-derived growth factor (PDGF) domain of VEGF-A. In some embodiments, the PDGF domain of VEGF-A comprises a fragment of VEGF-A ranging from about 40th, 41st, 42nd, 43rd, 44th, 45th, 46th, 46th, 47th, 48th, 49th, or 50th to about 130th, 131st, 132nd, 133rd, 134th, 135th, 136th, 137th, 138th, 139th, or 140th amino acids. In certain embodiments, the antigen binding polypeptides disclosed herein bind to a peptide comprising a VEGF-C heparin domain of VEGF-A. In some embodiments, the VEGF-C heparin domain of VEGF-A comprises a fragment of VEGF-A ranging from about 140th, 141st, 142nd, 143rd, 144th, 145th, 146th, 147th, 148th, 149th, or 150th to about 190th, 191st, 192nd, 193rd, 194th, 195th, 196th, 197th, 198th, 199th, 120th amino acids. In certain embodiments, the antigen binding polypeptides disclosed herein bind to VEGF-A from a species of human or a non-human (e.g., rabbits, canines (dogs), or porcine (pigs)).

[0073] In certain embodiments, the antigen binding polypeptides are anti-Human VEGF-A antigen binding polypeptides which bind to human VEGF-A at a K_D or EC_{50} of 100, 75, 60, 50, 40, 30, or 25 picomolar or less. In certain embodiments, the antigen binding polypeptides are anti-Human VEGF-A antigen binding polypeptides which bind to human VEGF at a K_D or EC_{50} of 100, 75, 60, 50, 40, 30, or 25 picomolar or less. In certain embodiments, the antigen binding polypeptides are anti-Human VEGF-A antigen binding polypeptides which bind to human VEGF at a K_D or EC_{50} of 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 picomolar or more. In certain embodiments, the antigen binding polypeptides disclosed herein bind to VEGF-A or a fragment thereof with a similar EC_{50} as the one between Faricimab and VEGF-A or a fragment thereof. In certain embodiments, the antigen binding polypeptides disclosed herein bind to VEGF-A or a fragment thereof with an EC_{50} 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400, 500 pM less than the one between Faricimab and VEGF-A or a fragment thereof.

[0074] In certain embodiments, the antigen binding polypeptides are anti-Human VEGF-A antigen binding polypeptides which inhibits an interaction of VEGF-A or a fragment thereof and a VEGF receptor. In certain embodiments, the antigen binding polypeptides are anti-Human VEGF-A antigen binding polypeptides which inhibits an interaction of VEGF-A or a fragment thereof and a VEGF receptor at an IC_{50} of 5 nM, 4 nM, 3 nM, 2 nM, 1 nM, 900 pM, 800 pM, 700 pM, 600 pM or less. In certain embodiments, the antigen binding polypeptides are anti-Human VEGF-A antigen binding polypeptides which inhibits an interaction of VEGF-A or a fragment thereof and a VEGF receptor at an IC_{50} of 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 picomolar or more. In certain embodiments, the antigen binding polypeptides disclosed herein inhibit the interaction of VEGF_A or a fragment thereof and the VEGF receptor at least 1-fold, 2-fold, 3-fold, 4-fold, 5-fold, 6-fold, 7-fold, 8-fold, 9-fold, or 10-fold stronger than Faricimab inhibits the interaction. In certain embodiments, the VEGF receptor is VEGF receptor 2/kinase insert domain receptor (KDR).

[0075] In certain embodiments, the antigen binding polypeptides disclosed herein bind to VEGF_B significantly less than to VEGF-A. In certain embodiments, the antigen binding polypeptides disclosed herein bind to VEGF-C significantly less than to VEGF-A. In certain embodiments, the antigen binding polypeptides disclosed herein bind to VEGF_D significantly less than to VEGF-A. In certain embodiments, the antigen binding polypeptides disclosed herein bind to PlGF-1 significantly less than to VEGF-A. In certain embodiments, the antigen binding polypeptides disclosed herein bind to PlGF-3 significantly less than to VEGF-A.

[0076] In certain embodiments, the antigen binding polypeptides are anti-Human ANG-2 antigen binding polypeptides which bind to human ANG-2 at a K_D or EC_{50} of 100, 75, 60, 55, 50, 40, 30, or 25 picomolar or less. In certain embodiments, the antigen binding polypeptides are anti-Human ANG-2 antigen binding polypeptides which bind to human ANG-2 at a K_D or EC_{50} of 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 picomolar or more. In certain embodiments, the antigen binding polypeptides bind to ANG-2 at least 10-fold, 20-fold, 30-fold, 40-fold, 50-fold, 60-fold, or 70-fold stronger than Faricimab binds to ANG-2.

[0077] In certain embodiments, the antigen binding polypeptides are anti-Human ANG-2 antigen binding polypeptides which inhibits an interaction of ANG-2 and an ANG-2 receptor. In certain embodiments, the antigen binding polypeptides are anti-Human VEGF-A antigen binding polypeptides which inhibits an interaction of ANG-2 and an ANG-2 receptor at an IC_{50} of 5 nM, 4 nM, 3 nM, 2 nM, 1 nM, 900 pM, 800 pM, 700 pM, 600 pM or less. In certain embodiments, the antigen binding polypeptides are anti-Human VEGF-A antigen binding polypeptides which inhibits an interaction of ANG-2 and an ANG-2 receptor at an IC_{50} of 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 picomolar or more. In some embodiments, the antigen binding polypeptides disclosed herein

inhibit the interaction of ANG-2 and the ANG-2 receptor at least 1-fold, 2-fold, 3-fold, 4-fold, 5-fold, 6-fold, 7-fold, 8-fold, 9-fold, 10-fold, 11-fold, 12-fold, 13-fold, 14-fold, or 15-fold stronger than Faricimab inhibits the interaction. In some embodiments, the ANG-2 receptor is a tyrosine kinase with immunoglobulin-like and EGF-like domains 2 receptor (Tie-2 receptor).

[0078] In certain embodiments, the antigen binding polypeptides are anti-Human VEGF-C antigen binding polypeptides which bind to human VEGF-C at a K_D or EC_{50} of 100, 75, 60, 50, 40, 30, or 25 picomolar or less. In certain embodiments, the antigen binding polypeptides are anti-Human VEGF-C antigen binding polypeptides which bind to human VEGF at a K_D or EC_{50} of 100, 75, 60, 50, 40, 30, or 25 picomolar or less. In certain embodiments, the antigen binding polypeptides are anti-Human VEGF-C antigen binding polypeptides which bind to human VEGF at a K_D or EC_{50} of 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 picomolar or more.

[0079] In certain embodiments, the antigen binding polypeptides are anti-Human ErbB3 antigen binding polypeptides which bind to human ErbB3 at a K_D or EC_{50} of 5000, 2000, 1000, 800, 600, 500, 300, 200, 100, 75, 60, 55, 50, 40, 30, or 25 picomolar or less. In certain embodiments, the antigen binding polypeptides are anti-Human ErbB3 antigen binding polypeptides which bind to human ErbB3 at a K_D or EC_{50} of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 50, 100, 200, or 500 picomolar or more.

[0080] In certain embodiments, the antigen binding polypeptides are anti-Human EGFR antigen binding polypeptides which bind to human EGFR at a K_D or EC_{50} of 5000, 2000, 1000, 800, 600, 500, 300, 200, 100, 75, 60, 55, 50, 40, 30, or 25 picomolar or less. In certain embodiments, the antigen binding polypeptides are anti-Human EGFR antigen binding polypeptides which bind to human EGFR at a K_D or EC_{50} of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 50, 100, 200, or 500 picomolar or more.

[0081] In certain embodiments, the antigen binding polypeptides are anti-Human ErbB2 antigen binding polypeptides which bind to human ErbB2 at a K_D or EC_{50} of 5000, 2000, 1000, 800, 600, 500, 300, 200, 100, 75, 60, 55, 50, 40, 30, or 25 picomolar or less. In certain embodiments, the antigen binding polypeptides are anti-Human ErbB2 antigen binding polypeptides which bind to human ErbB2 at a K_D or EC_{50} of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 50, 100, 200, or 500 picomolar or more.

[0082] In certain embodiments, the antigen binding polypeptides are anti-Human c-Met antigen binding polypeptides which bind to human c-Met at a K_D or EC_{50} of 5000, 2000, 1000, 800, 600, 500, 300, 200, 100, 75, 60, 55, 50, 40, 30, or 25 picomolar or less. In certain embodiments, the antigen binding polypeptides are anti-Human c-Met antigen binding polypeptides which bind to human c-Met at a K_D or EC_{50} of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 50, 100, 200, or 500 picomolar or more.

[0083] In certain embodiments, the antigen binding polypeptides are anti-Human PD-1 antigen binding polypeptides which bind to human PD-1 at a K_D or EC_{50} of 5000, 2000, 1000, 800, 600, 500, 300, 200, 100, 75, 60, 55, 50, 40, 30, or 25 picomolar or less. In certain embodiments, the antigen binding polypeptides are anti-Human PD-1 antigen binding polypeptides which bind to human PD-1 at a K_D or EC_{50} of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 50, 100, 200, or 500 picomolar or more.

[0084] In certain embodiments, the antigen binding polypeptides are anti-Human VEGF-A antigen binding polypeptides which inhibits an interaction of VEGF-A or a fragment thereof and a VEGF receptor. In certain embodiments, the antigen binding polypeptides are anti-Human VEGF-A antigen binding polypeptides which inhibits an interaction of VEGF-A or a fragment thereof and a VEGF receptor at an IC_{50} of 5 nM, 4 nM, 3 nM, 2 nM, 1 nM, 900 pM, 800 pM, 700 pM, 600 pM or less. In certain embodiments, the antigen binding polypeptides are anti-Human VEGF-A antigen binding polypeptides which inhibits an interaction of VEGF-A or a fragment thereof and a VEGF receptor at an IC_{50} of 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 picomolar or more. In certain embodiments, the antigen binding polypeptides disclosed herein inhibit the interaction of VEGF_ A or a fragment thereof and the VEGF receptor at least 1-fold, 2-fold, 3-fold, 4-fold, 5-fold, 6-fold, 7-fold, 8-fold, 9-fold, or 10-fold stronger than Faricimab inhibits the interaction. In certain embodiments, the VEGF receptor is VEGF receptor 2/kinase insert domain receptor (KDR).

[0085] In certain embodiments, the antigen binding polypeptides are anti-Human VEGF-A/ANG-2/VEGF-C trispecific antigen binding polypeptides which bind to human VEGF-A at a K_D or EC_{50} of 100, 75, 60, 50, 40, 30, or 25 picomolar or less. In certain embodiments, the antigen binding polypeptides are anti-Human VEGF/ANG-2 bispecific antigen binding polypeptides which bind to human VEGF-A at a K_D or EC_{50} of 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 picomolar or more.

[0086] In certain embodiments, the antigen binding polypeptides are anti-Human VEGF-A/ANG-2/VEGF-C trispecific antigen binding polypeptides which bind to human ANG-2 at a K_D or EC_{50} of 100, 75, 60, 50, 40, 30, or 25 picomolar or less. In certain embodiments, the antigen binding polypeptides are anti-Human VEGF/ANG-2/VEGF-C trispecific antigen binding polypeptides which bind to human ANG-2 at a K_D or EC_{50} of 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 picomolar or more.

[0087] In certain embodiments, the antigen binding polypeptides are anti-Human VEGF-A/ANG-2/VEGF-C trispecific antigen binding polypeptides which bind to human VEGF-C at a K_D or EC_{50} of 100, 75, 60, 50, 40, 30, or 25 picomolar or less. In certain embodiments, the antigen binding polypeptides are anti-Human VEGF/ANG-2/VEGF-C trispecific antigen binding

polypeptides which bind to human VEGF-C at a K_D or EC_{50} of 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 picomolar or more.

[0088] In certain embodiments, the antigen binding polypeptides are anti-Human ErbB3/VEGF-A/ANG-2/VEGF-C tetraspecific antigen binding polypeptides which bind to human ErbB3 at a K_D or EC_{50} of 1000, 800, 500, 200, 100, 75, 60, 50, 40, 30, or 25 picomolar or less.

[0089] In certain embodiments, the antigen binding polypeptides are anti-Human ErbB3/VEGF-A/ANG-2/VEGF-C tetraspecific antigen binding polypeptides which bind to human VEGF-A at a K_D or EC_{50} of 1000, 800, 500, 200, 100, 75, 60, 50, 40, 30, or 25 picomolar or less.

[0090] In certain embodiments, the antigen binding polypeptides are anti-Human ErbB3/VEGF-A/ANG-2/VEGF-C tetraspecific antigen binding polypeptides which bind to human ANG-2 at a K_D or EC_{50} of 5000, 1000, 800, 500, 200, 100, 75, 60, 50, 40, 30, or 25 picomolar or less.

[0091] In certain embodiments, the antigen binding polypeptides are anti-Human ErbB3/VEGF-A/ANG-2/VEGF-C tetraspecific antigen binding polypeptides which bind to human VEGF-C at a K_D or EC_{50} of 5000, 1000, 800, 500, 200, 100, 75, 60, 50, 40, 30, or 25 picomolar or less.

[0092] In certain embodiments, the antigen binding polypeptides are anti-Human EGFR/ErbB2/ErbB3 trispecific antigen binding polypeptides which bind to human EGFR at a K_D or EC_{50} of 5000, 1000, 800, 500, 200, 100, 75, 60, 50, 40, 30, or 25 picomolar or less.

[0093] In certain embodiments, the antigen binding polypeptides are anti-Human EGFR/ErbB2/ErbB3 trispecific antigen binding polypeptides which bind to human ErbB2 at a K_D or EC_{50} of 5000, 1000, 800, 500, 200, 100, 75, 60, 50, 40, 30, or 25 picomolar or less.

[0094] In certain embodiments, the antigen binding polypeptides are anti-Human EGFR/ErbB2/ErbB3 trispecific antigen binding polypeptides which bind to human ErbB3 at a K_D or EC_{50} of 5000, 1000, 800, 500, 200, 100, 75, 60, 50, 40, 30, or 25 picomolar or less.

[0095] In certain embodiments, the antigen binding polypeptides are anti-Human c-Met/EGFR/ErbB2/ErbB3 tetraspecific antigen binding polypeptides which bind to human c-MET at a K_D or EC_{50} of 5000, 1000, 800, 500, 200, 100, 75, 60, 50, 40, 30, or 25 picomolar or less.

[0096] In certain embodiments, the antigen binding polypeptides are anti-Human c-Met/EGFR/ErbB2/ErbB3 tetraspecific antigen binding polypeptides which bind to human EGFR at a K_D or EC_{50} of 5000, 1000, 800, 500, 200, 100, 75, 60, 50, 40, 30, or 25 picomolar or less.

[0097] In certain embodiments, the antigen binding polypeptides are anti-Human c-Met/EGFR/ErbB2/ErbB3 tetraspecific antigen binding polypeptides which bind to human ErbB2 at a K_D or EC_{50} of 5000, 1000, 800, 500, 200, 100, 75, 60, 50, 40, 30, or 25 picomolar or less.

[0098] In certain embodiments, the antigen binding polypeptides are anti-Human c-Met/EGFR/ErbB2/ErbB3 tetraspecific antigen binding polypeptides which bind to human ErbB3 at a K_D or EC_{50} of 5000, 1000, 800, 500, 200, 100, 75, 60, 50, 40, 30, or 25 picomolar or less.

[0099] In certain embodiments, the antigen binding polypeptides are anti-Human PD-1 antigen binding polypeptides which bind to human PD-1 at a K_D or EC_{50} of 5000, 1000, 800, 500, 200, 100, 75, 60, 50, 40, 30, or 25 picomolar or less.

[0100] In some embodiments, the antigen binding polypeptides disclosed herein are IgG antigen binding polypeptides. In some embodiments, the antigen binding polypeptides disclosed herein are IgE antigen binding polypeptides. In some embodiments, the antigen binding polypeptides disclosed herein are IgM antigen binding polypeptides. In some embodiments, the antigen binding polypeptides disclosed herein are IgA antigen binding polypeptides. In some embodiments, the antigen binding polypeptides disclosed herein are Fab, $F(ab)_2$, single-domain antibody, or single chain variable fragment (scFv).

[0101] In some embodiments, paired with one or more surrogate light chains, the antigen binding polypeptides disclosed herein are surrobodies. In some embodiments, the antigen binding fragment thereof is a surrobody antigen-binding fragment (Sab) or single chain variable fragment of a surrobody (scSv).

[0102] In some embodiments, one or more amino acid modifications may be introduced into the Fc region of an antigen binding polypeptide provided herein, thereby generating an Fc region variant. An Fc region herein is a C-terminal region of an immunoglobulin heavy chain that contains at least a portion of the constant region. An Fc region includes native sequence Fc regions and variant Fc regions. The Fc region variant may comprise a human Fc region sequence (e.g., a human IgG1, IgG2, IgG3 or IgG4 Fc region) comprising an amino acid modification (e.g., a substitution) at one or more amino acid positions.

[0103] In some embodiments, one or more amino acid modifications may be introduced into the Fc region of an antigen binding polypeptide provided herein, thereby generating an Fc region variant. An Fc region herein is a C-terminal region of an immunoglobulin heavy chain that contains at least a portion of the constant region. An Fc region includes native sequence Fc regions and variant Fc regions. The Fc region variant may comprise a human Fc region sequence (e.g., a human IgG1, IgG2, IgG3 or IgG4 Fc region) comprising an amino acid modification (e.g., a substitution) at one or more amino acid positions.

[0104] In some instances, the Fc region of an immunoglobulin is important for many important antibody functions (e.g. effector functions), such as antigen-dependent cellular cytotoxicity (ADCC), complement dependent cytotoxicity (CDC), and antibody-dependent cell-mediated phagocytosis (ADCP), result in killing of target cells, albeit by different mechanisms.

Accordingly, in some embodiments, the antigen binding polypeptides described herein comprise the variable domains of the invention combined with constant domains comprising different Fc regions, selected based on the biological activities of the antibody for the intended use. In certain

instances, Human IgGs, for example, can be classified into four subclasses, IgG1, IgG2, IgG3, and IgG4, and each of these comprises an Fc region having a unique profile for binding to one or more of Fcγ receptors (activating receptors FcγRI (CD64), FcγRIIA, FcγRIIC (CD32); FcγRIIIA and FcγRIIIB (CD16) and inhibiting receptor FcγRIIB), and for the first component of complement (C1q). Human IgG1 and IgG3 bind to all Fcγ receptors; IgG2 binds to FcγRIIA_{H131}, and with lower affinity to FcγRIIA_{R131} FcγRIIIA_{V158}; IgG4 binds to FcγRI, FcγRIIA, FcγRIIB, FcγRIIC, and FcγRIIIA_{V158}; and the inhibitory receptor FcγRIIB has a lower affinity for IgG1, IgG2 and IgG3 than all other Fcγ receptors. Studies have shown that FcγRI does not bind to IgG2, and FcγRIIIB does not bind to IgG2 or IgG4. Id. In general, with regard to ADCC activity, human IgG1≥IgG3>>IgG4≥IgG2.

[0105] In some embodiments, the antigen binding polypeptides of this disclosure are variants that possess reduced effector functions, which make it a desirable candidate for applications in which certain effector functions (such as complement fixation and ADCC) are unnecessary or deleterious. Such antibodies can have decreased complement-dependent cytotoxicity (CDC), antibody-dependent cell cytotoxicity (ADCC), or antibody dependent cellular phagocytosis (ADCP). In some embodiments, the antigen binding polypeptides of this disclosure are variants that possess increased effector functions for applications in which increased immunogenicity would be beneficial. Such antigen binding polypeptides can have increased CDC, ADCC, or ADCP, or a combination thereof. Non-limiting examples of *in vitro* assays to assess ADCC activity of a molecule of interest is described in U.S. Pat. No. 5,500,362 and 5,821,337.

Alternatively, non-radioactive assays methods may be employed (*e.g.*, ACTI™ and CytoTox 96® non-radioactive cytotoxicity assays). Useful effector cells for such assays include peripheral blood mononuclear cells (PBMC), monocytes, macrophages, and Natural Killer (NK) cells.

[0106] Antigen binding polypeptides can have increased half-lives and improved binding to the neonatal Fc receptor (FcRn) (*See e.g.*, US 2005/0014934). Such antigen binding polypeptides can comprise an Fc region with one or more substitutions therein which improve binding of the Fc region to FcRn, and include those with substitutions at one or more of Fc region residues: 238, 256, 265, 272, 286, 303, 305, 307, 311, 312, 317, 340, 356, 360, 362, 376, 378, 380, 382, 413, 424 or 434 according to the EU numbering system (*See e.g.*, U.S. Pat. No. 7,371,826). Other examples of Fc region variants are also contemplated (*See e.g.*, Duncan & Winter, *Nature* 322:738-40 (1988); U.S. Pat. Nos. 5,648,260 and 5,624,821; and WO94/29351).

[0107] In some embodiments, it may be desirable to create cysteine engineered antigen binding polypeptides, *e.g.*, “thioMAbs,” in which one or more residues of an antibody are substituted with cysteine residues. In some embodiments, the substituted residues occur at accessible sites of the antibody. Reactive thiol groups can be positioned at sites for conjugation to other moieties,

such as drug moieties or linker drug moieties, to create an immunoconjugate. In some embodiments, any one or more of the following residues may be substituted with cysteine: V205 (Kabat numbering) of the light chain; A118 (EU numbering) of the heavy chain; and S400 (EU numbering) of the heavy chain Fc region.

[0108] In some embodiments, an antigen binding polypeptide provided herein may be further modified to contain additional nonproteinaceous moieties that are known and available. The moieties suitable for derivatization of the antigen binding polypeptide include but are not limited to water soluble polymers. Non-limiting examples of water soluble polymers include, but are not limited to, polyethylene glycol (PEG), copolymers of ethylene glycol/propylene glycol, carboxymethylcellulose, dextran, polyvinyl alcohol, polyvinyl pyrrolidone, poly-1,3-dioxolane, poly-1,3,6-trioxane, ethylene/maleic anhydride copolymer, polyaminoacids (either homopolymers or random copolymers), and dextran or poly(n vinyl pyrrolidone)polyethylene glycol, polypropylene glycol homopolymers, polypropylene oxide/ethylene oxide co-polymers, polyoxyethylated polyols (e.g., glycerol), polyvinyl alcohol, and mixtures thereof. Polyethylene glycol propionaldehyde may have advantages in manufacturing due to its stability in water. The polymer may be of any molecular weight, and may be branched or unbranched. The number of polymers attached to the antigen binding polypeptide may vary, and if two or more polymers are attached, they can be the same or different molecules.

[0109] The antigen binding polypeptides described herein can be encoded by a nucleic acid. A nucleic acid is a type of polynucleotide comprising two or more nucleotide bases. In certain embodiments, the nucleic acid is a component of a vector that can be used to transfer the polypeptide encoding polynucleotide into a cell. As used herein, the term “vector” refers to a nucleic acid molecule capable of transporting another nucleic acid to which it has been linked. One type of vector is a genomic integrated vector, or “integrated vector,” which can become integrated into the chromosomal DNA of the host cell. Another type of vector is an “episomal” vector, e.g., a nucleic acid capable of extra-chromosomal replication. Vectors capable of directing the expression of genes to which they are operatively linked are referred to herein as “expression vectors.” Suitable vectors comprise plasmids, bacterial artificial chromosomes, yeast artificial chromosomes, viral vectors and the like. In the expression vectors regulatory elements such as promoters, enhancers, polyadenylation signals for use in controlling transcription can be derived from mammalian, microbial, viral or insect genes. The ability to replicate in a host, usually conferred by an origin of replication, and a selection gene to facilitate recognition of transformants may additionally be incorporated. Vectors derived from viruses, such as lentiviruses, retroviruses, adenoviruses, adeno-associated viruses, and the like, may be employed. Plasmid vectors can be linearized for integration into a genomic region. In certain embodiments,

the expression vector is a plasmid. In certain embodiments, the expression vector is a lentivirus, adenovirus, or adeno-associated virus. In certain embodiments, the expression vector is an adenovirus. In certain embodiments, the expression vector is an adeno-associated virus. In certain embodiments, the expression vector is a lentivirus. In certain embodiments, the expression vector described herein is used in a gene therapy. Accordingly, in some embodiments, the expression vector described herein is formulated for intravenous administration. In some embodiments, the expression vector described herein is formulated for intravitreal administration. [0110] As used herein, the terms “homologous,” “homology,” or “percent homology” when used herein to describe to an amino acid sequence or a nucleic acid sequence, relative to a reference sequence, can be determined using the formula described by Karlin and Altschul (Proc. Natl. Acad. Sci. USA 87: 2264-2268, 1990, modified as in Proc. Natl. Acad. Sci. USA 90:5873-5877, 1993). Such a formula is incorporated into the basic local alignment search tool (BLAST) programs of Altschul et al. (J. Mol. Biol. 215: 403-410, 1990). Percent homology of sequences can be determined using the most recent version of BLAST, as of the filing date of this application.

[0111] The nucleic acids encoding the antigen binding polypeptides described herein can be used to infect, transfect, transform, or otherwise render a suitable cell transgenic for the nucleic acid, thus enabling the production of antigen binding polypeptides for commercial or therapeutic uses. Standard cell lines and methods for the production of antigen binding polypeptides from a large scale cell culture are known in the art. *See e.g.*, Li et al., “Cell culture processes for monoclonal antibody production.” *Mabs*. 2010 Sep-Oct; 2(5): 466–477. In certain embodiments, the cell is a Eukaryotic cell. In certain embodiments, the Eukaryotic cell is a mammalian cell. In certain embodiments, the mammalian cell is a cell line useful for producing antigen binding polypeptides is a Chines Hamster Ovary cell (CHO) cell, an NS0 murine myeloma cell, or a PER.C6® cell. In certain embodiments, the nucleic acid encoding the antigen binding polypeptide is integrated into a genomic locus of a cell useful for producing antigen binding polypeptides. In certain embodiments, described herein is a method of making an antigen binding polypeptide comprising culturing a cell comprising a nucleic acid encoding an antigen binding polypeptide under conditions *in vitro* sufficient to allow production and secretion of said antigen binding polypeptide.

[0112] In certain embodiments, described herein, is a master cell bank comprising: (a) a mammalian cell line comprising a nucleic acid encoding an antigen binding polypeptide or bispecific antigen binding polypeptide described herein integrated at a genomic location; and (b) a cryoprotectant. In certain embodiments, the cryoprotectant comprises glycerol or DMSO. In certain embodiments, the master cell bank comprises: (a) a CHO cell line comprising a nucleic

acid encoding an antigen binding polypeptide or bispecific antigen binding polypeptide described herein integrated at a genomic location; and (b) a cryoprotectant. In certain embodiments, the cryoprotectant comprises glycerol or DMSO. In certain embodiments, the master cell bank is contained in a suitable vial or container able to withstand freezing by liquid nitrogen.

[0113] Also described herein are methods of making an antigen binding polypeptide described herein. Such methods comprise incubating a cell or cell-line comprising a nucleic acid encoding the antigen binding polypeptide in a cell culture medium under conditions sufficient to allow for expression and secretion of the antigen binding polypeptide, and further harvesting the antigen binding polypeptide from the cell culture medium. The harvesting can further comprise one or more purification steps to remove live cells, cellular debris, non-antigen binding polypeptide proteins or polypeptides, undesired salts, buffers, and medium components. In certain embodiments, the additional purification step(s) include centrifugation, ultracentrifugation, protein A, protein G, protein A/G, or protein L purification, and/or ion exchange chromatography.

[0114] “Treat,” “treatment,” or “treating,” as used herein refers to, *e.g.*, a deliberate intervention to a physiological disease state resulting in the reduction in severity of a disease or condition; the reduction in the duration of a condition course; the amelioration or elimination of one or more symptoms associated with a disease or condition; or the provision of beneficial effects to a subject with a disease or condition. Treatment does not require curing the underlying disease or condition.

[0115] A “therapeutically effective amount,” “effective dose,” “effective amount,” or “therapeutically effective dosage” of a drug or therapeutic agent is any amount of the drug that, when used alone or in combination with another therapeutic agent, protects a subject against the onset of a disease or promotes disease regression evidenced by a decrease in severity of disease symptoms, an increase in frequency and duration of disease symptom-free periods, or a prevention of impairment or disability due to the disease affliction. The ability of a therapeutic agent to promote disease regression can be evaluated using a variety of methods known to the skilled practitioner, such as in human subjects during clinical trials, in animal model systems predictive of efficacy in humans, or by assaying the activity of the agent in *in vitro* assays.

[0116] As used herein, “pharmaceutically acceptable” with reference to a carrier “excipient” or “diluent” includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like that are physiologically compatible. In some aspects, the carrier is suitable for intravenous, intramuscular, subcutaneous, parenteral, spinal or epidermal administration (*e.g.*, by injection or infusion). Depending on the route of administration, the active compound, *i.e.*, antibody, can be coated in a material to protect the

compound from the action of acids and other natural conditions that can inactivate the compound.

[0117] The pharmaceutical compounds described herein can include one or more pharmaceutically acceptable salts. A “pharmaceutically acceptable salt” refers to a salt that retains the desired biological activity of the parent compound and does not impart any undesired toxicological effects (see e.g., Berge, S.M., et al. (1977) J. Pharm. Sci. 66: 1-19). Examples of such salts include acid addition salts and base addition salts. Acid addition salts include those derived from nontoxic inorganic acids, such as hydrochloric, nitric, phosphoric, sulfuric, hydrobromic, hydroiodic, phosphorous and the like, as well as from nontoxic organic acids such as aliphatic mono- and dicarboxylic acids, phenyl- substituted alkanoic acids, hydroxy alkanoic acids, aromatic acids, aliphatic and aromatic sulfonic acids and the like. Base addition salts include those derived from alkaline earth metals, such as sodium, potassium, magnesium, calcium and the like, as well as from nontoxic organic amines, such as N,N'-dibenzylethylenediamine, N-methylglucamine, chlorprocaine, choline, diethanolamine, ethylenediamine, procaine and the like.

Multispecific antigen binding polypeptide

[0118] Described herein are multispecific antigen binding polypeptides. As shown in **FIG. 1** a trispecific binding polypeptide can comprise a single polypeptide chain comprising three repeats of an antigen binding moiety comprising a heavy chain variable region (VH) and a 1st constant domain of a heavy chain immunoglobulin (CH1). All three VH/CH1s may be the same creating three binding domains for a single antigen, or different creating one binding domain for three different antigens. Also contemplated is an embodiment where two of the VH/CH1s bind the same antigen and the third binds a different antigen. Also contemplated is an embodiment where all three of the VH/CH1s bind the same antigen. In certain embodiments, the antigen binding moieties may further comprise a 2nd constant domain of a heavy chain immunoglobulin (CH2) and/or a 3rd constant domain of a heavy chain immunoglobulin CH3. Any of the CH1, CH2, or CH3 domains may be an IgG1, IgG2, IgG3, or IgG4 isotype. Any of the CH1, CH2, or CH3 domains may be human. The heavy chains are paired with a surrogate light chain or a common light, wherein the surrogate/common light chain are identical, and can pair with all three heavy chains allowing for efficient encoding by a nucleic acid and production in a cell system. **FIGs. 2, 3, 4, 16A and 16B** show embodiments of the technology described in **FIG. 1** where Fab fragments can be utilized instead of surrogate light chain or common light chain technology. Such Fab fragments can be utilized, for example, the heavy and light chains of the Fab fragments preferentially pair using crossed domains or other mutations that promote correct heavy and light chain pairing (e.g., electrostatic steering, engineered disulfides, or knob-in-hole technology).

[0119] Described herein are multispecific antigen binding polypeptide comprising: a first antigen binding moiety, comprising a first heavy chain variable region; a second antigen binding moiety, comprising a second heavy chain variable region; and a third antigen binding moiety, comprising a third heavy chain variable region; wherein the first antigen binding moiety binds to a first target, the second antigen binding moiety binds to a second target, and the third antigen binding moiety binds to a third target, wherein the first antigen binding moiety, the second antigen binding moiety and the third antigen binding moiety are paired to a light chain polypeptide.

[0120] In some embodiments, the first antigen binding moiety, the second antigen binding moiety, and the third antigen binding moiety are directly connected without a linker. In some embodiments, a C-terminus of the first heavy chain variable region is directly connected to an N-terminus of the second heavy chain variable region. In some embodiments, a C-terminus of the second heavy chain variable region is directly connected to an N-terminus of the third heavy chain variable region. In some embodiments, a C-terminus of the first heavy chain variable region is directly connected to an N-terminus of the second heavy chain variable region, and wherein a C-terminus of the second heavy chain variable region is directly connected to an N-terminus of the third heavy chain variable region.

[0121] In some embodiments, the multispecific antigen binding polypeptide further comprises a fourth antigen binding moiety comprising a fourth heavy chain variable region, wherein the fourth antigen binding moiety binds to a fourth target, wherein the fourth antigen binding moiety is paired to the light chain polypeptide. In some embodiments, the first antigen binding moiety, the second antigen binding moiety, the third antigen binding moiety, and the fourth antigen binding moiety are directly connected without a linker. In some embodiments, a C-terminus of the third heavy chain variable region is directly connected to an N-terminus of the fourth heavy chain variable region. In some embodiments, the first antigen binding moiety, the second antigen binding moiety, the third antigen binding moiety, and/or the fourth antigen binding moiety are linked via a linker. In some embodiments, the linker couples the C-terminus of the third antigen binding moiety to the N-terminus of the fourth antigen binding moiety.

[0122] In some embodiments, the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety are linked via a linker. In some embodiments, the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety are covalently linked via the linker. In some embodiments, the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety are non-covalently linked via the linker. In some embodiments, the linker couples the C-terminus of the first antigen binding moiety to the N-terminus of the second antigen binding moiety. In some

embodiments, the linker couples the C-terminus of the second antigen binding moiety to the N-terminus of the third antigen binding moiety.

[0123] In some embodiments, the linker comprises an amino acid sequence with at least 90% sequence identity to SEQ ID NO: 151. In some embodiments, the linker comprises an amino acid sequence with at least 95% sequence identity to SEQ ID NO: 151. In some embodiments, the linker comprises an amino acid sequence with at least 97% sequence identity to SEQ ID NO: 151. In some embodiments, the linker comprises an amino acid sequence with at least 98% sequence identity to SEQ ID NO: 151. In some embodiments, the linker comprises an amino acid sequence with at least 99% sequence identity to SEQ ID NO: 151. In some embodiments, the linker comprises an amino acid sequence of SEQ ID NO: 151. In some embodiments, the linker comprises an amino acid sequence of Gly – Ser.

[0124] In some embodiments, the light chain polypeptide paired to the first antigen binding moiety, the second antigen binding moiety, and the third antigen binding moiety comprise the same amino acid sequence. In some embodiments, the light chain polypeptide paired to the first antigen binding moiety, the second antigen binding moiety, and the third antigen binding moiety comprise different amino acid sequences. In some embodiments, the light chain polypeptide comprises a light chain constant region comprising one or more amino acid substitutions from a heavy chain first constant region (CH1).

[0125] In some embodiments, the light chain polypeptide comprises a light chain constant region comprising one or more amino acid substitutions from a heavy chain first constant region (CH1) and the light chain comprises an amino acid sequence comprising at least 90% sequence identity to the amino acid sequence set forth in SEQ ID NO: 111 or 112. In some embodiments, the light chain polypeptide comprises a light chain constant region comprising one or more amino acid substitutions from a heavy chain first constant region (CH1) and the light chain comprises an amino acid sequence comprising at least 95% sequence identity to the amino acid sequence set forth in SEQ ID NO: 111 or 112. In some embodiments, the light chain polypeptide comprises a light chain constant region comprising one or more amino acid substitutions from a heavy chain first constant region (CH1) and the light chain comprises an amino acid sequence comprising at least 97% sequence identity to the amino acid sequence set forth in SEQ ID NO: 111 or 112. In some embodiments, the light chain polypeptide comprises a light chain constant region comprising one or more amino acid substitutions from a heavy chain first constant region (CH1) and the light chain comprises an amino acid sequence comprising at least 98% sequence identity to the amino acid sequence set forth in SEQ ID NO: 111 or 112. In some embodiments, the light chain polypeptide comprises a light chain constant region comprising one or more amino acid substitutions from a heavy chain first constant region (CH1) and the light chain comprises an

amino acid sequence comprising at least 99% sequence identity to the amino acid sequence set forth in SEQ ID NO: 111 or 112. In some embodiments, the light chain polypeptide comprises a light chain constant region comprising one or more amino acid substitutions from a heavy chain first constant region (CH1) and the light chain comprises an amino acid sequence comprising the amino acid sequence set forth in SEQ ID NO: 111 or 112.

[0126] In some embodiments, the light chain polypeptide comprises a light chain constant region comprising one or more amino acid substitutions from a heavy chain first constant region (CH1) and the light chain comprises an amino acid sequence comprising at least 90% sequence identity to the amino acid sequence set forth in SEQ ID NO: 121 or 122. In some embodiments, the light chain polypeptide comprises a light chain constant region comprising one or more amino acid substitutions from a heavy chain first constant region (CH1) and the light chain comprises an amino acid sequence comprising at least 95% sequence identity to the amino acid sequence set forth in SEQ ID NO: 121 or 122. In some embodiments, the light chain polypeptide comprises a light chain constant region comprising one or more amino acid substitutions from a heavy chain first constant region (CH1) and the light chain comprises an amino acid sequence comprising at least 97% sequence identity to the amino acid sequence set forth in SEQ ID NO: 121 or 122. In some embodiments, the light chain polypeptide comprises a light chain constant region comprising one or more amino acid substitutions from a heavy chain first constant region (CH1) and the light chain comprises an amino acid sequence comprising at least 98% sequence identity to the amino acid sequence set forth in SEQ ID NO: 121 or 122. In some embodiments, the light chain polypeptide comprises a light chain constant region comprising one or more amino acid substitutions from a heavy chain first constant region (CH1) and the light chain comprises an amino acid sequence comprising at least 99% sequence identity to the amino acid sequence set forth in SEQ ID NO: 121 or 122. In some embodiments, the light chain polypeptide comprises a light chain constant region comprising one or more amino acid substitutions from a heavy chain first constant region (CH1) and the light chain comprises an amino acid sequence comprising the amino acid sequence set forth in SEQ ID NO: 121 or 122.

[0127] In some embodiments, the light chain polypeptide comprises a light chain constant region comprising one or more amino acid substitutions from a heavy chain first constant region (CH1) and the light chain comprises an amino acid sequence comprising at least 90% sequence identity to the amino acid sequence set forth in SEQ ID NO: 131 or 132. In some embodiments, the light chain polypeptide comprises a light chain constant region comprising one or more amino acid substitutions from a heavy chain first constant region (CH1) and the light chain comprises an amino acid sequence comprising at least 95% sequence identity to the amino acid sequence set forth in SEQ ID NO: 131 or 132. In some embodiments, the light chain polypeptide comprises a

light chain constant region comprising one or more amino acid substitutions from a heavy chain first constant region (CH1) and the light chain comprises an amino acid sequence comprising at least 97% sequence identity to the amino acid sequence set forth in SEQ ID NO: 131 or 132. In some embodiments, the light chain polypeptide comprises a light chain constant region comprising one or more amino acid substitutions from a heavy chain first constant region (CH1) and the light chain comprises an amino acid sequence comprising at least 98% sequence identity to the amino acid sequence set forth in SEQ ID NO: 131 or 132. In some embodiments, the light chain polypeptide comprises a light chain constant region comprising one or more amino acid substitutions from a heavy chain first constant region (CH1) and the light chain comprises an amino acid sequence comprising at least 99% sequence identity to the amino acid sequence set forth in SEQ ID NO: 131 or 132. In some embodiments, the light chain polypeptide comprises a light chain constant region comprising one or more amino acid substitutions from a heavy chain first constant region (CH1) and the light chain comprises an amino acid sequence comprising the amino acid sequence set forth in SEQ ID NO: 131 or 132.

[0128] In some embodiments, the light chain polypeptide is a universal light chain polypeptide. In some embodiments, the universal light chain is a common light chain. In some embodiments, the universal light chain is a surrogate light chain. In some embodiments, the surrogate light chain polypeptide comprises a VpreB sequence conjugated to a $\lambda 5$ sequence.

[0129] In some embodiments, the VpreB sequence comprises an amino acid sequence comprising at least 90% sequence identity to the amino acid sequence set forth in SEQ ID NO: 101. In some embodiments, the VpreB sequence comprises an amino acid sequence comprising at least 95% sequence identity to the amino acid sequence set forth in SEQ ID NO: 101. In some embodiments, the VpreB sequence comprises an amino acid sequence comprising at least 97% sequence identity to the amino acid sequence set forth in SEQ ID NO: 101. In some embodiments, the VpreB sequence comprises an amino acid sequence comprising at least 98% sequence identity to the amino acid sequence set forth in SEQ ID NO: 101. In some embodiments, the VpreB sequence comprises an amino acid sequence comprising at least 99% sequence identity to the amino acid sequence set forth in SEQ ID NO: 101. In some embodiments, the VpreB sequence comprises an amino acid sequence set forth in SEQ ID NO: 101.

[0130] In some embodiments, the $\lambda 5$ sequence comprises an amino acid sequence comprising at least 90% sequence identity to the amino acid sequence set forth in SEQ ID NO: 106. In some embodiments, the $\lambda 5$ sequence comprises an amino acid sequence comprising at least 95% sequence identity to the amino acid sequence set forth in SEQ ID NO: 106. In some embodiments, the $\lambda 5$ sequence comprises an amino acid sequence comprising at least 97%

sequence identity to the amino acid sequence set forth in SEQ ID NO: 106. In some embodiments, the $\lambda 5$ sequence comprises an amino acid sequence comprising at least 98% sequence identity to the amino acid sequence set forth in SEQ ID NO: 106. In some embodiments, the $\lambda 5$ sequence comprises an amino acid sequence comprising at least 99% sequence identity to the amino acid sequence set forth in SEQ ID NO: 106. In some embodiments, the $\lambda 5$ sequence comprises an amino acid sequence set forth in SEQ ID NO: 106.

[0131] In some embodiments, the surrogate light chain polypeptide comprises: a light chain complementarity determining region 1 (LCDR1) comprising the amino acid sequence set forth in SEQ ID NO: 103; a light chain complementarity determining region 2 (LCDR2) comprising the amino acid sequence set forth in SEQ ID NO: 104; and a light chain complementarity determining region 3 (LCDR3) comprising the amino acid sequence set forth in SEQ ID NO: 105.

[0132] In some embodiments, the surrogate light chain polypeptide comprises an amino acid sequence comprising at least 85% sequence identity to the amino acid sequence set forth in SEQ ID NO: 102. In some embodiments, the surrogate light chain polypeptide comprises an amino acid sequence comprising at least 90% sequence identity to the amino acid sequence set forth in SEQ ID NO: 102. In some embodiments, the surrogate light chain polypeptide comprises an amino acid sequence comprising at least 95% sequence identity to the amino acid sequence set forth in SEQ ID NO: 102. In some embodiments, the surrogate light chain polypeptide comprises an amino acid sequence comprising at least 96% sequence identity to the amino acid sequence set forth in SEQ ID NO: 102. In some embodiments, the surrogate light chain polypeptide comprises an amino acid sequence comprising at least 97% sequence identity to the amino acid sequence set forth in SEQ ID NO: 102. In some embodiments, the surrogate light chain polypeptide comprises an amino acid sequence comprising at least 98% sequence identity to the amino acid sequence set forth in SEQ ID NO: 102. In some embodiments, the surrogate light chain polypeptide comprises an amino acid sequence comprising at least 99% sequence identity to the amino acid sequence set forth in SEQ ID NO: 102. In some embodiments, the surrogate light chain polypeptide comprises an amino acid sequence set forth in SEQ ID NO: 102.

[0133] In some embodiments, the multispecific binding polypeptide comprises a common light chain. In some embodiments, the common light chain polypeptide comprises an amino acid sequence comprising at least 85% sequence identity to the amino acid sequence set forth in SEQ ID NO: 303. In some embodiments, the common light chain polypeptide comprises an amino acid sequence comprising at least 90% sequence identity to the amino acid sequence set forth in SEQ ID NO: 303. In some embodiments, the common light chain polypeptide comprises an

amino acid sequence comprising at least 95% sequence identity to the amino acid sequence set forth in SEQ ID NO: 303. In some embodiments, the common light chain polypeptide comprises an amino acid sequence comprising at least 96% sequence identity to the amino acid sequence set forth in SEQ ID NO: 303. In some embodiments, the common light chain polypeptide comprises an amino acid sequence comprising at least 97% sequence identity to the amino acid sequence set forth in SEQ ID NO: 303. In some embodiments, the common light chain polypeptide comprises an amino acid sequence comprising at least 98% sequence identity to the amino acid sequence set forth in SEQ ID NO: 303. In some embodiments, the common light chain polypeptide comprises an amino acid sequence comprising at least 99% sequence identity to the amino acid sequence set forth in SEQ ID NO: 303. In some embodiments, the common light chain polypeptide comprises an amino acid sequence set forth in SEQ ID NO: 303.

[0134] In some embodiments, the multispecific antigen binding polypeptide comprises at least three antigen binding moieties that bind to at least three targets. In some embodiments, the multispecific antigen binding polypeptide comprises at least four antigen binding moieties that bind to at least four targets. In some embodiments, the multispecific antigen binding polypeptide comprises at least five antigen binding moieties that bind to at least five targets. In some embodiments, the multispecific antigen binding polypeptide comprises at least six antigen binding moieties that bind the at least six targets.

[0135] In some embodiments, the multispecific antigen binding polypeptide comprises at least one crossed domain. In some embodiments, the multispecific antigen binding polypeptide comprises at least two crossed domains. In some embodiments, the multispecific antigen binding polypeptide comprises at least three crossed domains. In some embodiments, the multispecific antigen binding polypeptide comprises at least four crossed domains. In some embodiments, the multispecific antigen binding polypeptide comprises at least five crossed domains. In some embodiments, the multispecific antigen binding polypeptide comprises at least six crossed domains.

[0136] Exemplary multispecific antigen binding polypeptides are illustrated in **FIGs. 2-4**. In some embodiments, the first antigen binding moiety comprises a crossed domain. In some embodiments, the first antigen binding moiety comprises a crossed domain. In some embodiments, the second antigen binding moiety comprises a crossed domain. In some embodiments, the third antigen binding moiety comprises a crossed domain. In some embodiments, each of the first antigen binding moiety and the second antigen binding moiety comprises a crossed domain. In some embodiments, each of the first antigen binding moiety and the third antigen binding moiety comprises a crossed domain. In some embodiments, each of the second antigen binding moiety and the third antigen binding moiety comprises a crossed domain.

In some embodiments, each of first antigen binding moiety, the second antigen binding moiety and the third antigen binding moiety comprises a crossed domain. In some embodiments, each of first antigen binding moiety, the second antigen binding moiety and the fourth antigen binding moiety comprises a crossed domain. In some embodiments, each of first antigen binding moiety, the second antigen binding moiety and the fourth antigen binding moiety comprises a crossed domain. In some embodiments, each of first antigen binding moiety, the second antigen binding moiety and the fourth antigen binding moiety comprises a crossed domain. In some embodiments, each of first antigen binding moiety, the second antigen binding moiety, the third antigen binding moiety, and the fourth antigen binding moiety comprises a crossed domain.

[0137] In some embodiments, the first, second, and third antigen binding moiety bind antigens on different polypeptides. In some embodiments, the first, second, and third antigen binding moiety bind antigens on the same polypeptide.

[0138] In some embodiments, each of the first antigen binding moiety, the second antigen binding moiety and the third antigen binding moiety is non-covalently paired to the surrogate light chain polypeptide. In some embodiments, each of the first antigen binding moiety, the second antigen binding moiety and the third antigen binding moiety is covalently paired to the surrogate light chain polypeptide.

[0139] In some embodiments, the first antigen binding moiety comprises a first heavy chain variable region (VH) and a heavy chain first constant region (CH1). In some embodiments, the second antigen binding moiety comprises a second heavy chain variable region (VH) and a heavy chain first constant region (CH1). In some embodiments, the third antigen binding moiety comprises a third heavy chain variable region (VH) and a heavy chain first constant region (CH1). In some embodiments, the heavy chain first constant region comprises an amino acid sequence with at least 80%, at least 90%, at least 95%, at least 97%, at least 98%, at least 99%, or at least 100% identity to the amino acid sequence set forth in SEQ ID NO: 141.

[0140] In some embodiments, the first antigen binding moiety comprises a first heavy chain variable region (VH), a heavy chain first constant region (CH1), a heavy chain second constant region (CH2), and/or a heavy chain third constant region (CH3). In some embodiments, the second antigen binding moiety comprises a second heavy chain variable region (VH), a heavy chain first constant region (CH1), a heavy chain second constant region (CH2), and/or a heavy chain third constant region (CH3). In some embodiments, the third antigen binding moiety comprises a third heavy chain variable region (VH), a heavy chain first constant region (CH1), a heavy chain second constant region (CH2), and/or a heavy chain third constant region (CH3).

VEGF-A/ANG-2/VEGF-C trispecific antigen binding polypeptide

[0141] Described herein are trispecific antigen binding polypeptides targeting VEGF-A, ANG-2, and VEGF-C. Current therapies targeting only one of these targets, e.g. anti-VEGF-A monotherapy for the treatment of ocular diseases, require frequent ocular injections and lead to inconsistent outcomes. Trispecific antigen binding polypeptides described herein possess certain advantages, such as high binding affinities to multiple targets to enhance biological activity, reduced risk of immunogenicity, and improved and scalable cost-efficient manufacturability.

[0142] In some embodiments, the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety binds to VEGF-A. In some embodiments, the first target, the second target and/or the third target is VEGF-A or a fragment thereof. In some embodiments, the multispecific antigen binding polypeptide binds to VEGF-A or a fragment thereof with an EC₅₀ of about 1000, 500, 200, 100, 50, 20, 10, 8, 5, 3, 2, or 1 picomolar or less. In some embodiments, the multispecific antigen binding polypeptide binds to VEGF-A or a fragment thereof with an EC₅₀ of about 5 picomolar or less. In some embodiments, the multispecific antigen binding polypeptide binds to VEGF-A or a fragment thereof at least 2-fold, at least 3-fold, at least 5-fold, at least 8-fold, at least 10-fold, at least 20-fold, or at least 50-fold stronger than faricimab. In some embodiments, the multispecific antigen binding polypeptide binds to VEGF-A or a fragment thereof at least 8-fold stronger than faricimab.

[0143] In some embodiments, the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety binds to ANG-2. In some embodiments, the first target, the second target and/or the third target is ANG-2 or a fragment thereof. In some embodiments, the multispecific antigen binding polypeptide binds to ANG-2 or a fragment thereof with an EC₅₀ of about 1000, 500, 200, 100, 50, 20, 10, 8, 5, 3, 2, or 1 picomolar or less. In some embodiments, the multispecific antigen binding polypeptide binds to ANG-2 or a fragment thereof with an EC₅₀ of about 11 picomolar or less. In some embodiments, the multispecific antigen binding polypeptide binds to VEGF-A or a fragment thereof at least 5-fold, at least 20-fold, at least 50-fold, at least 100-fold, at least 200-fold, at least 300-fold, or at least 500-fold stronger than faricimab. In some embodiments, the multispecific antigen binding polypeptide binds to ANG-2 or a fragment thereof at least 300-fold stronger than faricimab.

[0144] In some embodiments, the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety binds to VEGF-C. In some embodiments, the first target, the second target and/or the third target is VEGF-C or a fragment thereof. In some embodiments, the multispecific antigen binding polypeptide binds to VEGF-C or a fragment thereof with an EC₅₀ of about 1000, 500, 200, 100, 50, 20, 10, 8, 5, 3, 2, or 1 picomolar or less.

In some embodiments, the multispecific antigen binding polypeptide binds to VEGF-C or a fragment thereof with an EC₅₀ of about 19 picomolar or less.

[0145] In some embodiments, the first target is VEGF-A or fragment thereof, the second target is ANG-2 or a fragment thereof, and the third target is VEGF-C or a fragment thereof. In some embodiments, the first target is VEGF-A or fragment thereof, the second target is VEGF-C or a fragment thereof, and the third target is ANG-2 or a fragment thereof. In some embodiments, the first target is VEGF-C or fragment thereof, the second target is ANG-2 or a fragment thereof, and the third target is VEGF-A or a fragment thereof. In some embodiments, the first target is VEGF-C or fragment thereof, the second target is VEGF-A or a fragment thereof, and the third target is ANG-2 or a fragment thereof. In some embodiments, the first target is ANG-2 or fragment thereof, the second target is VEGF-C or a fragment thereof, and the third target is VEGF-A or a fragment thereof. In some embodiments, the first target is ANG-2 or fragment thereof, the second target is VEGF-A or a fragment thereof, and the third target is VEGF-C or a fragment thereof.

[0146] In some embodiments, the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety binds to VEGF-A and comprises an immunoglobulin heavy chain variable region comprising: a heavy chain complementarity determining region 1 (HCDR1) comprising the amino acid sequence set forth in SEQ ID NO: 3; a heavy chain complementarity determining region 2 (HCDR2) comprising the amino acid sequence set forth in SEQ ID NO: 4; and/or a heavy chain complementarity determining region 3 (HCDR3) comprising the amino acid sequence set forth in SEQ ID NO: 5; wherein the heavy chain variable region binds to VEGF-A upon pairing with the universal light chain polypeptide.

[0147] In some embodiments, the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety binds to VEGF-A and comprises immunoglobulin heavy chain variable region comprising an amino acid sequence comprising at least 85% identity to the amino acid sequence set forth in SEQ ID NO: 1. In some embodiments, the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety binds to VEGF-A and comprises immunoglobulin heavy chain variable region comprising an amino acid sequence comprising at least 90% identity to the amino acid sequence set forth in SEQ ID NO: 1. In some embodiments, the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety binds to VEGF-A and comprises immunoglobulin heavy chain variable region comprising an amino acid sequence comprising at least 95% identity to the amino acid sequence set forth in SEQ ID NO: 1. In some embodiments, the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety binds to VEGF-A and comprises immunoglobulin heavy chain variable region

comprises an amino acid sequence comprising at least 96% identity to the amino acid sequence set forth in SEQ ID NO: 1. In some embodiments, the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety binds to VEGF-A and comprises immunoglobulin heavy chain variable region comprises an amino acid sequence comprising at least 97% identity to the amino acid sequence set forth in SEQ ID NO: 1. In some embodiments, the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety binds to VEGF-A and comprises immunoglobulin heavy chain variable region comprises an amino acid sequence comprising at least 98% identity to the amino acid sequence set forth in SEQ ID NO: 1. In some embodiments, the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety binds to VEGF-A and comprises immunoglobulin heavy chain variable region comprises an amino acid sequence comprising at least 99% identity to the amino acid sequence set forth in SEQ ID NO: 1. In some embodiments, the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety binds to VEGF-A and comprises immunoglobulin heavy chain variable region comprises an amino acid sequence set forth in SEQ ID NO: 1.

[0148] In some embodiments, the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety binds to VEGF-A and comprises immunoglobulin heavy chain variable region comprises an amino acid sequence comprising at least 85% identity to the amino acid sequence set forth in SEQ ID NO: 2. In some embodiments, the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety binds to VEGF-A and comprises immunoglobulin heavy chain variable region comprises an amino acid sequence comprising at least 90% identity to the amino acid sequence set forth in SEQ ID NO: 2. In some embodiments, the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety binds to VEGF-A and comprises immunoglobulin heavy chain variable region comprises an amino acid sequence comprising at least 95% identity to the amino acid sequence set forth in SEQ ID NO: 2. In some embodiments, the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety binds to VEGF-A and comprises immunoglobulin heavy chain variable region comprises an amino acid sequence comprising at least 96% identity to the amino acid sequence set forth in SEQ ID NO: 2. In some embodiments, the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety binds to VEGF-A and comprises immunoglobulin heavy chain variable region comprises an amino acid sequence comprising at least 97% identity to the amino acid sequence set forth in SEQ ID NO: 2. In some embodiments, the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety binds to VEGF-A and comprises immunoglobulin heavy chain variable region

comprises an amino acid sequence comprising at least 98% identity to the amino acid sequence set forth in SEQ ID NO: 2. In some embodiments, the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety binds to VEGF-A and comprises immunoglobulin heavy chain variable region comprises an amino acid sequence comprising at least 99% identity to the amino acid sequence set forth in SEQ ID NO: 2. In some embodiments, the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety binds to VEGF-A and comprises immunoglobulin heavy chain variable region comprises an amino acid sequence set forth in SEQ ID NO: 2.

[0149] In some embodiments, the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety binds to ANG-2 and comprises an immunoglobulin heavy chain variable region comprising: a heavy chain complementarity determining region 1 (HCDR1) comprising the amino acid sequence set forth in SEQ ID NO: 13; a heavy chain complementarity determining region 2 (HCDR2) comprising the amino acid sequence set forth in SEQ ID NO: 14; and/or a heavy chain complementarity determining region 3 (HCDR3) comprising the amino acid sequence set forth in SEQ ID NO: 15; wherein the heavy chain variable region binds to ANG-2 upon pairing with the universal light chain polypeptide.

[0150] In some embodiments, the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety binds to ANG-2 and comprises immunoglobulin heavy chain variable region comprises an amino acid sequence comprising at least 85% identity to the amino acid sequence set forth in SEQ ID NO: 11. In some embodiments, the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety binds to ANG-2 and comprises immunoglobulin heavy chain variable region comprises an amino acid sequence comprising at least 90% identity to the amino acid sequence set forth in SEQ ID NO: 11. In some embodiments, the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety binds to ANG-2 and comprises immunoglobulin heavy chain variable region comprises an amino acid sequence comprising at least 95% identity to the amino acid sequence set forth in SEQ ID NO: 11. In some embodiments, the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety binds to ANG-2 and comprises immunoglobulin heavy chain variable region comprises an amino acid sequence comprising at least 96% identity to the amino acid sequence set forth in SEQ ID NO: 11. In some embodiments, the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety binds to ANG-2 and comprises immunoglobulin heavy chain variable region comprises an amino acid sequence comprising at least 97% identity to the amino acid sequence set forth in SEQ ID NO: 11. In some embodiments, the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety binds

to ANG-2 and comprises immunoglobulin heavy chain variable region comprises an amino acid sequence comprising at least 98% identity to the amino acid sequence set forth in SEQ ID NO:

11. In some embodiments, the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety binds to ANG-2 and comprises immunoglobulin heavy chain variable region comprises an amino acid sequence comprising at least 99% identity to the amino acid sequence set forth in SEQ ID NO: 11. In some embodiments, the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety binds to ANG-2 and comprises immunoglobulin heavy chain variable region comprises an amino acid sequence set forth in SEQ ID NO: 11.

[0151] In some embodiments, the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety binds to ANG-2 and comprises immunoglobulin heavy chain variable region comprises an amino acid sequence comprising at least 85% identity to the amino acid sequence set forth in SEQ ID NO: 12. In some embodiments, the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety binds to ANG-2 and comprises immunoglobulin heavy chain variable region comprises an amino acid sequence comprising at least 90% identity to the amino acid sequence set forth in SEQ ID NO: 12. In some embodiments, the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety binds to ANG-2 and comprises immunoglobulin heavy chain variable region comprises an amino acid sequence comprising at least 95% identity to the amino acid sequence set forth in SEQ ID NO: 12. In some embodiments, the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety binds to ANG-2 and comprises immunoglobulin heavy chain variable region comprises an amino acid sequence comprising at least 96% identity to the amino acid sequence set forth in SEQ ID NO: 12. In some embodiments, the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety binds to ANG-2 and comprises immunoglobulin heavy chain variable region comprises an amino acid sequence comprising at least 97% identity to the amino acid sequence set forth in SEQ ID NO: 12. In some embodiments, the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety binds to ANG-2 and comprises immunoglobulin heavy chain variable region comprises an amino acid sequence comprising at least 98% identity to the amino acid sequence set forth in SEQ ID NO: 12. In some embodiments, the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety binds to ANG-2 and comprises immunoglobulin heavy chain variable region comprises an amino acid sequence comprising at least 99% identity to the amino acid sequence set forth in SEQ ID NO: 12. In some embodiments, the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety binds

to ANG-2 and comprises immunoglobulin heavy chain variable region comprises an amino acid sequence set forth in SEQ ID NO: 12.

[0152] In some embodiments, the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety binds to VEGF-C and comprises an immunoglobulin heavy chain variable region comprising: a heavy chain complementarity determining region 1 (HCDR1) comprising the amino acid sequence set forth in SEQ ID NO: 23; a heavy chain complementarity determining region 2 (HCDR2) comprising the amino acid sequence set forth in SEQ ID NO: 24; and/or a heavy chain complementarity determining region 3 (HCDR3) comprising the amino acid sequence set forth in SEQ ID NO: 25; wherein the heavy chain variable region binds to VEGF-C upon pairing with the universal light chain polypeptide.

[0153] In some embodiments, the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety binds to VEGF-C and comprises immunoglobulin heavy chain variable region comprises an amino acid sequence comprising at least 85% identity to the amino acid sequence set forth in SEQ ID NO: 21. In some embodiments, the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety binds to VEGF-C and comprises immunoglobulin heavy chain variable region comprises an amino acid sequence comprising at least 90% identity to the amino acid sequence set forth in SEQ ID NO: 21. In some embodiments, the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety binds to VEGF-C and comprises immunoglobulin heavy chain variable region comprises an amino acid sequence comprising at least 95% identity to the amino acid sequence set forth in SEQ ID NO: 21. In some embodiments, the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety binds to VEGF-C and comprises immunoglobulin heavy chain variable region comprises an amino acid sequence comprising at least 96% identity to the amino acid sequence set forth in SEQ ID NO: 21. In some embodiments, the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety binds to VEGF-C and comprises immunoglobulin heavy chain variable region comprises an amino acid sequence comprising at least 97% identity to the amino acid sequence set forth in SEQ ID NO: 21. In some embodiments, the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety binds to VEGF-C and comprises immunoglobulin heavy chain variable region comprises an amino acid sequence comprising at least 98% identity to the amino acid sequence set forth in SEQ ID NO: 21. In some embodiments, the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety binds to VEGF-C and comprises immunoglobulin heavy chain variable region comprises an amino acid sequence comprising at least 99% identity to the amino acid sequence set forth in SEQ ID NO:

21. In some embodiments, the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety binds to VEGF-C and comprises immunoglobulin heavy chain variable region comprises an amino acid sequence set forth in SEQ ID NO: 21.

[0154] In some embodiments, the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety binds to VEGF-C and comprises immunoglobulin heavy chain variable region comprises an amino acid sequence comprising at least 85% identity to the amino acid sequence set forth in SEQ ID NO: 22. In some embodiments, the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety binds to VEGF-C and comprises immunoglobulin heavy chain variable region comprises an amino acid sequence comprising at least 90% identity to the amino acid sequence set forth in SEQ ID NO: 22. In some embodiments, the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety binds to VEGF-C and comprises immunoglobulin heavy chain variable region comprises an amino acid sequence comprising at least 95% identity to the amino acid sequence set forth in SEQ ID NO: 22. In some embodiments, the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety binds to VEGF-C and comprises immunoglobulin heavy chain variable region comprises an amino acid sequence comprising at least 96% identity to the amino acid sequence set forth in SEQ ID NO: 22. In some embodiments, the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety binds to VEGF-C and comprises immunoglobulin heavy chain variable region comprises an amino acid sequence comprising at least 97% identity to the amino acid sequence set forth in SEQ ID NO: 22. In some embodiments, the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety binds to VEGF-C and comprises immunoglobulin heavy chain variable region comprises an amino acid sequence comprising at least 98% identity to the amino acid sequence set forth in SEQ ID NO: 22. In some embodiments, the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety binds to VEGF-C and comprises immunoglobulin heavy chain variable region comprises an amino acid sequence comprising at least 99% identity to the amino acid sequence set forth in SEQ ID NO: 22. In some embodiments, the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety binds to VEGF-C and comprises immunoglobulin heavy chain variable region comprises an amino acid sequence set forth in SEQ ID NO: 22.

[0155] In some embodiments, the first, second, or third antigen binding moiety comprise a heavy chain first constant region (CH1) comprising one or more amino acid substitutions from a light chain constant region. In some embodiments, the first antigen binding moiety comprises a first heavy chain variable region (VH) and a heavy chain first constant region (CH1). In some

embodiments, the second antigen binding moiety comprises a second heavy chain variable region (VH) and a heavy chain first constant region (CH1). In some embodiments, the first antigen binding moiety comprises a third heavy chain variable region (VH) and a heavy chain first constant region (CH1). In some embodiments, the multispecific antigen binding polypeptide comprises an amino acid sequence comprising at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in any one of SEQ ID NOs: 201 to 205.

[0156] In some embodiments, the multispecific antigen binding polypeptide comprises an amino acid sequence comprising at least 85% identity to the amino acid sequence set forth in SEQ ID NO: 201. In some embodiments, the multispecific antigen binding polypeptide comprises an amino acid sequence comprising at least 90% identity to the amino acid sequence set forth in SEQ ID NO: 201. In some embodiments, the multispecific antigen binding polypeptide comprises an amino acid sequence comprising at least 95% identity to the amino acid sequence set forth in SEQ ID NO: 201. In some embodiments, the multispecific antigen binding polypeptide comprises an amino acid sequence comprising at least 96% identity to the amino acid sequence set forth in SEQ ID NO: 201. In some embodiments, the multispecific antigen binding polypeptide comprises an amino acid sequence comprising at least 97% identity to the amino acid sequence set forth in SEQ ID NO: 201. In some embodiments, the multispecific antigen binding polypeptide comprises an amino acid sequence comprising at least 98% identity to the amino acid sequence set forth in SEQ ID NO: 201. In some embodiments, the multispecific antigen binding polypeptide comprises an amino acid sequence comprising at least 99% identity to the amino acid sequence set forth in SEQ ID NO: 201. In some embodiments, the multispecific antigen binding polypeptide comprises an amino acid sequence comprising the amino acid sequence set forth in SEQ ID NO: 201.

[0157] In some embodiments, the multispecific antigen binding polypeptide comprises an amino acid sequence comprising at least 85% identity to the amino acid sequence set forth in SEQ ID NO: 202. In some embodiments, the multispecific antigen binding polypeptide comprises an amino acid sequence comprising at least 90% identity to the amino acid sequence set forth in SEQ ID NO: 202. In some embodiments, the multispecific antigen binding polypeptide comprises an amino acid sequence comprising at least 95% identity to the amino acid sequence set forth in SEQ ID NO: 202. In some embodiments, the multispecific antigen binding polypeptide comprises an amino acid sequence comprising at least 96% identity to the amino acid sequence set forth in SEQ ID NO: 202. In some embodiments, the multispecific antigen binding polypeptide comprises an amino acid sequence comprising at least 97% identity to the amino acid sequence set forth in SEQ ID NO: 202. In some embodiments, the multispecific antigen binding polypeptide comprises an amino acid sequence comprising at least 98% identity

to the amino acid sequence set forth in SEQ ID NO: 202. In some embodiments, the multispecific antigen binding polypeptide comprises an amino acid sequence comprising at least 99% identity to the amino acid sequence set forth in SEQ ID NO: 202. In some embodiments, the multispecific antigen binding polypeptide comprises an amino acid sequence comprising the amino acid sequence set forth in SEQ ID NO: 202.

[0158] In some embodiments, the multispecific antigen binding polypeptide comprises an amino acid sequence comprising at least 85% identity to the amino acid sequence set forth in SEQ ID NO: 203. In some embodiments, the multispecific antigen binding polypeptide comprises an amino acid sequence comprising at least 90% identity to the amino acid sequence set forth in SEQ ID NO: 203. In some embodiments, the multispecific antigen binding polypeptide comprises an amino acid sequence comprising at least 95% identity to the amino acid sequence set forth in SEQ ID NO: 203. In some embodiments, the multispecific antigen binding polypeptide comprises an amino acid sequence comprising at least 96% identity to the amino acid sequence set forth in SEQ ID NO: 203. In some embodiments, the multispecific antigen binding polypeptide comprises an amino acid sequence comprising at least 97% identity to the amino acid sequence set forth in SEQ ID NO: 203. In some embodiments, the multispecific antigen binding polypeptide comprises an amino acid sequence comprising at least 98% identity to the amino acid sequence set forth in SEQ ID NO: 203. In some embodiments, the multispecific antigen binding polypeptide comprises an amino acid sequence comprising at least 99% identity to the amino acid sequence set forth in SEQ ID NO: 203. In some embodiments, the multispecific antigen binding polypeptide comprises an amino acid sequence comprising the amino acid sequence set forth in SEQ ID NO: 203.

[0159] In some embodiments, the heavy chain first constant region comprises an amino acid sequence with at least 80% identity to the amino acid sequence set forth in SEQ ID NO: 141. In some embodiments, the heavy chain first constant region comprises an amino acid sequence with at least 90% identity to the amino acid sequence set forth in SEQ ID NO: 141. In some embodiments, the heavy chain first constant region comprises an amino acid sequence with at least 95% identity to the amino acid sequence set forth in SEQ ID NO: 141. In some embodiments, the heavy chain first constant region comprises an amino acid sequence with at least 97% identity to the amino acid sequence set forth in SEQ ID NO: 141. In some embodiments, the heavy chain first constant region comprises an amino acid sequence with at least 98% identity to the amino acid sequence set forth in SEQ ID NO: 141. In some embodiments, the heavy chain first constant region comprises an amino acid sequence with at least 99% identity to the amino acid sequence set forth in SEQ ID NO: 141. In some

embodiments, the heavy chain first constant region comprises the amino acid sequence set forth in SEQ ID NO: 141.

[0160] In some embodiments, the multispecific antigen binding polypeptide comprises an amino acid sequence comprising at least 85% identity to the amino acid sequence set forth in SEQ ID NO: 402. In some embodiments, the multispecific antigen binding polypeptide comprises an amino acid sequence comprising at least 90% identity to the amino acid sequence set forth in SEQ ID NO: 402. In some embodiments, the multispecific antigen binding polypeptide comprises an amino acid sequence comprising at least 95% identity to the amino acid sequence set forth in SEQ ID NO: 402. In some embodiments, the multispecific antigen binding polypeptide comprises an amino acid sequence comprising at least 96% identity to the amino acid sequence set forth in SEQ ID NO: 402. In some embodiments, the multispecific antigen binding polypeptide comprises an amino acid sequence comprising at least 97% identity to the amino acid sequence set forth in SEQ ID NO: 402. In some embodiments, the multispecific antigen binding polypeptide comprises an amino acid sequence comprising at least 98% identity to the amino acid sequence set forth in SEQ ID NO: 402. In some embodiments, the multispecific antigen binding polypeptide comprises an amino acid sequence comprising at least 99% identity to the amino acid sequence set forth in SEQ ID NO: 402. In some embodiments, the multispecific antigen binding polypeptide comprises an amino acid sequence comprising the amino acid sequence set forth in SEQ ID NO: 402.

[0161] In some embodiments, the multispecific antigen binding polypeptide comprises an amino acid sequence comprising at least 85% identity to the amino acid sequence set forth in SEQ ID NO: 403. In some embodiments, the multispecific antigen binding polypeptide comprises an amino acid sequence comprising at least 90% identity to the amino acid sequence set forth in SEQ ID NO: 403. In some embodiments, the multispecific antigen binding polypeptide comprises an amino acid sequence comprising at least 95% identity to the amino acid sequence set forth in SEQ ID NO: 403. In some embodiments, the multispecific antigen binding polypeptide comprises an amino acid sequence comprising at least 96% identity to the amino acid sequence set forth in SEQ ID NO: 403. In some embodiments, the multispecific antigen binding polypeptide comprises an amino acid sequence comprising at least 97% identity to the amino acid sequence set forth in SEQ ID NO: 403. In some embodiments, the multispecific antigen binding polypeptide comprises an amino acid sequence comprising at least 98% identity to the amino acid sequence set forth in SEQ ID NO: 403. In some embodiments, the multispecific antigen binding polypeptide comprises an amino acid sequence comprising at least 99% identity to the amino acid sequence set forth in SEQ ID NO: 403. In some embodiments,

the multispecific antigen binding polypeptide comprises an amino acid sequence comprising the amino acid sequence set forth in SEQ ID NO: 403.

[0162] In some embodiments, the multispecific antigen binding polypeptide comprises an amino acid sequence comprising at least 85% identity to the amino acid sequence set forth in SEQ ID NO: 404. In some embodiments, the multispecific antigen binding polypeptide comprises an amino acid sequence comprising at least 90% identity to the amino acid sequence set forth in SEQ ID NO: 404. In some embodiments, the multispecific antigen binding polypeptide comprises an amino acid sequence comprising at least 95% identity to the amino acid sequence set forth in SEQ ID NO: 404. In some embodiments, the multispecific antigen binding polypeptide comprises an amino acid sequence comprising at least 96% identity to the amino acid sequence set forth in SEQ ID NO: 404. In some embodiments, the multispecific antigen binding polypeptide comprises an amino acid sequence comprising at least 97% identity to the amino acid sequence set forth in SEQ ID NO: 404. In some embodiments, the multispecific antigen binding polypeptide comprises an amino acid sequence comprising at least 98% identity to the amino acid sequence set forth in SEQ ID NO: 404. In some embodiments, the multispecific antigen binding polypeptide comprises an amino acid sequence comprising at least 99% identity to the amino acid sequence set forth in SEQ ID NO: 404. In some embodiments, the multispecific antigen binding polypeptide comprises an amino acid sequence comprising the amino acid sequence set forth in SEQ ID NO: 404.

[0163] In some embodiments, the multispecific antigen binding polypeptide comprises an amino acid sequence comprising at least 85% identity to the amino acid sequence set forth in SEQ ID NO: 405. In some embodiments, the multispecific antigen binding polypeptide comprises an amino acid sequence comprising at least 90% identity to the amino acid sequence set forth in SEQ ID NO: 405. In some embodiments, the multispecific antigen binding polypeptide comprises an amino acid sequence comprising at least 95% identity to the amino acid sequence set forth in SEQ ID NO: 405. In some embodiments, the multispecific antigen binding polypeptide comprises an amino acid sequence comprising at least 96% identity to the amino acid sequence set forth in SEQ ID NO: 405. In some embodiments, the multispecific antigen binding polypeptide comprises an amino acid sequence comprising at least 97% identity to the amino acid sequence set forth in SEQ ID NO: 405. In some embodiments, the multispecific antigen binding polypeptide comprises an amino acid sequence comprising at least 98% identity to the amino acid sequence set forth in SEQ ID NO: 405. In some embodiments, the multispecific antigen binding polypeptide comprises an amino acid sequence comprising at least 99% identity to the amino acid sequence set forth in SEQ ID NO: 405. In some embodiments,

the multispecific antigen binding polypeptide comprises an amino acid sequence comprising the amino acid sequence set forth in SEQ ID NO: 405.

[0164] Described herein in one aspect is a multispecific antigen binding polypeptide comprising: (a) a first antigen binding moiety, comprising a first heavy chain variable region (VH) and a heavy chain first constant region (CH1); (b) a second antigen binding moiety, comprising a second heavy chain variable region (VH) and a second heavy chain first constant region (CH1); and (c) a third antigen binding moiety, comprising a third heavy chain variable region (VH) and a third heavy chain first constant region (CH1); wherein the first antigen binding moiety binds to a first target, the second antigen binding moiety binds to a second target, and the third antigen binding moiety binds to a third target, wherein the first antigen binding moiety, the second antigen binding moiety, and the third antigen binding moiety are non-covalently paired to a light chain polypeptide. In certain embodiments, the light chain polypeptide is a surrogate light chain polypeptide. In certain embodiments, the surrogate light chain polypeptide comprises a VpreB sequence fused to a $\lambda 5$ sequence. In certain embodiments, the surrogate light chain polypeptide comprises an amino acid sequence comprising at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 102. In certain embodiments, the surrogate light chain polypeptide comprises the amino acid sequence set forth in SEQ ID NO: 102. In certain embodiments, the first antigen binding moiety, the second antigen binding moiety, and the third antigen binding moiety are independently selected from the list consisting of VEGF-A, VEGF-C, and ANG-2. In certain embodiments, a C-terminus of the first heavy chain variable region or the first antigen binding moiety is directly connected to an N-terminus of the second heavy chain variable region. In certain embodiments, a C-terminus of the second heavy chain variable region or the second antigen binding moiety is directly connected to an N-terminus of the third heavy chain variable region. In certain embodiments, a C-terminus of the first heavy chain variable region or the first antigen binding moiety is directly connected to an N-terminus of the second heavy chain variable region, and wherein a C-terminus of the second heavy chain variable region or the second antigen binding moiety is directly connected to an N-terminus of the third heavy chain variable region. In certain embodiments, the multispecific antigen binding polypeptide comprises an amino acid sequence comprising at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 201. In certain embodiments, the multispecific antigen binding polypeptide comprises an amino acid sequence comprising at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 202. In certain embodiments, the multispecific antigen binding polypeptide comprises at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 203. In certain embodiments, the first, second, and

third antigen binding moiety comprise or consist of the amino acid sequence set forth in SEQ ID NO: 201. In certain embodiments, the first, second, and third antigen binding moiety comprise or consist of the amino acid sequence set forth in SEQ ID NO: 202. In certain embodiments, the first, second, and third antigen binding moiety comprise or consist of the amino acid sequence set forth in SEQ ID NO: 203. In certain embodiments, the multispecific antigen binding polypeptide is encoded by a nucleic acid. In certain embodiments, described is a method of treating a disease in an individual comprising administering to the individual the multispecific antigen binding polypeptide, the nucleic acid or plurality of nucleic acids encoding the multispecific antigen binding polypeptide, or pharmaceutical composition, thereby treating the disease. In certain embodiments, the disease is an ocular disease. In certain embodiments, the ocular disease comprises macular degeneration. In certain embodiments, the macular degeneration is neovascular age-related macular degeneration. In certain embodiments, wherein the ocular disease comprises diabetic macular edema. In certain embodiments, the ocular disease comprises retinal vein occlusion. In certain embodiments, the disease is a cancer.

ErbB3/VEGF-A/ANG-2/VEGF-C tetraspecific antigen binding polypeptide

[0165] In some embodiments, the first antigen binding moiety, the second antigen binding moiety, the third antigen binding moiety, and/or the fourth antigen binding moiety binds to ErbB3. In some embodiments, the first target, the second target, the third target and/or the fourth target is ErbB3 or a fragment thereof. In some embodiments, the multispecific antigen binding polypeptide binds to ErbB3 or a fragment thereof with an EC₅₀ of about 1000, 500, 200, 100, 50, 20, 10, 8, 5, 3, 2, or 1 picomolar or less.

[0166] In some embodiments, the first antigen binding moiety, the second antigen binding moiety, the third antigen binding moiety, and/or the fourth antigen binding moiety binds to VEGF-A. In some embodiments, the first target, the second target, the third target and/or the fourth target is VEGF-A or a fragment thereof. In some embodiments, the multispecific antigen binding polypeptide binds to VEGF-A or a fragment thereof with an EC₅₀ of about 1000, 500, 200, 100, 50, 20, 10, 8, 5, 3, 2, or 1 picomolar or less.

[0167] In some embodiments, the first antigen binding moiety, the second antigen binding moiety, the third antigen binding moiety, and/or the fourth antigen binding moiety binds to ANG-2. In some embodiments, the first target, the second target, the third target and/or the fourth target is ANG-2 or a fragment thereof. In some embodiments, the multispecific antigen binding polypeptide binds to ANG-2 or a fragment thereof with an EC₅₀ of about 1000, 500, 200, 100, 50, 20, 10, 8, 5, 3, 2, or 1 picomolar or less.

[0168] In some embodiments, the first antigen binding moiety, the second antigen binding moiety, the third antigen binding moiety, and/or the fourth antigen binding moiety binds to VEGF-C. In some embodiments, the first target, the second target, the third target and/or the fourth target is VEGF-C or a fragment thereof. In some embodiments, the multispecific antigen binding polypeptide binds to VEGF-C or a fragment thereof with an EC₅₀ of about 1000, 500, 200, 100, 50, 20, 10, 8, 5, 3, 2, or 1 picomolar or less.

[0169] In some embodiments, the first target is ErbB3 or fragment thereof, the second target is VEGF-A or a fragment thereof, the third target is ANG-2 or a fragment thereof, and the fourth target is VEGF-C or a fragment thereof. In some embodiments, the first target is VEGF-A or fragment thereof, the second target is VEGF-C or a fragment thereof, the third target is ANG-2 or a fragment thereof, and the fourth target is ErbB3. In some embodiments, the first target is VEGF-C or fragment thereof, the second target is ANG-2 or a fragment thereof, the third target is VEGF-A or a fragment thereof, and the fourth target is ErbB3. In some embodiments, the first target is VEGF-C or fragment thereof, the second target is VEGF-A or a fragment thereof, the third target is ANG-2 or a fragment thereof, and the fourth target is ErbB3. In some embodiments, the first target is ANG-2 or fragment thereof, the second target is VEGF-C or a fragment thereof, the third target is ErbB3 or a fragment thereof, and the fourth target is VEGF-A.

[0170] In some embodiments, the first, second, third or fourth antigen binding moiety comprise a heavy chain first constant region (CH1) comprising one or more amino acid substitutions from a light chain constant region. In some embodiments, the first, second, third and fourth antigen binding moiety comprise an amino acid sequence comprising at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NOs: 301.

[0171] In some embodiments, the first, second, third and fourth antigen binding moiety comprise an amino acid sequence comprising at least 85% identity to the amino acid sequence set forth in SEQ ID NO: 301. In some embodiments, the first, second, third, and fourth antigen binding moiety comprise an amino acid sequence comprising at least 90% identity to the amino acid sequence set forth in SEQ ID NO: 301. In some embodiments, the first, second, third, and fourth antigen binding moiety comprise an amino acid sequence comprising at least 95% identity to the amino acid sequence set forth in SEQ ID NO: 301. In some embodiments, the first, second, third, and fourth antigen binding moiety comprise an amino acid sequence comprising at least 96% identity to the amino acid sequence set forth in SEQ ID NO: 301. In some embodiments, the first, second, third, and fourth antigen binding moiety comprise an amino acid sequence comprising at least 97% identity to the amino acid sequence set forth in SEQ ID NO: 301. In some embodiments, the first, second, third, and fourth antigen binding moiety comprise

an amino acid sequence comprising at least 98% identity to the amino acid sequence set forth in SEQ ID NO: 301. In some embodiments, the first, second, third, and fourth antigen binding moiety comprise an amino acid sequence comprising at least 99% identity to the amino acid sequence set forth in SEQ ID NO: 201. In some embodiments, the first, second, third, and fourth antigen binding moiety comprise an amino acid sequence comprising the amino acid sequence set forth in SEQ ID NO: 201.

[0172] In some embodiments, each of the first antigen binding moiety, the second antigen binding moiety, the third antigen binding moiety, and/or the fourth antigen binding moiety is paired to the surrogate light chain polypeptide. In some embodiments, the surrogate light chain polypeptide comprises an amino acid sequence at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 102.

EGFR/ErbB2 /ErbB3 trispecific antigen binding polypeptide

[0173] In some embodiments, the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety binds to EGFR. In some embodiments, the first target, the second target and/or the third target is EGFR or a fragment thereof. In some embodiments, the multispecific antigen binding polypeptide binds to EGFR or a fragment thereof with an EC₅₀ of about 1000, 500, 200, 100, 50, 20, 10, 8, 5, 3, 2, or 1 picomolar or less. In some embodiments, the multispecific antigen binding polypeptide binds to ErbB2 or a fragment thereof with an EC₅₀ of about 360 picomolar or less.

[0174] In some embodiments, the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety binds to ErbB2. In some embodiments, the first target, the second target and/or the third target is ErbB2 or a fragment thereof. In some embodiments, the multispecific antigen binding polypeptide binds to ErbB2 or a fragment thereof with an EC₅₀ of about 1000, 500, 200, 100, 50, 20, 10, 8, 5, 3, 2, or 1 picomolar or less. In some embodiments, the multispecific antigen binding polypeptide binds to ErbB2 or a fragment thereof with an EC₅₀ of about 52 picomolar or less.

[0175] In some embodiments, the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety binds to ErbB3. In some embodiments, the first target, the second target and/or the third target is ErbB3 or a fragment thereof. In some embodiments, the multispecific antigen binding polypeptide binds to ErbB3 or a fragment thereof with an EC₅₀ of about 5000, 2000, 1000, 500, 200, 100, 50, 20, 10, 8, 5, 3, 2, or 1 picomolar or less. In some embodiments, the multispecific antigen binding polypeptide binds to ErbB3 or a fragment thereof with an EC₅₀ of about 3000 picomolar or less.

[0176] In some embodiments, the first target is EGFR or fragment thereof, the second target is ErbB2 or a fragment thereof, and the third target is ErbB3 or a fragment thereof. In some embodiments, the first target is EGFR or fragment thereof, the second target is ErbB3 or a fragment thereof, and the third target is ErbB2 or a fragment thereof. In some embodiments, the first target is ErbB2 or fragment thereof, the second target is ErbB3 or a fragment thereof, and the third target is EGFR or a fragment thereof. In some embodiments, the first target is ErbB2 or fragment thereof, the second target is EGFR or a fragment thereof, and the third target is ErbB3 or a fragment thereof. In some embodiments, the first target is ErbB3 or fragment thereof, the second target is EGFR or a fragment thereof, and the third target is ErbB2 or a fragment thereof. In some embodiments, the first target is ErbB3 or fragment thereof, the second target is ErbB3 or a fragment thereof, and the third target is EGFR or a fragment thereof.

[0177] In some embodiments, the first, second, or third antigen binding moiety comprise a heavy chain first constant region (CH1) comprising one or more amino acid substitutions from a light chain constant region. In some embodiments, the first antigen binding moiety comprises a first heavy chain variable region (VH) and a heavy chain first constant region (CH1). In some embodiments, the second antigen binding moiety comprises a second heavy chain variable region (VH) and a heavy chain first constant region (CH1). In some embodiments, the first antigen binding moiety comprises a third heavy chain variable region (VH) and a heavy chain first constant region (CH1). In some embodiments, the first, second, and third antigen binding moiety comprise an amino acid sequence comprising at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth SEQ ID NO: 302.

[0178] In some embodiments, the first, second, and third antigen binding moiety comprise an amino acid sequence comprising at least 85% identity to the amino acid sequence set forth in SEQ ID NO: 302. In some embodiments, the first, second, and third antigen binding moiety comprise an amino acid sequence comprising at least 90% identity to the amino acid sequence set forth in SEQ ID NO: 302. In some embodiments, the first, second, and third antigen binding moiety comprise an amino acid sequence comprising at least 95% identity to the amino acid sequence set forth in SEQ ID NO: 302. In some embodiments, the first, second, and third antigen binding moiety comprise an amino acid sequence comprising at least 96% identity to the amino acid sequence set forth in SEQ ID NO: 302. In some embodiments, the first, second, and third antigen binding moiety comprise an amino acid sequence comprising at least 97% identity to the amino acid sequence set forth in SEQ ID NO: 302. In some embodiments, the first, second, and third antigen binding moiety comprise an amino acid sequence comprising at least 98% identity to the amino acid sequence set forth in SEQ ID NO: 302. In some embodiments, the first, second, and third antigen binding moiety comprise an amino acid sequence comprising

at least 99% identity to the amino acid sequence set forth in SEQ ID NO: 302. In some embodiments, the first, second, and third antigen binding moiety comprise an amino acid sequence comprising the amino acid sequence set forth in SEQ ID NO: 302.

[0179] In some embodiments, each of the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety is paired to the common light chain polypeptide. In some embodiments, the common light chain polypeptide comprises an amino acid sequence at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 303.

c-Met/EGFR/ErbB2/ErbB3 tetraspecific antigen binding polypeptide

[0180] In some embodiments, the first antigen binding moiety, the second antigen binding moiety, the third antigen binding moiety, and/or the fourth antigen binding moiety binds to c-Met. In some embodiments, the first target, the second target, the third target and/or the fourth target is c-Met or a fragment thereof. In some embodiments, the multispecific antigen binding polypeptide binds to c-Met or a fragment thereof with an EC₅₀ of about 1000, 500, 200, 100, 50, 20, 10, 8, 5, 3, 2, or 1 picomolar or less. In some embodiments, the multispecific antigen binding polypeptide binds to c-Met or a fragment thereof with an EC₅₀ of about 0.21 nanomolar or less.

[0181] In some embodiments, the first antigen binding moiety, the second antigen binding moiety, the third antigen binding moiety, and/or the fourth antigen binding moiety binds to EGFR. In some embodiments, the first target, the second target, the third target and/or the fourth target is EGFR or a fragment thereof. In some embodiments, the multispecific antigen binding polypeptide binds to EGFR or a fragment thereof with an EC₅₀ of about 1000, 500, 200, 100, 50, 20, 10, 8, 5, 3, 2, or 1 picomolar or less. In some embodiments, the multispecific antigen binding polypeptide binds to EGFR or a fragment thereof with an EC₅₀ of about 0.33 nanomolar or less.

[0182] In some embodiments, the first antigen binding moiety, the second antigen binding moiety, the third antigen binding moiety, and/or the fourth antigen binding moiety binds to ErbB2. In some embodiments, the first target, the second target, the third target and/or the fourth target is ErbB2 or a fragment thereof. In some embodiments, the multispecific antigen binding polypeptide binds to ErbB2 or a fragment thereof with an EC₅₀ of about 1000, 500, 200, 100, 50, 20, 10, 8, 5, 3, 2, or 1 picomolar or less. In some embodiments, the multispecific antigen binding polypeptide binds to ErbB2 or a fragment thereof with an EC₅₀ of about 51 picomolar or less.

[0183] In some embodiments, the first antigen binding moiety, the second antigen binding moiety, the third antigen binding moiety, and/or the fourth antigen binding moiety binds to ErbB3. In some embodiments, the first target, the second target, the third target and/or the fourth

target is ErbB3 or a fragment thereof. In some embodiments, the multispecific antigen binding polypeptide binds to ErbB3 or a fragment thereof with an EC50 of about 1000, 500, 200, 100, 50, 20, 10, 8, 5, 3, 2, or 1 picomolar or less. In some embodiments, the multispecific antigen binding polypeptide binds to ErbB3 or a fragment thereof with an EC50 of about 2.8 nanomolar or less.

[0184] In some embodiments, the first, second, third or fourth antigen binding moiety comprise a heavy chain first constant region (CH1) comprising one or more amino acid substitutions from a light chain constant region. In some embodiments, the first, second, third and fourth antigen binding moiety comprise an amino acid sequence comprising at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NOs: 304.

[0185] In some embodiments, the first, second, third and fourth antigen binding moiety comprise an amino acid sequence comprising at least 85% identity to the amino acid sequence set forth in SEQ ID NO: 304. In some embodiments, the first, second, third, and fourth antigen binding moiety comprise an amino acid sequence comprising at least 90% identity to the amino acid sequence set forth in SEQ ID NO: 304. In some embodiments, the first, second, third, and fourth antigen binding moiety comprise an amino acid sequence comprising at least 95% identity to the amino acid sequence set forth in SEQ ID NO: 304. In some embodiments, the first, second, third, and fourth antigen binding moiety comprise an amino acid sequence comprising at least 96% identity to the amino acid sequence set forth in SEQ ID NO: 304. In some embodiments, the first, second, third, and fourth antigen binding moiety comprise an amino acid sequence comprising at least 97% identity to the amino acid sequence set forth in SEQ ID NO: 304. In some embodiments, the first, second, third, and fourth antigen binding moiety comprise an amino acid sequence comprising at least 98% identity to the amino acid sequence set forth in SEQ ID NO: 304. In some embodiments, the first, second, third, and fourth antigen binding moiety comprise an amino acid sequence comprising at least 99% identity to the amino acid sequence set forth in SEQ ID NO: 304. In some embodiments, the first, second, third, and fourth antigen binding moiety comprise an amino acid sequence comprising the amino acid sequence set forth in SEQ ID NO: 304.

[0186] In some embodiments, each of the first antigen binding moiety, the second antigen binding moiety, the third antigen binding moiety, and/or the fourth antigen binding moiety is paired to the common light chain polypeptide. In some embodiments, the common light chain polypeptide comprises an amino acid sequence at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 303.

[0187] In some embodiments, the first antigen binding moiety, the second antigen binding moiety, the third antigen binding moiety, and/or the fourth antigen binding moiety comprises a crossed domain. In some embodiments, the second antigen binding moiety comprises a crossed

domain. In some embodiments, the third antigen binding moiety comprises a crossed domain. In some embodiments, the fourth antigen binding moiety comprises a crossed domain.

[0188] In some embodiments, the first, second, third and fourth antigen binding moiety comprise an amino acid sequence comprising at least 85% identity to the amino acid sequence set forth in SEQ ID NO: 308. In some embodiments, the first, second, third, and fourth antigen binding moiety comprise an amino acid sequence comprising at least 90% identity to the amino acid sequence set forth in SEQ ID NO: 308. In some embodiments, the first, second, third, and fourth antigen binding moiety comprise an amino acid sequence comprising at least 95% identity to the amino acid sequence set forth in SEQ ID NO: 308. In some embodiments, the first, second, third, and fourth antigen binding moiety comprise an amino acid sequence comprising at least 96% identity to the amino acid sequence set forth in SEQ ID NO: 308. In some embodiments, the first, second, third, and fourth antigen binding moiety comprise an amino acid sequence comprising at least 97% identity to the amino acid sequence set forth in SEQ ID NO: 308. In some embodiments, the first, second, third, and fourth antigen binding moiety comprise an amino acid sequence comprising at least 98% identity to the amino acid sequence set forth in SEQ ID NO: 308. In some embodiments, the first, second, third, and fourth antigen binding moiety comprise an amino acid sequence comprising at least 99% identity to the amino acid sequence set forth in SEQ ID NO: 308. In some embodiments, the first, second, third, and fourth antigen binding moiety comprise an amino acid sequence comprising the amino acid sequence set forth in SEQ ID NO: 308.

[0189] In some embodiments, each of the first antigen binding moiety, the second antigen binding moiety, the third antigen binding moiety, and/or the fourth antigen binding moiety is paired to the common light chain polypeptide. In some embodiments, the common light chain polypeptide comprises an amino acid sequence at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 309.

[0190] In some embodiments, the first antigen binding moiety, the second antigen binding moiety, the third antigen binding moiety, and/or the fourth antigen binding moiety is paired to a domain swapped surrogate light chain polypeptide, wherein the domain swapped surrogate light chain comprises a VpreB sequence fused to a heavy chain first constant region (CH1). In some embodiments, the domain swapped surrogate light chain polypeptide comprises an amino acid sequence at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 132.

[0191] In some embodiments, the first antigen binding moiety, the second antigen binding moiety, the third antigen binding moiety, and/or the fourth antigen binding moiety comprises at least two crossed domains. In some embodiments, the first antigen binding moiety, the second

antigen binding moiety, the third antigen binding moiety, and/or the fourth antigen binding moiety comprises at least three crossed domains. In some embodiments, the first antigen binding moiety, the second antigen binding moiety, the third antigen binding moiety, and/or the fourth antigen binding moiety comprises at least four crossed domains. In some embodiments, each of the first antigen binding moiety and the second antigen binding moiety comprises a crossed domain. In some embodiments, each of the first antigen binding moiety and the third antigen binding moiety comprises a crossed domain. In some embodiments, each of the first antigen binding moiety and the fourth antigen binding moiety comprises a crossed domain. In some embodiments, each of the second antigen binding moiety and the third antigen binding moiety comprises a crossed domain. In some embodiments, each of the first antigen binding moiety, the third antigen binding moiety, and the fourth antigen binding moiety comprises a crossed domain. [0192] In some embodiments, the first, second, third and fourth antigen binding moiety comprise an amino acid sequence comprising at least 85% identity to the amino acid sequence set forth in SEQ ID NO: 310. In some embodiments, the first, second, third, and fourth antigen binding moiety comprise an amino acid sequence comprising at least 90% identity to the amino acid sequence set forth in SEQ ID NO: 310. In some embodiments, the first, second, third, and fourth antigen binding moiety comprise an amino acid sequence comprising at least 95% identity to the amino acid sequence set forth in SEQ ID NO: 310. In some embodiments, the first, second, third, and fourth antigen binding moiety comprise an amino acid sequence comprising at least 96% identity to the amino acid sequence set forth in SEQ ID NO: 310. In some embodiments, the first, second, third, and fourth antigen binding moiety comprise an amino acid sequence comprising at least 97% identity to the amino acid sequence set forth in SEQ ID NO: 310. In some embodiments, the first, second, third, and fourth antigen binding moiety comprise an amino acid sequence comprising at least 98% identity to the amino acid sequence set forth in SEQ ID NO: 310. In some embodiments, the first, second, third, and fourth antigen binding moiety comprise an amino acid sequence comprising at least 99% identity to the amino acid sequence set forth in SEQ ID NO: 310. In some embodiments, the first, second, third, and fourth antigen binding moiety comprise an amino acid sequence comprising the amino acid sequence set forth in SEQ ID NO: 310.

[0193] In some embodiments, the first antigen binding moiety, the second antigen binding moiety, the third antigen binding moiety, and/or the fourth antigen binding moiety is paired to a domain swapped common light chain polypeptide, wherein the domain swapped common light chain comprises a light chain variable region (VL) fused to a heavy chain first constant region (CH1). In some embodiments, the domain swapped common light chain polypeptide comprises

an amino acid sequence at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 311.

[0194] In some embodiments, each of the first antigen binding moiety, the second antigen binding moiety, the third antigen binding moiety, and/or the fourth antigen binding moiety is paired to the surrogate light chain polypeptide. In some embodiments, the surrogate light chain polypeptide comprises an amino acid sequence at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 102.

PD-1 monospecific antigen binding polypeptide

[0195] In some embodiments, the first target, the second target, and the third target are the same. In some embodiments, the first target, the second target, and the third target are PD-1 or a fragment thereof. In some embodiments, the multispecific antigen binding polypeptide binds to PD-1 or a fragment thereof. In some embodiments, the multispecific antigen binding polypeptide binds to PD-1 or a fragment thereof with an EC₅₀ of about 1000, 500, 200, 100, 50, 20, 10, 8, 5, 3, 2, or 1 picomolar or less. In some embodiments, the multispecific antigen binding polypeptide binds to PD-1 or a fragment thereof with an EC₅₀ of about 90 picomolar or less.

[0196] In some embodiments, the first, second, and third antigen binding moiety comprise an amino acid sequence comprising at least 85% identity to the amino acid sequence set forth in SEQ ID NO: 305. In some embodiments, the first, second, and third antigen binding moiety comprise an amino acid sequence comprising at least 90% identity to the amino acid sequence set forth in SEQ ID NO: 305. In some embodiments, the first, second, and third antigen binding moiety comprise an amino acid sequence comprising at least 95% identity to the amino acid sequence set forth in SEQ ID NO: 305. In some embodiments, the first, second, third, and fourth antigen binding moiety comprise an amino acid sequence comprising at least 96% identity to the amino acid sequence set forth in SEQ ID NO: 305. In some embodiments, the first, second, third, and fourth antigen binding moiety comprise an amino acid sequence comprising at least 97% identity to the amino acid sequence set forth in SEQ ID NO: 305. In some embodiments, the first, second, third, and fourth antigen binding moiety comprise an amino acid sequence comprising at least 98% identity to the amino acid sequence set forth in SEQ ID NO: 305. In some embodiments, the first, second, third, and fourth antigen binding moiety comprise an amino acid sequence comprising at least 99% identity to the amino acid sequence set forth in SEQ ID NO: 305. In some embodiments, the first, second, third, and fourth antigen binding moiety comprise an amino acid sequence comprising the amino acid sequence set forth in SEQ ID NO: 305.

[0197] In some embodiments, each of the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety is paired to the common light chain polypeptide. In some embodiments, the common light chain polypeptide comprises an amino acid sequence at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 307.

[0198] In some embodiments, the first target, the second target, the third target, and the fourth target are the same. In some embodiments, the first target, the second target, the third target, and the fourth target are PD-1 or a fragment thereof. In some embodiments, the multispecific antigen binding polypeptide binds to PD-1 or a fragment thereof. In some embodiments, the multispecific antigen binding polypeptide binds to PD-1 or a fragment thereof with an EC₅₀ of about 1000, 500, 200, 100, 50, 20, 10, 8, 5, 3, 2, or 1 picomolar or less. In some embodiments, the multispecific antigen binding polypeptide binds to PD-1 or a fragment thereof with an EC₅₀ of about 60 picomolar or less.

[0199] In some embodiments, the first, second, third, or fourth antigen binding moiety comprises a first heavy chain variable region (VH), a heavy chain first constant region (CH1), a heavy chain second constant region (CH2), and/or a heavy chain third constant region (CH3). In some embodiments, the first, second, third, and fourth antigen binding moiety comprise an amino acid sequence comprising at least 85% identity to the amino acid sequence set forth in SEQ ID NO: 306. In some embodiments, the first, second, third, and fourth antigen binding moiety comprise an amino acid sequence comprising at least 90% identity to the amino acid sequence set forth in SEQ ID NO: 306. In some embodiments, the first, second, third, and fourth antigen binding moiety comprise an amino acid sequence comprising at least 95% identity to the amino acid sequence set forth in SEQ ID NO: 306. In some embodiments, the first, second, third, and fourth antigen binding moiety comprise an amino acid sequence comprising at least 96% identity to the amino acid sequence set forth in SEQ ID NO: 306. In some embodiments, the first, second, third, and fourth antigen binding moiety comprise an amino acid sequence comprising at least 97% identity to the amino acid sequence set forth in SEQ ID NO: 306. In some embodiments, the first, second, third, and fourth antigen binding moiety comprise an amino acid sequence comprising at least 98% identity to the amino acid sequence set forth in SEQ ID NO: 306. In some embodiments, the first, second, third, and fourth antigen binding moiety comprise an amino acid sequence comprising at least 99% identity to the amino acid sequence set forth in SEQ ID NO: 306. In some embodiments, the first, second, third, and fourth antigen binding moiety comprise an amino acid sequence comprising the amino acid sequence set forth in SEQ ID NO: 306.

[0200] In some embodiments, each of the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety is paired to the common light chain polypeptide. In some embodiments, the common light chain polypeptide comprises an amino acid sequence at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 307.

Multispecific antigen binding polypeptide with direct linkage between antigen binding moieties

[0201] In another aspect, described herein are multispecific antigen binding polypeptides comprising: a first antigen binding moiety, comprising a first heavy chain variable region and a first heavy chain first constant region (CH1) paired with a first light chain; and a second antigen binding moiety, comprising a second heavy chain variable region and a second heavy chain first constant region (CH1) paired with a second light chain; wherein a C to terminus of the first CH1 is coupled to an N-terminus of the second heavy chain variable region wherein the first antigen binding moiety binds to a first target, the second antigen binding moiety binds to a second target. In some embodiments, the first light chain and the second light chain are a common light chain. In some embodiments, the first light chain and the second light chain are a surrogate light chain. In some embodiments, the first antigen binding moiety and the second antigen binding moiety are directly coupled without a linker.

[0202] In some embodiments, the surrogate light chain polypeptide comprises a VpreB sequence conjugated to a $\lambda 5$ sequence. In some embodiments, the VpreB sequence comprises an amino acid sequence comprising at least 90% sequence identity to the amino acid sequence set forth in SEQ ID NO: 101. In some embodiments, the VpreB sequence comprises an amino acid sequence comprising at least 95% sequence identity to the amino acid sequence set forth in SEQ ID NO: 101. In some embodiments, the VpreB sequence comprises an amino acid sequence comprising at least 97% sequence identity to the amino acid sequence set forth in SEQ ID NO: 101. In some embodiments, the VpreB sequence comprises an amino acid sequence comprising at least 98% sequence identity to the amino acid sequence set forth in SEQ ID NO: 101. In some embodiments, the VpreB sequence comprises an amino acid sequence comprising at least 99% sequence identity to the amino acid sequence set forth in SEQ ID NO: 101. In some embodiments, the VpreB sequence comprises an amino acid sequence set forth in SEQ ID NO: 101.

[0203] In some embodiments, the $\lambda 5$ sequence comprises an amino acid sequence comprising at least 90% sequence identity to the amino acid sequence set forth in SEQ ID NO: 106. In some embodiments, the $\lambda 5$ sequence comprises an amino acid sequence comprising at least 95%

sequence identity to the amino acid sequence set forth in SEQ ID NO: 106. In some embodiments, the $\lambda 5$ sequence comprises an amino acid sequence comprising at least 97% sequence identity to the amino acid sequence set forth in SEQ ID NO: 106. In some embodiments, the $\lambda 5$ sequence comprises an amino acid sequence comprising at least 98% sequence identity to the amino acid sequence set forth in SEQ ID NO: 106. In some embodiments, the $\lambda 5$ sequence comprises an amino acid sequence comprising at least 99% sequence identity to the amino acid sequence set forth in SEQ ID NO: 106. In some embodiments, the $\lambda 5$ sequence comprises an amino acid sequence set forth in SEQ ID NO: 106.

[0204] In some embodiments, the surrogate light chain polypeptide comprises: a light chain complementarity determining region 1 (LCDR1) comprising the amino acid sequence set forth in SEQ ID NO: 103; a light chain complementarity determining region 2 (LCDR2) comprising the amino acid sequence set forth in SEQ ID NO: 104; and a light chain complementarity determining region 3 (LCDR3) comprising the amino acid sequence set forth in SEQ ID NO: 105.

[0205] In some embodiments, the surrogate light chain polypeptide comprises an amino acid sequence comprising at least 85% sequence identity to the amino acid sequence set forth in SEQ ID NO: 102. In some embodiments, the surrogate light chain polypeptide comprises an amino acid sequence comprising at least 90% sequence identity to the amino acid sequence set forth in SEQ ID NO: 102. In some embodiments, the surrogate light chain polypeptide comprises an amino acid sequence comprising at least 95% sequence identity to the amino acid sequence set forth in SEQ ID NO: 102. In some embodiments, the surrogate light chain polypeptide comprises an amino acid sequence comprising at least 96% sequence identity to the amino acid sequence set forth in SEQ ID NO: 102. In some embodiments, the surrogate light chain polypeptide comprises an amino acid sequence comprising at least 97% sequence identity to the amino acid sequence set forth in SEQ ID NO: 102. In some embodiments, the surrogate light chain polypeptide comprises an amino acid sequence comprising at least 98% sequence identity to the amino acid sequence set forth in SEQ ID NO: 102. In some embodiments, the surrogate light chain polypeptide comprises an amino acid sequence comprising at least 99% sequence identity to the amino acid sequence set forth in SEQ ID NO: 102. In some embodiments, the surrogate light chain polypeptide comprises an amino acid sequence set forth in SEQ ID NO: 102.

[0206] In some embodiments, each of the first antigen binding moiety and/or the second antigen binding moiety is non-covalently paired to the surrogate light chain polypeptide. In some embodiments, each of the first antigen binding moiety and/or the second antigen binding moiety is covalently paired to the surrogate light chain polypeptide. In some embodiments, the first and

second antigen binding moiety bind antigens on different polypeptides. In some embodiments, the first and second antigen binding moiety bind antigens on the same polypeptide.

[0207] In some embodiments, the first antigen binding moiety comprises a first heavy chain variable region (VH) and a heavy chain first constant region (CH1). In some embodiments, the second antigen binding moiety comprises a second heavy chain variable region (VH) and a heavy chain first constant region (CH1). In some embodiments, the heavy chain first constant region comprises an amino acid sequence with at least 80%, at least 90%, at least 95%, at least 97%, at least 98%, at least 99%, or at least 100% identity to the amino acid sequence set forth in SEQ ID NO: 141.

[0208] In some embodiments, the first antigen binding moiety comprises a first heavy chain variable region (VH), a heavy chain first constant region (CH1), a heavy chain second constant region (CH2), and/or a heavy chain third constant region (CH3). In some embodiments, the second antigen binding moiety comprises a second heavy chain variable region (VH), a heavy chain first constant region (CH1), a heavy chain second constant region (CH2), and/or a heavy chain third constant region (CH3).

[0209] In some embodiments, the first target, and or the second target is VEGF-A or a fragment thereof. In some embodiments, the multispecific antigen binding polypeptide binds to VEGF-A or a fragment thereof with an EC50 of about 1000, 500, 200, 100, 50, 20, 10, 8, 5, 3, 2, or 1 picomolar or less. In some embodiments, the multispecific antigen binding polypeptide binds to VEGF-A or a fragment thereof with an EC50 of about 5 picomolar or less. In some embodiments, the multispecific antigen binding polypeptide binds to VEGF-A or a fragment thereof at least 2-fold, at least 3-fold, at least 5-fold, at least 8-fold, at least 10-fold, at least 20-fold, or at least 50-fold stronger than faricimab. In some embodiments, the multispecific antigen binding polypeptide binds to VEGF-A or a fragment thereof at least 8-fold stronger than faricimab.

[0210] In some embodiments, the first target, and or the second target is ANG-2 or a fragment thereof. In some embodiments, the multispecific antigen binding polypeptide binds to ANG-2 or a fragment thereof with an EC50 of about 1000, 500, 200, 100, 50, 20, 10, 8, 5, 3, 2, or 1 picomolar or less. In some embodiments, the multispecific antigen binding polypeptide binds to ANG-2 or a fragment thereof with an EC50 of about 11 picomolar or less. In some embodiments, the multispecific antigen binding polypeptide binds to VEGF-A or a fragment thereof at least 5-fold, at least 20-fold, at least 50-fold, at least 100-fold, at least 200-fold, at least 300-fold, or at least 500-fold stronger than faricimab. In some embodiments, the multispecific antigen binding polypeptide binds to ANG-2 or a fragment thereof at least 300-fold stronger than faricimab.

[0211] In some embodiments, the first target, and or the second target is VEGF-C or a fragment thereof. In some embodiments, the multispecific antigen binding polypeptide binds to VEGF-C or a fragment thereof with an EC50 of about 1000, 500, 200, 100, 50, 20, 10, 8, 5, 3, 2, or 1 picomolar or less. In some embodiments, the multispecific antigen binding polypeptide binds to VEGF-C or a fragment thereof with an EC50 of about 19 picomolar or less.

[0212] In some embodiments, the first target and the second target are independently selected from VEGF-A or fragment thereof, ANG-2 or a fragment thereof, and VEGF-C or a fragment thereof. In some embodiments, the first and/or second antigen binding moiety bind antigens on different polypeptides. In some embodiments, the first and/or second antigen binding moiety bind antigens on the same polypeptide.

[0213] In some embodiments, the first antigen binding moiety and/or the second antigen binding moiety binds to VEGF-A and comprises an immunoglobulin heavy chain variable region comprising: a heavy chain complementarity determining region 1 (HCDR1) comprising the amino acid sequence set forth in SEQ ID NO: 3; a heavy chain complementarity determining region 2 (HCDR2) comprising the amino acid sequence set forth in SEQ ID NO: 4; and/or a heavy chain complementarity determining region 3 (HCDR3) comprising the amino acid sequence set forth in SEQ ID NO: 5; wherein the heavy chain variable region binds to VEGF-A upon pairing with the universal light chain polypeptide. In some embodiments, the first antigen binding moiety and/or the second antigen binding moiety binds to VEGF-C and comprises immunoglobulin heavy chain variable region comprises an amino acid sequence comprising at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 1. In some embodiments, the first antigen binding moiety and/or the second antigen binding moiety binds to VEGF-C and comprises immunoglobulin heavy chain variable region comprises an amino acid sequence comprising at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 2.

[0214] In some embodiments, the first antigen binding moiety and/or the second antigen binding moiety binds to ANG-2 and comprises an immunoglobulin heavy chain variable region comprising: a heavy chain complementarity determining region 1 (HCDR1) comprising the amino acid sequence set forth in SEQ ID NO: 13; a heavy chain complementarity determining region 2 (HCDR2) comprising the amino acid sequence set forth in SEQ ID NO: 14; and/or a heavy chain complementarity determining region 3 (HCDR3) comprising the amino acid sequence set forth in SEQ ID NO: 15; wherein the heavy chain variable region binds to ANG-2 upon pairing with the universal light chain polypeptide. In some embodiments, the first antigen binding moiety and/or the second antigen binding moiety binds to ANG-2 and comprises immunoglobulin heavy chain variable region comprises an amino acid sequence comprising at

least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 11. In some embodiments, the first antigen binding moiety and/or the second antigen binding moiety binds to ANG-2 and comprises immunoglobulin heavy chain variable region comprising an amino acid sequence comprising at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 12.

[0215] In some embodiments, the first antigen binding moiety and/or the second antigen binding moiety binds to VEGF-C and comprises an immunoglobulin heavy chain variable region comprising: a heavy chain complementarity determining region 1 (HCDR1) comprising the amino acid sequence set forth in SEQ ID NO: 23; a heavy chain complementarity determining region 2 (HCDR2) comprising the amino acid sequence set forth in SEQ ID NO: 24; and/or a heavy chain complementarity determining region 3 (HCDR3) comprising the amino acid sequence set forth in SEQ ID NO: 25; wherein the heavy chain variable region binds to VEGF-C upon pairing with the universal light chain polypeptide.

[0216] In some embodiments, the first antigen binding moiety and/or the second antigen binding moiety binds to VEGF-C and comprises immunoglobulin heavy chain variable region comprising an amino acid sequence comprising at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 21. In some embodiments, the first antigen binding moiety and/or the second antigen binding moiety binds to VEGF-C and comprises immunoglobulin heavy chain variable region comprising an amino acid sequence comprising at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 22.

[0217] In some embodiments, the multispecific antigen binding polypeptide comprises an amino acid sequence comprising at least 85% identity to the amino acid sequence set forth in SEQ ID NO: 401. In some embodiments, the multispecific antigen binding polypeptide comprises an amino acid sequence comprising at least 90% identity to the amino acid sequence set forth in SEQ ID NO: 401. In some embodiments, the multispecific antigen binding polypeptide comprises an amino acid sequence comprising at least 95% identity to the amino acid sequence set forth in SEQ ID NO: 401. In some embodiments, the multispecific antigen binding polypeptide comprises an amino acid sequence comprising at least 96% identity to the amino acid sequence set forth in SEQ ID NO: 401. In some embodiments, the multispecific antigen binding polypeptide comprises an amino acid sequence comprising at least 97% identity to the amino acid sequence set forth in SEQ ID NO: 401. In some embodiments, the multispecific antigen binding polypeptide comprises an amino acid sequence comprising at least 98% identity to the amino acid sequence set forth in SEQ ID NO: 401. In some embodiments, the multispecific antigen binding polypeptide comprises an amino acid sequence comprising at least 99% identity to the amino acid sequence set forth in SEQ ID NO: 401. In some embodiments, the multispecific antigen binding polypeptide comprises an amino acid sequence comprising at least 100% identity to the amino acid sequence set forth in SEQ ID NO: 401.

99% identity to the amino acid sequence set forth in SEQ ID NO: 401. In some embodiments, the multispecific antigen binding polypeptide comprises an amino acid sequence comprising the amino acid sequence set forth in SEQ ID NO: 401.

[0218] In some embodiments, the multispecific antigen binding polypeptide comprises an amino acid sequence comprising at least 85% identity to the amino acid sequence set forth in SEQ ID NO: 406. In some embodiments, the multispecific antigen binding polypeptide comprises an amino acid sequence comprising at least 90% identity to the amino acid sequence set forth in SEQ ID NO: 406. In some embodiments, the multispecific antigen binding polypeptide comprises an amino acid sequence comprising at least 95% identity to the amino acid sequence set forth in SEQ ID NO: 406. In some embodiments, the multispecific antigen binding polypeptide comprises an amino acid sequence comprising at least 96% identity to the amino acid sequence set forth in SEQ ID NO: 406. In some embodiments, the multispecific antigen binding polypeptide comprises an amino acid sequence comprising at least 97% identity to the amino acid sequence set forth in SEQ ID NO: 406. In some embodiments, the multispecific antigen binding polypeptide comprises an amino acid sequence comprising at least 98% identity to the amino acid sequence set forth in SEQ ID NO: 406. In some embodiments, the multispecific antigen binding polypeptide comprises an amino acid sequence comprising at least 99% identity to the amino acid sequence set forth in SEQ ID NO: 406. In some embodiments, the multispecific antigen binding polypeptide comprises an amino acid sequence comprising the amino acid sequence set forth in SEQ ID NO: 406.

VEGF-A antigen binding polypeptide

[0219] Described herein is a vascular endothelial growth factor A (VEGF-A) antigen binding polypeptide or antigen binding fragment thereof comprising: a heavy chain complementarity determining region 1 (HCDR1) comprising the amino acid sequence set forth in SEQ ID NO: 3; a heavy chain complementarity determining region 2 (HCDR2) comprising the amino acid sequence set forth in SEQ ID NO: 4; and/or a heavy chain complementarity determining region 3 (HCDR3) comprising the amino acid sequence set forth in SEQ ID NO: 5; wherein the antigen binding polypeptide binds to VEGF-A.

[0220] In some embodiments, the VEGF-A antigen binding polypeptide or antigen binding fragment comprises a heavy chain variable region comprising an amino acid sequence comprising at least 85% identity to the amino acid sequence set forth in SEQ ID NO: 1. In some embodiments, the VEGF-A antigen binding polypeptide or antigen binding fragment comprises a heavy chain variable region comprising an amino acid sequence comprising at least 90% identity

to the amino acid sequence set forth in SEQ ID NO: 1. In some embodiments, the VEGF-A antigen binding polypeptide or antigen binding fragment comprises a heavy chain variable region comprising an amino acid sequence comprising at least 95% identity to the amino acid sequence set forth in SEQ ID NO: 1. In some embodiments, the VEGF-A antigen binding polypeptide or antigen binding fragment comprises a heavy chain variable region comprising an amino acid sequence comprising at least 96% identity to the amino acid sequence set forth in SEQ ID NO: 1. In some embodiments, the VEGF-A antigen binding polypeptide or antigen binding fragment comprises a heavy chain variable region comprising an amino acid sequence comprising at least 97% identity to the amino acid sequence set forth in SEQ ID NO: 1. In some embodiments, the VEGF-A antigen binding polypeptide or antigen binding fragment comprises a heavy chain variable region comprising an amino acid sequence comprising at least 98% identity to the amino acid sequence set forth in SEQ ID NO: 1. In some embodiments, the VEGF-A antigen binding polypeptide or antigen binding fragment comprises a heavy chain variable region comprising an amino acid sequence comprising at least 99% identity to the amino acid sequence set forth in SEQ ID NO: 1. In some embodiments, the VEGF-A antigen binding polypeptide or antigen binding fragment comprises a heavy chain variable region comprising an amino acid sequence set forth in SEQ ID NO: 1.

[0221] In some embodiments, the VEGF-A antigen binding polypeptide or antigen binding fragment comprises a heavy chain variable region comprising an amino acid sequence comprising at least 85% identity to the amino acid sequence set forth in SEQ ID NO: 2. In some embodiments, the VEGF-A antigen binding polypeptide or antigen binding fragment comprises a heavy chain variable region comprising an amino acid sequence comprising at least 90% identity to the amino acid sequence set forth in SEQ ID NO: 2. In some embodiments, the VEGF-A antigen binding polypeptide or antigen binding fragment comprises a heavy chain variable region comprising an amino acid sequence comprising at least 95% identity to the amino acid sequence set forth in SEQ ID NO: 2. In some embodiments, the VEGF-A antigen binding polypeptide or antigen binding fragment comprises a heavy chain variable region comprising an amino acid sequence comprising at least 96% identity to the amino acid sequence set forth in SEQ ID NO: 2. In some embodiments, the VEGF-A antigen binding polypeptide or antigen binding fragment comprises a heavy chain variable region comprising an amino acid sequence comprising at least 97% identity to the amino acid sequence set forth in SEQ ID NO: 2. In some embodiments, the VEGF-A antigen binding polypeptide or antigen binding fragment comprises a heavy chain variable region comprising an amino acid sequence comprising at least 98% identity to the amino acid sequence set forth in SEQ ID NO: 2. In some embodiments, the VEGF-A antigen binding polypeptide or antigen binding fragment comprises a heavy chain variable region comprising an

amino acid sequence comprising at least 99% identity to the amino acid sequence set forth in SEQ ID NO: 2. In some embodiments, the VEGF-A antigen binding polypeptide or antigen binding fragment comprises a heavy chain variable region comprising an amino acid sequence set forth in SEQ ID NO: 2.

[0222] In some embodiments, the VEGF-A antigen binding polypeptide or antigen binding fragment further comprises a surrogate light chain.

ANG-2 antigen binding polypeptide

[0223] Described herein is an angiopoietin 2 (ANG-2) antigen binding polypeptide or antigen binding fragment thereof comprising: a heavy chain complementarity determining region 1 (HCDR1) comprising the amino acid sequence set forth in SEQ ID NO: 13; a heavy chain complementarity determining region 2 (HCDR2) comprising the amino acid sequence set forth in SEQ ID NO: 14; and/or a heavy chain complementarity determining region 3 (HCDR3) comprising the amino acid sequence set forth in SEQ ID NO: 15; wherein the polypeptide binds to ANG-2.

[0224] In some embodiments, the ANG-2 antigen binding polypeptide or antigen binding fragment comprises a heavy chain variable region comprising an amino acid sequence comprising at least 85% identity to the amino acid sequence set forth in SEQ ID NO: 11. In some embodiments, the ANG-2 antigen binding polypeptide or antigen binding fragment comprises a heavy chain variable region comprising an amino acid sequence comprising at least 90% identity to the amino acid sequence set forth in SEQ ID NO: 11. In some embodiments, the ANG-2 antigen binding polypeptide or antigen binding fragment comprises a heavy chain variable region comprising an amino acid sequence comprising at least 95% identity to the amino acid sequence set forth in SEQ ID NO: 11. In some embodiments, the ANG-2 antigen binding polypeptide or antigen binding fragment comprises a heavy chain variable region comprising an amino acid sequence comprising at least 96% identity to the amino acid sequence set forth in SEQ ID NO: 11. In some embodiments, the ANG-2 antigen binding polypeptide or antigen binding fragment comprises a heavy chain variable region comprising an amino acid sequence comprising at least 97% identity to the amino acid sequence set forth in SEQ ID NO: 11. In some embodiments, the ANG-2 antigen binding polypeptide or antigen binding fragment comprises a heavy chain variable region comprising an amino acid sequence comprising at least 98% identity to the amino acid sequence set forth in SEQ ID NO: 11. In some embodiments, the ANG-2 antigen binding polypeptide or antigen binding fragment comprises a heavy chain variable region comprising an amino acid sequence comprising at least 99% identity to the amino acid sequence set forth in SEQ ID NO: 11. In some embodiments, the ANG-2 antigen binding

polypeptide or antigen binding fragment comprises a heavy chain variable region comprising an amino acid sequence set forth in SEQ ID NO: 11.

[0225] In some embodiments, the ANG-2 antigen binding polypeptide or antigen binding fragment comprises a heavy chain variable region comprising an amino acid sequence comprising at least 85% identity to the amino acid sequence set forth in SEQ ID NO: 12. In some embodiments, the ANG-2 antigen binding polypeptide or antigen binding fragment comprises a heavy chain variable region comprising an amino acid sequence comprising at least 90% identity to the amino acid sequence set forth in SEQ ID NO: 12. In some embodiments, the ANG-2 antigen binding polypeptide or antigen binding fragment comprises a heavy chain variable region comprising an amino acid sequence comprising at least 95% identity to the amino acid sequence set forth in SEQ ID NO: 12. In some embodiments, the ANG-2 antigen binding polypeptide or antigen binding fragment comprises a heavy chain variable region comprising an amino acid sequence comprising at least 96% identity to the amino acid sequence set forth in SEQ ID NO: 12. In some embodiments, the ANG-2 antigen binding polypeptide or antigen binding fragment comprises a heavy chain variable region comprising an amino acid sequence comprising at least 97% identity to the amino acid sequence set forth in SEQ ID NO: 12. In some embodiments, the ANG-2 antigen binding polypeptide or antigen binding fragment comprises a heavy chain variable region comprising an amino acid sequence comprising at least 98% identity to the amino acid sequence set forth in SEQ ID NO: 12. In some embodiments, the ANG-2 antigen binding polypeptide or antigen binding fragment comprises a heavy chain variable region comprising an amino acid sequence comprising at least 99% identity to the amino acid sequence set forth in SEQ ID NO: 12. In some embodiments, the ANG-2 antigen binding polypeptide or antigen binding fragment comprises a heavy chain variable region comprising an amino acid sequence set forth in SEQ ID NO: 12.

[0226] In some embodiments, the ANG-2 antigen binding polypeptide or antigen binding fragment further comprises a surrogate light chain.

VEGF-C antigen binding polypeptide

[0227] Described herein is a vascular endothelial growth factor C (VEGF-C) antigen binding polypeptide or antigen binding fragment thereof comprising: a heavy chain complementarity determining region 1 (HCDR1) comprising the amino acid sequence set forth in SEQ ID NO: 23; a heavy chain complementarity determining region 2 (HCDR2) comprising the amino acid sequence set forth in SEQ ID NO: 24; and/or a heavy chain complementarity determining region 3 (HCDR3) comprising the amino acid sequence set forth in SEQ ID NO: 25; wherein the antigen binding polypeptide binds to VEGF-C.

[0228] In some embodiments, the VEGF-C antigen binding polypeptide or antigen binding fragment comprises a heavy chain variable region comprising an amino acid sequence comprising at least 85% identity to the amino acid sequence set forth in SEQ ID NO: 21. In some embodiments, the VEGF-C antigen binding polypeptide or antigen binding fragment comprises a heavy chain variable region comprising an amino acid sequence comprising at least 90% identity to the amino acid sequence set forth in SEQ ID NO: 21. In some embodiments, the VEGF-C antigen binding polypeptide or antigen binding fragment comprises a heavy chain variable region comprising an amino acid sequence comprising at least 95% identity to the amino acid sequence set forth in SEQ ID NO: 21. In some embodiments, the VEGF-C antigen binding polypeptide or antigen binding fragment comprises a heavy chain variable region comprising an amino acid sequence comprising at least 96% identity to the amino acid sequence set forth in SEQ ID NO: 21. In some embodiments, the VEGF-C antigen binding polypeptide or antigen binding fragment comprises a heavy chain variable region comprising an amino acid sequence comprising at least 97% identity to the amino acid sequence set forth in SEQ ID NO: 21. In some embodiments, the VEGF-C antigen binding polypeptide or antigen binding fragment comprises a heavy chain variable region comprising an amino acid sequence comprising at least 98% identity to the amino acid sequence set forth in SEQ ID NO: 21. In some embodiments, the VEGF-C antigen binding polypeptide or antigen binding fragment comprises a heavy chain variable region comprising an amino acid sequence comprising at least 99% identity to the amino acid sequence set forth in SEQ ID NO: 21. In some embodiments, the VEGF-C antigen binding polypeptide or antigen binding fragment comprises a heavy chain variable region comprising an amino acid sequence set forth in SEQ ID NO: 21.

[0229] In some embodiments, the VEGF-C antigen binding polypeptide or antigen binding fragment comprises a heavy chain variable region comprising an amino acid sequence comprising at least 85% identity to the amino acid sequence set forth in SEQ ID NO: 22. In some embodiments, the VEGF-C antigen binding polypeptide or antigen binding fragment comprises a heavy chain variable region comprising an amino acid sequence comprising at least 90% identity to the amino acid sequence set forth in SEQ ID NO: 22. In some embodiments, the VEGF-C antigen binding polypeptide or antigen binding fragment comprises a heavy chain variable region comprising an amino acid sequence comprising at least 95% identity to the amino acid sequence set forth in SEQ ID NO: 22. In some embodiments, the VEGF-C antigen binding polypeptide or antigen binding fragment comprises a heavy chain variable region comprising an amino acid sequence comprising at least 96% identity to the amino acid sequence set forth in SEQ ID NO: 22. In some embodiments, the VEGF-C antigen binding polypeptide or antigen binding fragment comprises a heavy chain variable region comprising an amino acid sequence

comprising at least 97% identity to the amino acid sequence set forth in SEQ ID NO: 22. In some embodiments, the VEGF-C antigen binding polypeptide or antigen binding fragment comprises a heavy chain variable region comprising an amino acid sequence comprising at least 98% identity to the amino acid sequence set forth in SEQ ID NO: 22. In some embodiments, the VEGF-C antigen binding polypeptide or antigen binding fragment comprises a heavy chain variable region comprising an amino acid sequence comprising at least 99% identity to the amino acid sequence set forth in SEQ ID NO: 22. In some embodiments, the VEGF-C antigen binding polypeptide or antigen binding fragment comprises a heavy chain variable region comprising an amino acid sequence set forth in SEQ ID NO: 22.

[0230] In some embodiments, the VEGF-C antigen binding polypeptide or antigen binding fragment further comprises a surrogate light chain.

[0231] Described herein the multispecific binding polypeptide may comprise a means for binding any one of ANG-2, VEGF-C, or VEGF-A. Described herein the multispecific binding polypeptide may comprise a means for binding any two of ANG-2, VEGF-C, or VEGF-A. Described herein the multispecific binding polypeptide may comprise a means for binding any three of ANG-2, VEGF-C, or VEGF-A. The binding means of the antibodies described herein comprise the variable regions and/or CDRs described herein. The means may exhibit binding at a K_D to a specified target lower than 1 millimolar as measured by surface plasmon resonance. The means may exhibit binding at a K_D lower than 100 nanomolar as measured by surface plasmon resonance. The means may exhibit binding at a K_D lower than 50 nanomolar as measured by surface plasmon resonance. The means may exhibit binding at a K_D lower than 20 nanomolar as measured by surface plasmon resonance. The means may exhibit binding at a K_D lower than 10 nanomolar as measured by surface plasmon resonance.

Vectors

[0232] Some embodiments disclosed herein relate to nucleic acids encoding the multispecific antigen binding polypeptide as disclosed herein. Some embodiments disclosed herein relate to expression vectors comprising the nucleic acids as disclosed herein. In some instances, the expression vector is a RNA vector. In some instances, the expression vector is plasmid or linearized DNA vector. In some instances, the expression vector is a viral vector.

[0233] The term “viral vector” is widely used to refer either to a nucleic acid molecule that includes virus-derived nucleic acid elements that typically facilitate transfer of the nucleic acid molecule or integration into the genome of a cell, or to a viral particle that mediates nucleic acid transfer. In some embodiments, the viral vector is an adenovirus. In some embodiments, the

viral vector is an adeno-associated virus. In some embodiments, the viral vector is a lentivirus virus.

[0234] The nucleic acids described above can be contained within a vector that is capable of directing their expression in, for example, a cell that has been transduced with the vector. Suitable vectors for use in eukaryotic cells are known in the art and are commercially available or readily prepared by a skilled artisan. Additional vectors can also be found, for example, in Ausubel, F. M., *et al.*, Current Protocols in Molecular Biology, (Current Protocol, 1994) and Sambrook *et al.*, "Molecular Cloning: A Laboratory Manual," 2nd Ed. (1989).

[0235] Accordingly, in some instances, the multispecific antigen binding polypeptides of the present disclosure can be expressed from vectors, generally expression vectors. The vectors are useful for autonomous replication in a host cell or may be integrated into the genome of a host cell upon introduction into the host cell, and thereby are replicated along with the host genome (*e.g.*, non-episomal mammalian vectors). Expression vectors are capable of directing the expression of coding sequences to which they are operably linked. In general, expression vectors of utility in recombinant DNA techniques are often in the form of plasmids (vectors). However, other forms of expression vectors, such as viral vectors (*e.g.*, replication defective retroviruses, adenoviruses, and adeno-associated viruses) are also included.

[0236] DNA vectors can be introduced into eukaryotic cells via conventional transformation or transfection techniques. Suitable methods for transforming or transfecting host cells can be found in Sambrook *et al.*, (1989) Molecular Cloning: A Laboratory Manual (2nd ed., Cold Spring Harbor Laboratory Press, Plainview, N.Y.) and other standard molecular biology laboratory manuals.

[0237] Viral particles typically include viral components, and sometimes also host cell components, in addition to nucleic acid(s). Retroviral vectors used herein contain structural and functional genetic elements, or portions thereof, that are primarily derived from a retrovirus. Retroviral lentivirus vectors contain structural and functional genetic elements, or portions thereof including LTRs, that are primarily derived from a lentivirus (a sub-type of retrovirus).

[0238] In some instances, the nucleic acid molecules are delivered by viral or non-viral delivery vehicles known in the art. For example, the nucleic acid molecule can be stably integrated in the host genome, or can be episomally replicating, or present in the recombinant host cell as a mini-circle expression vector for stable or transient expression. Accordingly, in some instances, the nucleic acid molecule is maintained and replicated in the recombinant host cell as an episomal unit. In some instances, the nucleic acid molecule is stably integrated into the genome of the recombinant cell. Stable integration can also be accomplished using classical random genomic recombination techniques or with more precise genome editing techniques such as using guide

RNA-directed CRISPR/Cas9, DNA-guided endonuclease genome editing NgAgo (Natronobacterium gregoryi Argonaute), or TALENs genome editing (transcription activator-like effector nucleases). In some instances, the nucleic acid molecule is present in the recombinant host cell as a mini circle expression vector for stable or transient expression.

[0239] The nucleic acid molecules can be encapsulated in a viral capsid or a lipid nanoparticle. Alternatively, endonuclease polypeptide(s) can be delivered by viral or non-viral delivery vehicles known in the art, such as electroporation or lipid nanoparticles. For example, introduction of nucleic acids into cells may be achieved using viral transduction methods. In a non-limiting example, adeno-associated virus (AAV) is a non-enveloped virus that can be engineered to deliver nucleic acids to target cells via viral transduction. Several AAV serotypes have been described, and all of the known serotypes can infect cells from multiple diverse tissue types. AAV is capable of transducing a wide range of species and tissues in vivo with no evidence of toxicity, and it generates relatively mild innate and adaptive immune responses.

[0240] Lentiviral systems are also useful for nucleic acid delivery and gene therapy via viral transduction. Lentiviral vectors offer several attractive properties as gene-delivery vehicles, including: (i) sustained gene delivery through stable vector integration into the host cell genome; (ii) the ability to infect both dividing and non-dividing cells; (iii) broad tissue tropisms, including important gene- and cell-therapy -target cell types; (iv) no expression of viral proteins after vector transduction; (v) the ability to deliver complex genetic elements, such as polycistronic or intron-containing sequences; (vi) a potentially safer integration site profile (*e.g.*, by targeting a site for integration that has little or no oncogenic potential); and (vii) a relatively easy system for vector manipulation and production.

Therapeutic methods

[0241] In certain embodiments, the antigen binding polypeptides can be administered to a subject in need thereof by any route suitable for the administration of antigen binding polypeptide-containing pharmaceutical compositions, such as, for example, topically, subcutaneously, intravenously, or intravitreally. In certain embodiments, the antigen binding polypeptide or pharmaceutical composition comprising the antigen binding polypeptide is administered intravenously. In certain embodiments, the antigen binding polypeptide or pharmaceutical composition comprising the antigen binding polypeptide is administered intravitreally. In certain embodiments, the antigen binding polypeptide or pharmaceutical composition comprising the antigen binding polypeptide is administered topically. In certain embodiments, the antigen binding polypeptide or pharmaceutical composition comprising the antigen binding polypeptide is administered subcutaneously.

[0242] In certain embodiments, the antigen binding polypeptides are administered on a suitable dosage schedule, for example, weekly, twice weekly, monthly, twice monthly, once every two weeks, once every three weeks, or once a month, once every two months, once every three months, once every four months, once every five months, or once every six months, etc. The antigen binding polypeptides can be administered in any therapeutically effective amount. In certain embodiments, the therapeutically acceptable amount is between about 0.1 mg/kg and about 50 mg/kg. In certain embodiments, the therapeutically acceptable amount is between about 1 mg/kg and about 40 mg/kg. In certain embodiments, the therapeutically acceptable amount is between about 1 mg/kg and about 20 mg/kg. In certain embodiments, the therapeutically acceptable amount is between about 1 mg/kg and about 10 mg/kg. In certain embodiments, the therapeutically acceptable amount is between about 5 mg/kg and about 30 mg/kg. In certain embodiments, the therapeutically acceptable amount is between about 5 mg/kg and about 20 mg/kg. Intravitreal dosage concentrations can range from 50 mg/ml to 150 mg/ml for intravitreal use. Therapeutically effective amounts include amounts sufficient to ameliorate one or more symptoms associated with the disease or affliction to be treated.

[0243] In certain embodiments, disclosed herein, are antigen binding polypeptides useful for the treatment of a disease of the eye. In certain embodiments, the disease of the eye is associated with age or another comorbidity such as diabetes mellitus. In certain embodiments, the disease of the eye is macular degeneration. In certain embodiments, the macular degeneration is age related. In certain embodiments, the macular degeneration is diabetes related. In certain embodiments, the macular degeneration is wet macular degeneration. In certain embodiments, the disease of the eye is branch retinal vein occlusion. In certain embodiments, the disease of the eye is central retinal vein occlusion.

[0244] In certain embodiments, disclosed herein, are multispecific antigen binding polypeptides useful for the treatment of a cancer.

[0245] Also described herein is the multispecific antigen binding polypeptide, the nucleic acid or plurality of nucleic acids encoding the multispecific antigen binding polypeptide, or pharmaceutical composition of any one of this disclosure, for use in the manufacture of a medicament for treating a disease in an individual. In certain embodiments, the disease is an ocular disease. In certain embodiments, the ocular disease comprises macular degeneration. In certain embodiments, the macular degeneration is neovascular age-related macular degeneration. In certain embodiments, the ocular disease comprises diabetic macular edema. In certain embodiments, the ocular disease comprises retinal vein occlusion. In certain embodiments, the disease is a cancer.

[0246] Also described herein is the multispecific antigen binding polypeptide, the nucleic acid or plurality of nucleic acids encoding the multispecific antigen binding polypeptide, or pharmaceutical composition of this disclosure, for use in a method of treating a disease in an individual. In certain embodiments, the disease is an ocular disease. In certain embodiments, the ocular disease comprises macular degeneration. In certain embodiments, the macular degeneration is neovascular age-related macular degeneration. In certain embodiments, the ocular disease comprises diabetic macular edema. In certain embodiments, the ocular disease comprises retinal vein occlusion. In certain embodiments, the disease is a cancer.

Pharmaceutically acceptable excipients, carriers, and diluents

[0247] In certain embodiments, the multispecific antigen binding polypeptides of the current disclosure are included in a pharmaceutical composition comprising one or more pharmaceutically acceptable excipients, carriers, and diluents. Pharmaceutically acceptable excipients, carriers and diluents can be included to increase shelf-life, stability, or the administrability of the antigen binding polypeptide. Such compounds include salts, pH buffers, detergents, anti-coagulants, and preservatives. In certain embodiments, the antigen binding polypeptides of the current disclosure are administered suspended in a sterile solution. In certain embodiments, the solution comprises about 0.9% NaCl. In certain embodiments, the solution comprises about 5.0% dextrose. In certain embodiments, the solution further comprises one or more of: buffers, for example, acetate, citrate, histidine, succinate, phosphate, bicarbonate and hydroxymethylaminomethane (Tris); surfactants, for example, polysorbate 80 (Tween 80), polysorbate 20 (Tween 20), and poloxamer 188; polyol/disaccharide/polysaccharides, for example, glucose, dextrose, mannose, mannitol, sorbitol, sucrose, trehalose, and dextran 40; amino acids, for example, glycine or arginine; antioxidants, for example, ascorbic acid, methionine; or chelating agents, for example, EDTA or EGTA.

[0248] In certain embodiments, the antigen binding polypeptides of the current disclosure can be shipped/stored lyophilized and reconstituted before administration. In certain embodiments, lyophilized antigen binding polypeptide formulations comprise a bulking agent such as, mannitol, sorbitol, sucrose, trehalose, dextran 40, or combinations thereof. The lyophilized formulation can be contained in a vial comprised of glass or other suitable non-reactive material. The antigen binding polypeptides when formulated, whether reconstituted or not, can be buffered at a certain pH, generally less than 7.0. In certain embodiments, the pH can be between 4.5 and 7.0, 4.5 and 6.5, 4.5 and 6.0, 4.5 and 5.5, 4.5 and 5.0, or 5.0 and 6.0.

[0249] Also described herein are kits comprising one or more of the antigen binding polypeptides described herein in a suitable container and one or more additional components

selected from: instructions for use; a diluent, an excipient, a carrier, and a device for administration.

[0250] In certain embodiments, described herein is a method of preparing a treatment for a disease of the eye comprising admixing one or more pharmaceutically acceptable excipients, carriers, or diluents and an antigen binding polypeptide of the current disclosure. In certain embodiments, described herein is a method of preparing a cancer treatment for storage or shipping comprising lyophilizing one or more antigen binding polypeptides of the current disclosure.

List of numbered embodiments

[0251] Embodiment 1. A multispecific antigen binding polypeptide comprising:

- a. a first antigen binding moiety, comprising a first heavy chain variable region;
- b. a second antigen binding moiety, comprising a second heavy chain variable region; and
- c. a third antigen binding moiety, comprising a third heavy chain variable region;

wherein the first antigen binding moiety binds to a first target, the second antigen binding moiety binds to a second target, and the third antigen binding moiety binds to a third target, wherein the first antigen binding moiety, the second antigen binding moiety, and the third antigen binding moiety are paired to a light chain polypeptide.

[0252] Embodiment 2. The multispecific antigen binding polypeptide of embodiment 1, wherein the first antigen binding moiety, the second antigen binding moiety, and the third antigen binding moiety are directly connected without a linker.

[0253] Embodiment 3. The multispecific antigen binding polypeptide of embodiment 2, wherein a C-terminus of the first heavy chain variable region is directly connected to an N-terminus of the second heavy chain variable region.

[0254] Embodiment 4. The multispecific antigen binding polypeptide of embodiment 2, wherein a C-terminus of the second heavy chain variable region is directly connected to an N-terminus of the third heavy chain variable region.

[0255] Embodiment 5. The multispecific antigen binding polypeptide of any one of embodiments 2 to 4, wherein a C-terminus of the first heavy chain variable region is directly connected to an N-terminus of the second heavy chain variable region, and wherein a C-terminus of the second heavy chain variable region is directly connected to an N-terminus of the third heavy chain variable region.

[0256] Embodiment 6. The multispecific antigen binding polypeptide of embodiment 1, wherein the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety are linked via a linker.

[0257] Embodiment 7. The multispecific antigen binding polypeptide of embodiment 6, wherein the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety are covalently linked via the linker.

[0258] Embodiment 8. The multispecific antigen binding polypeptide of embodiment 6, wherein the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety are non-covalently linked via the linker.

[0259] Embodiment 9. The multispecific antigen binding polypeptide of any one of embodiments 2 to 8, wherein the linker couples the C-terminus of the first antigen binding moiety to the N-terminus of the second antigen binding moiety.

[0260] Embodiment 10. The multispecific antigen binding polypeptide of any one of embodiments 2 to 8, wherein the linker couples the C-terminus of the second antigen binding moiety to the N-terminus of the third antigen binding moiety.

[0261] Embodiment 11. The multispecific antigen binding polypeptide of any one of embodiments 1 to 10, further comprising a fourth antigen binding moiety, wherein the fourth antigen binding moiety comprises a fourth heavy chain variable region, wherein the fourth antigen binding moiety binds to a fourth target, wherein the fourth antigen binding moiety is paired to a light chain polypeptide.

[0262] Embodiment 12. The multispecific antigen binding polypeptide of embodiment 11, wherein the first antigen binding moiety, the second antigen binding moiety, the third antigen binding moiety, and the fourth antigen binding moiety are directly connected without a linker.

[0263] Embodiment 13. The multispecific antigen binding polypeptide of embodiment 12, wherein a C-terminus of the third heavy chain variable region is directly connected to an N-terminus of the fourth heavy chain variable region.

[0264] Embodiment 14. The multispecific antigen binding polypeptide of embodiment 11, wherein the first antigen binding moiety, the second antigen binding moiety, the third antigen binding moiety, and/or the fourth antigen binding moiety are linked via a linker.

[0265] Embodiment 15. The multispecific antigen binding polypeptide of embodiment 14, wherein the linker couples the C-terminus of the third antigen binding moiety to the N-terminus of the fourth antigen binding moiety.

[0266] Embodiment 16. The multispecific antigen binding polypeptide of any one of embodiments 6 to 15, wherein the linker comprises the amino acid sequence of SEQ ID NO: 151.

[0267] Embodiment 17. The multispecific antigen binding polypeptide of any one of embodiments 1-16, wherein the first antigen binding moiety, the second antigen binding moiety, the third antigen binding moiety, and/or the fourth antigen binding moiety comprises a crossed domain.

[0268] Embodiment 18. The multispecific antigen binding polypeptide of any one of embodiments 1-16, wherein the first antigen binding moiety, the second antigen binding moiety, the third antigen binding moiety, and/or the fourth antigen binding moiety comprises at least two crossed domains, wherein the at least two crossed domains are comprised in at least two different antigen binding moieties.

[0269] Embodiment 19. The multispecific antigen binding polypeptide of any one of embodiments 1-16, wherein the first antigen binding moiety, the second antigen binding moiety, the third antigen binding moiety, and/or the fourth antigen binding moiety comprises at least three crossed domains wherein the at least three crossed domains are comprised in at least three different antigen binding moieties.

[0270] Embodiment 20. The multispecific antigen binding polypeptide of any one of embodiments 1 to 19, wherein the light chain polypeptide paired to the first antigen binding moiety, the second antigen binding moiety, and the third antigen binding moiety comprise the same amino acid sequence.

[0271] Embodiment 21. The multispecific antigen binding polypeptide of any one of embodiments 1 to 19, wherein the light chain polypeptide paired to the first antigen binding moiety, the second antigen binding moiety, and the third antigen binding moiety comprise different amino acid sequences.

[0272] Embodiment 22. The multispecific antigen binding polypeptide of any one of embodiments 1 to 19, wherein the light chain polypeptide paired to the first antigen binding moiety, the second antigen binding moiety, the third antigen binding moiety, and the fourth antigen binding moiety comprise the same amino acid sequence.

[0273] Embodiment 23. The multispecific antigen binding polypeptide of any one of embodiments 1 to 19, wherein the light chain polypeptide paired to the first antigen binding moiety, the second antigen binding moiety, the third antigen binding moiety, and the fourth antigen binding moiety comprise different amino acid sequences.

[0274] Embodiment 24. The multispecific antigen binding polypeptide of any one of embodiments 1 to 23, wherein the light chain polypeptide comprises a light chain constant region comprising one or more amino acid substitutions from a heavy chain first constant region (CH1).

[0275] Embodiment 25. The multispecific antigen binding polypeptide of embodiment 24, wherein the light chain polypeptide comprises a light chain constant region comprises one or

more amino acid substitutions from a heavy chain first constant region (CH1) and the light chain comprises an amino acid sequence comprising at least 90%, at least 95%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to the amino acid sequence set forth in SEQ ID NO: 111 or 112.

[0276] Embodiment 26. The multispecific antigen binding polypeptide of embodiment 24, wherein the light chain polypeptide comprises a light chain constant region comprises one or more amino acid substitutions from a heavy chain first constant region (CH1) and the light chain comprises an amino acid sequence comprising at least 90%, at least 95%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to the amino acid sequence set forth in SEQ ID NO: 121 or 122.

[0277] Embodiment 27. The multispecific antigen binding polypeptide of embodiment 24, wherein the light chain polypeptide comprises a light chain constant region comprises one or more amino acid substitutions from a heavy chain first constant region (CH1) and the light chain comprises an amino acid sequence comprising at least 90%, at least 95%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to the amino acid sequence set forth in SEQ ID NO: 131 or 132.

[0278] Embodiment 28. The multispecific antigen binding polypeptide of any one of embodiments 1 to 23, wherein the light chain polypeptide is a universal light chain polypeptide.

[0279] Embodiment 29. The multispecific antigen binding polypeptide of embodiment 28, wherein the universal light chain polypeptide is a common light chain polypeptide.

[0280] Embodiment 30. The multispecific antigen binding polypeptide of embodiment 28, wherein the universal light chain polypeptide is a surrogate light chain polypeptide.

[0281] Embodiment 31. The multispecific antigen binding polypeptide of embodiment 30, wherein the surrogate light chain polypeptide comprises a VpreB sequence fused to a $\lambda 5$ sequence.

[0282] Embodiment 32. The multispecific antigen binding polypeptide of embodiment 31, wherein the VpreB sequence comprises an amino acid sequence comprising at least 90%, at least 95%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to the amino acid sequence set forth in SEQ ID NO: 101.

[0283] Embodiment 33. The multispecific antigen binding polypeptide of embodiment 31, wherein the $\lambda 5$ sequence comprises an amino acid sequence comprising at least 90%, at least 95%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to the amino acid sequence set forth in SEQ ID NO: 106.

[0284] Embodiment 34. The multispecific antigen binding polypeptide of any one of embodiments 30 to 33, wherein the surrogate light chain polypeptide comprises:

- a. a light chain complementarity determining region 1 (LCDR1) comprising the amino acid sequence set forth in SEQ ID NO: 103;
- b. a light chain complementarity determining region 2 (LCDR2) comprising the amino acid sequence set forth in SEQ ID NO: 104; and/or
- c. a light chain complementarity determining region 3 (LCDR3) comprising the amino acid sequence set forth in SEQ ID NO: 105.

[0285] Embodiment 35. The multispecific antigen binding polypeptide of any one of embodiments 30 to 34, wherein the surrogate light chain polypeptide comprises an amino acid sequence comprising at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 102.

[0286] Embodiment 36. The multispecific antigen binding polypeptide of embodiment 29, wherein the common light chain polypeptide comprises an amino acid sequence comprising at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 303.

[0287] Embodiment 37. The multispecific antigen binding polypeptide of any one of embodiments 1 to 36, wherein the first target, the second target and/or the third target is VEGF-A or a fragment thereof.

[0288] Embodiment 38. The multispecific antigen binding polypeptide of embodiment 37, wherein the multispecific antigen binding polypeptide binds to VEGF-A or a fragment thereof with an EC₅₀ of about 5 picomolar or less.

[0289] Embodiment 39. The multispecific antigen binding polypeptide of embodiment 37 or 38, wherein the multispecific antigen binding polypeptide binds with an affinity to VEGF-A or a fragment thereof at least 8-fold stronger than faricimab.

[0290] Embodiment 40. The multispecific antigen binding polypeptide of any one of embodiments 37-39, wherein the multispecific antigen binding polypeptide inhibits the interaction of VEGF-A and the VEGF-A receptor.

[0291] Embodiment 41. The multispecific antigen binding polypeptide of embodiment 40, wherein the multispecific antigen binding polypeptide inhibits the interaction of VEGF-A and the VEGF-A receptor with an IC₅₀ of about 18 nanomolar or less.

[0292] Embodiment 42. The multispecific antigen binding polypeptide of embodiment 40, wherein the multispecific antigen binding polypeptide inhibits the interaction of VEGF-A and the VEGF-A receptor at least 1.3-fold stronger than faricimab.

[0293] Embodiment 43. The multispecific antigen binding polypeptide of any one of embodiments 1 to 42, wherein the first target, the second target, and/or the third target is ANG-2 or a fragment thereof.

[0294] Embodiment 44. The multispecific antigen binding polypeptide of embodiment 43, wherein the multispecific antigen binding polypeptide binds to ANG-2 or a fragment thereof with an EC₅₀ of about 11 picomolar or less.

[0295] Embodiment 45. The multispecific antigen binding polypeptide of embodiment 43 or 44, wherein the multispecific antigen binding polypeptide binds with an affinity to ANG-2 or a fragment thereof at least 300-fold stronger than faricimab.

[0296] Embodiment 46. The multispecific antigen binding polypeptide of any one of embodiments 43-45, wherein the multispecific antigen binding polypeptide inhibits the interaction of ANG-2 and the ANG-2 receptor.

[0297] Embodiment 47. The multispecific antigen binding polypeptide of embodiment 46, wherein the multispecific antigen binding polypeptide inhibits the interaction of ANG-2 and the ANG-2 receptor with an IC₅₀ of about 3.1 nanomolar or less.

[0298] Embodiment 48. The multispecific antigen binding polypeptide of embodiment 46, wherein the multispecific antigen binding polypeptide inhibits the interaction of ANG-2 and the ANG-2 receptor at least 12-fold stronger than faricimab.

[0299] Embodiment 49. The multispecific antigen binding polypeptide of any one of embodiments 1 to 48, wherein the first target, the second target and/or the third target is VEGF-C or a fragment thereof.

[0300] Embodiment 50. The multispecific antigen binding polypeptide of embodiment 49, wherein the multispecific antigen binding polypeptide binds to VEGF-C or a fragment thereof with an EC₅₀ of about 19 picomolar or less.

[0301] Embodiment 51. The multispecific antigen binding polypeptide of any one of embodiments 49-50, wherein the multispecific antigen binding polypeptide inhibits the interaction of VEGF-C and the VEGF-C receptor.

[0302] Embodiment 52. The multispecific antigen binding polypeptide of embodiment 40, wherein the multispecific antigen binding polypeptide inhibits the interaction of VEGF-C and the VEGF-C receptor with an IC₅₀ of about 3.8 nanomolar or less.

[0303] Embodiment 53. The multispecific antigen binding polypeptide of any one of embodiments 1 to 52, wherein the first target is VEGF-A or fragment thereof, the second target is ANG-2 or a fragment thereof, and the third target is VEGF-C or a fragment thereof.

[0304] Embodiment 54. The multispecific antigen binding polypeptide of any one of embodiments 1 to 53, wherein the first, second, and third antigen binding moiety bind different polypeptide antigens.

[0305] Embodiment 55. The multispecific antigen binding polypeptide of any one of embodiments 1 to 53, wherein the first, second, and third antigen binding moiety bind the same polypeptide antigens.

[0306] Embodiment 56. The multispecific antigen binding polypeptide of any one of embodiments 1 to 55, wherein the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety binds to VEGF-A.

[0307] Embodiment 57. The multispecific antigen binding polypeptide of embodiment 56, wherein the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety binds to VEGF-A and comprises an immunoglobulin heavy chain variable region comprising:

- a. a heavy chain complementarity determining region 1 (HCDR1) comprising the amino acid sequence set forth in SEQ ID NO: 3;
- b. a heavy chain complementarity determining region 2 (HCDR2) comprising the amino acid sequence set forth in SEQ ID NO: 4; and/or
- c. a heavy chain complementarity determining region 3 (HCDR3) comprising the amino acid sequence set forth in SEQ ID NO: 5;

wherein the heavy chain variable region binds to VEGF-A upon pairing with the light chain polypeptide.

[0308] Embodiment 58. The multispecific antigen binding polypeptide of embodiment 56, wherein the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety comprises an immunoglobulin heavy chain variable region comprising an amino acid sequence comprising at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 1.

[0309] Embodiment 59. The multispecific antigen binding polypeptide of embodiment 56, wherein the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety comprises an amino acid sequence comprising at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 2.

[0310] Embodiment 60. The multispecific antigen binding polypeptide of any one of embodiments 1 to 55, wherein the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety binds to ANG-2.

[0311] Embodiment 61. The multispecific antigen binding polypeptide of embodiment 60, wherein the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety binds to ANG-2 and comprises an immunoglobulin heavy chain variable region comprising:

- a. a heavy chain complementarity determining region 1 (HCDR1) comprising the amino acid sequence set forth in SEQ ID NO: 13;
- b. a heavy chain complementarity determining region 2 (HCDR2) comprising the amino acid sequence set forth in SEQ ID NO: 14; and/or
- c. a heavy chain complementarity determining region 3 (HCDR3) comprising the amino acid sequence set forth in SEQ ID NO: 15;

wherein the heavy chain variable region binds to ANG-2 upon pairing with the light chain polypeptide.

[0312] Embodiment 62. The multispecific antigen binding polypeptide of embodiment 60, wherein the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety comprises an immunoglobulin heavy chain variable region comprising an amino acid sequence comprising at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 11.

[0313] Embodiment 63. The multispecific antigen binding polypeptide of embodiment 60, wherein the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety comprises an amino acid sequence comprising at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 12.

[0314] Embodiment 64. The multispecific antigen binding polypeptide of any one of embodiments 1 to 55, wherein the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety binds to VEGF-C.

[0315] Embodiment 65. The multispecific antigen binding polypeptide of embodiment 64, wherein the first antigen binding moiety, the second antigen binding moiety, or the third antigen binding moiety binds to VEGF-C and comprises an immunoglobulin heavy chain variable region comprising:

- a. a heavy chain complementarity determining region 1 (HCDR1) comprising the amino acid sequence set forth in SEQ ID NO: 23;
- b. a heavy chain complementarity determining region 2 (HCDR2) comprising the amino acid sequence set forth in SEQ ID NO: 24; and/or
- c. a heavy chain complementarity determining region 3 (HCDR3) comprising the amino acid sequence set forth in SEQ ID NO: 25;

wherein the heavy chain variable region binds to VEGF-C upon pairing with the light chain polypeptide.

[0316] Embodiment 66. The multispecific antigen binding polypeptide of embodiment 64, wherein the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety comprises an immunoglobulin heavy chain variable region comprises an

amino acid sequence comprising at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 21.

[0317] Embodiment 67. The multispecific antigen binding polypeptide of embodiment 60, wherein the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety comprises an amino acid sequence comprising at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 22.

[0318] Embodiment 68. The multispecific antigen binding polypeptide of any one of embodiments 1 to 67, wherein each of the first antigen binding moiety, the second antigen binding moiety and the third antigen binding moiety is non-covalently paired to the surrogate light chain polypeptide.

[0319] Embodiment 69. The multispecific antigen binding polypeptide of any one of embodiments 1 to 67, wherein each of the first antigen binding moiety, the second antigen binding moiety and the third antigen binding moiety is covalently paired to the surrogate light chain polypeptide.

[0320] Embodiment 70. The multispecific antigen binding polypeptide of any one of embodiments 1 to 69, wherein the first, second, or third antigen binding moiety comprise a heavy chain first constant region (CH1) comprising one or more amino acid substitutions from a light chain constant region.

[0321] Embodiment 71. The multispecific antigen binding polypeptide of any one of embodiments 1 to 70, wherein the first antigen binding moiety comprises a first heavy chain variable region (VH) and a heavy chain first constant region (CH1).

[0322] Embodiment 72. The multispecific antigen binding polypeptide of any one of embodiments 1 to 70, wherein the second antigen binding moiety comprises a second heavy chain variable region (VH) and a heavy chain first constant region (CH1).

[0323] Embodiment 73. The multispecific antigen binding polypeptide of any one of embodiments 1 to 70, wherein the third antigen binding moiety comprises a third heavy chain variable region (VH) and a heavy chain first constant region (CH1).

[0324] Embodiment 74. The multispecific antigen binding polypeptide of any one of embodiments 71 to 73, wherein the heavy chain first constant region comprises an amino acid sequence with at least 80%, at least 90%, at least 95%, at least 97%, at least 98%, at least 99%, or at least 100% identity to the amino acid sequence set forth in SEQ ID NO: 141.

[0325] Embodiment 75. The multispecific antigen binding polypeptide of any one of embodiments 1 to 74, wherein the multispecific antigen binding polypeptide comprises an amino acid sequence comprising at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in any one of SEQ ID NOs: 201 to 205.

[0326] Embodiment 76. The multispecific antigen binding polypeptide of any one of embodiments 1 to 74, wherein the multispecific antigen binding polypeptide comprises an amino acid sequence comprising at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 201.

[0327] Embodiment 77. The multispecific antigen binding polypeptide of any one of embodiments 1 to 74, wherein the multispecific antigen binding polypeptide comprises an amino acid sequence comprising at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 202.

[0328] Embodiment 78. The multispecific antigen binding polypeptide of any one of embodiments 1 to 74, wherein the multispecific antigen binding polypeptide comprises at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 203.

[0329] Embodiment 79. The multispecific antigen binding polypeptide of any one of embodiments 76 to 78, wherein the first, second, and third antigen binding moiety comprise or consist of the amino acid sequence set forth in any one of SEQ ID NOs: 201 to 203.

[0330] Embodiment 80. The multispecific antigen binding polypeptide of any one of embodiments 76 to 78, wherein the first, second, and third antigen binding moiety comprise or consist of the amino acid sequence set forth in SEQ ID NO: 201.

[0331] Embodiment 81. The multispecific antigen binding polypeptide of any one of embodiments 76 to 78, wherein the first, second, and third antigen binding moiety comprise or consist of the amino acid sequence set forth in SEQ ID NO: 202.

[0332] Embodiment 82. The multispecific antigen binding polypeptide of any one of embodiments 76 to 78, wherein the first, second, and third antigen binding moiety comprise or consist of the amino acid sequence set forth in SEQ ID NO: 203.

[0333] Embodiment 83. The multispecific antigen binding polypeptide of any one of embodiments 1 to 82, wherein the first antigen binding moiety comprises a first heavy chain variable region (VH), a heavy chain first constant region (CH1), a heavy chain second constant region (CH2), and/or a heavy chain third constant region (CH3).

[0334] Embodiment 84. The multispecific antigen binding polypeptide of any one of embodiments 1 to 82, wherein the second antigen binding moiety comprises a second heavy chain variable region (VH), a heavy chain first constant region (CH1), a heavy chain second constant region (CH2), and/or a heavy chain third constant region (CH3).

[0335] Embodiment 85. The multispecific antigen binding polypeptide of any one of embodiments 1 to 82, wherein the third antigen binding moiety comprises a third heavy chain

variable region (VH), a heavy chain first constant region (CH1), a heavy chain second constant region (CH2), and/or a heavy chain third constant region (CH3).

[0336] Embodiment 86. The multispecific antigen binding polypeptide of any one of embodiments 11 to 82, wherein the fourth antigen binding moiety comprises a fourth heavy chain variable region (VH), a heavy chain first constant region (CH1), a heavy chain second constant region (CH2), and/or a heavy chain third constant region (CH3).

[0337] Embodiment 87. The multispecific antigen binding polypeptide of any one of embodiments 11 to 86, wherein the first target, the second target, the third target, and/or the fourth target is ErbB3 or a fragment thereof.

[0338] Embodiment 88. The multispecific antigen binding polypeptide of embodiment 87, wherein the multispecific antigen binding polypeptide binds to ErbB3 or a fragment thereof with an EC50 of about 0.57 nanomolar or less.

[0339] Embodiment 89. The multispecific antigen binding polypeptide of any one of embodiments 11 to 86, wherein the first target, the second target, the third target, and/or the fourth target is VEGF-A or a fragment thereof.

[0340] Embodiment 90. The multispecific antigen binding polypeptide of embodiment 89, wherein the multispecific antigen binding polypeptide binds to VEGF-A or a fragment thereof with an EC50 of about 24 picomolar or less.

[0341] Embodiment 91. The multispecific antigen binding polypeptide of any one of embodiments 11 to 86, wherein the first target, the second target, the third target, and/or the fourth target is ANG-2 or a fragment thereof.

[0342] Embodiment 92. The multispecific antigen binding polypeptide of embodiment 91, wherein the multispecific antigen binding polypeptide binds to ANG-2 or a fragment thereof with an EC50 of about 32 picomolar or less.

[0343] Embodiment 93. The multispecific antigen binding polypeptide of any one of embodiments 11 to 86, wherein the first target, the second target, the third target, and/or the fourth target is VEGF-C or a fragment thereof.

[0344] Embodiment 94. The multispecific antigen binding polypeptide of embodiment 93, wherein the multispecific antigen binding polypeptide binds to VEGF-C or a fragment thereof with an EC50 of about 4.3 nanomolar or less.

[0345] Embodiment 95. The multispecific antigen binding polypeptide of any one of embodiments 11 to 86 and 87 to 94, wherein the first target is ErbB3 or fragment thereof, the second target is VEGF-A or a fragment thereof, the third target is ANG-2 or a fragment thereof, and the fourth target is VEGF-C or a fragment thereof.

[0346] Embodiment 96. The multispecific antigen binding polypeptide of any one of embodiments 11 to 86 and 87 to 95, wherein the multispecific antigen binding polypeptide comprises an amino acid sequence comprising at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 301.

[0347] Embodiment 97. The multispecific antigen binding polypeptide of any one of embodiments 11 to 86 and 87-96, wherein each of the first antigen binding moiety, the second antigen binding moiety, the third antigen binding moiety, and/or the fourth antigen binding moiety is paired to the surrogate light chain polypeptide.

[0348] Embodiment 98. The multispecific antigen binding polypeptide of any one of embodiments 11 to 86 and 87-97, wherein the surrogate light chain polypeptide comprises an amino acid sequence at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 102.

[0349] Embodiment 99. The multispecific antigen binding polypeptide of any one of embodiments 1 to 86, wherein the first target, the second target, and/or the third target, is EGFR or a fragment thereof.

[0350] Embodiment 100. The multispecific antigen binding polypeptide of embodiment 99, wherein the multispecific antigen binding polypeptide binds to EGFR or a fragment thereof with an EC₅₀ of about 0.36 nanomolar or less.

[0351] Embodiment 101. The multispecific antigen binding polypeptide of any one of embodiments 1 to 86, wherein the first target, the second target, and/or the third target is ErbB2 or a fragment thereof.

[0352] Embodiment 102. The multispecific antigen binding polypeptide of embodiment 101, wherein the multispecific antigen binding polypeptide binds to ErbB2 or a fragment thereof with an EC₅₀ of about 52 picomolar or less.

[0353] Embodiment 103. The multispecific antigen binding polypeptide of any one of embodiments 1 to 86, wherein the first target, the second target, and/or the third target is ErbB3 or a fragment thereof.

[0354] Embodiment 104. The multispecific antigen binding polypeptide of embodiment 103, wherein the multispecific antigen binding polypeptide binds to ErbB3 or a fragment thereof with an EC₅₀ of about 3 nanomolar or less.

[0355] Embodiment 105. The multispecific antigen binding polypeptide of any one of embodiments 1 to 86 and 99-104, wherein the first target is EGFR or fragment thereof, the second target is ErbB2 or a fragment thereof, and the third target is ErbB3 or a fragment thereof.

[0356] Embodiment 106. The multispecific antigen binding polypeptide of any one of embodiments 1 to 86 and 99-105, wherein the multispecific antigen binding polypeptide

comprises an amino acid sequence comprising at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 302.

[0357] Embodiment 107. The multispecific antigen binding polypeptide of any one of embodiments 1 to 86 and 99-106, wherein each of the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety is paired to the common light chain polypeptide.

[0358] Embodiment 108. The multispecific antigen binding polypeptide of any one of embodiments 1 to 86 and 99-107, wherein the common light chain polypeptide comprises an amino acid sequence at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 303.

[0359] Embodiment 109. The multispecific antigen binding polypeptide of any one of embodiments 1 to 86, wherein the first target, the second target, the third target, and/or the fourth target is c-Met or a fragment thereof.

[0360] Embodiment 110. The multispecific antigen binding polypeptide of embodiment 109, wherein the multispecific antigen binding polypeptide binds to c-Met or a fragment thereof with an EC₅₀ of about 0.21 nanomolar or less.

[0361] Embodiment 111. The multispecific antigen binding polypeptide of any one of embodiments 1 to 86, wherein the first target, the second target, the third target, and/or the fourth target is EGFR or a fragment thereof.

[0362] Embodiment 112. The multispecific antigen binding polypeptide of embodiment 111, wherein the multispecific antigen binding polypeptide binds to EGFR or a fragment thereof with an EC₅₀ of about 0.33 nanomolar or less.

[0363] Embodiment 113. The multispecific antigen binding polypeptide of any one of embodiments 1 to 86, wherein the first target, the second target, the third target, and/or the fourth target is ErbB2 or a fragment thereof.

[0364] Embodiment 114. The multispecific antigen binding polypeptide of embodiment 113, wherein the multispecific antigen binding polypeptide binds to ErbB2 or a fragment thereof with an EC₅₀ of about 51 picomolar or less.

[0365] Embodiment 115. The multispecific antigen binding polypeptide of any one of embodiments 1 to 86, wherein the first target, the second target, the third target, and/or the fourth target is ErbB3 or a fragment thereof.

[0366] Embodiment 116. The multispecific antigen binding polypeptide of embodiment 115, wherein the multispecific antigen binding polypeptide binds to ErbB3 or a fragment thereof with an EC₅₀ of about 2.8 nanomolar or less.

[0367] Embodiment 117. The multispecific antigen binding polypeptide of any one of embodiments 11 to 86 and 109-116, wherein the first target is cMet or fragment thereof, the second target is EGFR or a fragment thereof, the third target is ErbB2 or a fragment thereof, and the fourth target is ErbB3 or a fragment thereof.

[0368] Embodiment 118. The multispecific antigen binding polypeptide of any one of embodiments 11 to 86 and 109 to 117, wherein the multispecific antigen binding polypeptide comprises an amino acid sequence comprising at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 304.

[0369] Embodiment 119. The multispecific antigen binding polypeptide of any one of embodiments 11 to 86 and 109 to 118, wherein each of the first antigen binding moiety, the second antigen binding moiety, the third antigen binding moiety, and/or the fourth antigen binding moiety is paired to the common light chain polypeptide.

[0370] Embodiment 120. The multispecific antigen binding polypeptide of embodiment 119, wherein the common light chain polypeptide comprises an amino acid sequence at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 303.

[0371] Embodiment 121. The multispecific antigen binding polypeptide of any one of embodiments 11 to 86 and 109 to 117, wherein the first antigen binding moiety, the second antigen binding moiety, the third antigen binding moiety, and/or the fourth antigen binding moiety comprises a crossed domain.

[0372] Embodiment 122. The multispecific antigen binding polypeptide of any one of embodiments 11 to 86 and 109 to 117, wherein the second antigen binding moiety comprises a crossed domain.

[0373] Embodiment 123. The multispecific antigen binding polypeptide of any one of embodiments 120 to 121, wherein the multispecific antigen binding polypeptide comprises an amino acid sequence comprising at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 308.

[0374] Embodiment 124. The multispecific antigen binding polypeptide of any one of embodiments 1 to 36 and 109 to 123, wherein each of the first antigen binding moiety, the second antigen binding moiety, the third antigen binding moiety, and/or the fourth antigen binding moiety is paired to the common light chain polypeptide.

[0375] Embodiment 125. The multispecific antigen binding polypeptide of embodiment 124, wherein the common light chain polypeptide comprises an amino acid sequence at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 309.

[0376] Embodiment 126. The multispecific antigen binding polypeptide of any one of embodiments 1 to 86 and 109 to 123, wherein the first antigen binding moiety, the second antigen binding moiety, the third antigen binding moiety, and/or the fourth antigen binding moiety is paired to a domain swapped surrogate light chain polypeptide, wherein the domain swapped surrogate light chain comprises a VpreB sequence fused to a heavy chain first constant region (CH1).

[0377] Embodiment 127. The multispecific antigen binding polypeptide of embodiment 126, wherein the domain swapped surrogate light chain polypeptide comprises an amino acid sequence at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 132.

[0378] Embodiment 128. The multispecific antigen binding polypeptide of any one of embodiments 1 to 86 and 109 to 117, wherein the first antigen binding moiety, the second antigen binding moiety, the third antigen binding moiety, and/or the fourth antigen binding moiety comprises at least two crossed domains.

[0379] Embodiment 129. The multispecific antigen binding polypeptide of any one of embodiments 1 to 86 and 109 to 117, wherein the first antigen binding moiety, the second antigen binding moiety, the third antigen binding moiety, and/or the fourth antigen binding moiety comprises at least three crossed domains.

[0380] Embodiment 130. The multispecific antigen binding polypeptide of any one of embodiments 1 to 86 and 109 to 117, wherein the first antigen binding moiety, the second antigen binding moiety, the third antigen binding moiety, and/or the fourth antigen binding moiety comprises at least four crossed domains.

[0381] Embodiment 131. The multispecific antigen binding polypeptide of embodiment 130, wherein each of the first antigen binding moiety, the third antigen binding moiety, and the fourth antigen binding moiety comprises a crossed domain.

[0382] Embodiment 132. The multispecific antigen binding polypeptide of any one of embodiments 1 to 86, 109 and 131, wherein the multispecific antigen binding polypeptide comprises an amino acid sequence comprising at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 310.

[0383] Embodiment 133. The multispecific antigen binding polypeptide of any one of embodiments 1 to 86 and 109-132, wherein each of the first antigen binding moiety, the second antigen binding moiety, the third antigen binding moiety, and/or the fourth antigen binding moiety is paired to a domain swapped common light chain polypeptide, wherein the domain swapped common light chain comprises a light chain variable region (VL) fused to a heavy chain first constant region (CH1).

[0384] Embodiment 134. The multispecific antigen binding polypeptide of embodiment 133, wherein the domain swapped surrogate light chain polypeptide comprises an amino acid sequence at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 311.

[0385] Embodiment 135. The multispecific antigen binding polypeptide of any one of embodiments 1 to 36 and 109-134, wherein each of the first antigen binding moiety, the second antigen binding moiety, the third antigen binding moiety, and/or the fourth antigen binding moiety is paired to the surrogate light chain polypeptide.

[0386] Embodiment 136. The multispecific antigen binding polypeptide of embodiment 135, wherein the surrogate light chain polypeptide comprises an amino acid sequence at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 102.

[0387] Embodiment 137. The multispecific antigen binding polypeptide of any one of embodiments 1-86, wherein the first target, the second target, and the third target are the same.

[0388] Embodiment 138. The multispecific antigen binding polypeptide of any one of embodiments 1-86, wherein the first target, the second target, and the third target are PD-1 or a fragment thereof.

[0389] Embodiment 139. The multispecific antigen binding polypeptide of any one of embodiments 1-86, wherein the multispecific antigen binding polypeptide binds to PD-1 or a fragment thereof.

[0390] Embodiment 140. The multispecific antigen binding polypeptide of embodiment 139, wherein the multispecific antigen binding polypeptide binds to PD-1 or a fragment thereof with an EC₅₀ of about 90 picomolar or less.

[0391] Embodiment 141. The multispecific antigen binding polypeptide of any one of embodiments 137 to 140, wherein the multispecific antigen binding polypeptide comprises an amino acid sequence comprising at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 305.

[0392] Embodiment 142. The multispecific antigen binding polypeptide of any one of embodiments 137 to 141, wherein each of the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety is paired to the common light chain polypeptide.

[0393] Embodiment 143. The multispecific antigen binding polypeptide of embodiment 142, wherein the common light chain polypeptide comprises an amino acid sequence at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 307.

[0394] Embodiment 144. The multispecific antigen binding polypeptide of any one of embodiments 11 to 86, wherein the first target, the second target, the third target, and the fourth target are the same.

[0395] Embodiment 145. The multispecific antigen binding polypeptide of any one of embodiments 11 to 86, wherein the first target, the second target, the third target, and the fourth target are PD-1 or a fragment thereof.

[0396] Embodiment 146. The multispecific antigen binding polypeptide of any one of embodiments 11 to 86, wherein the multispecific antigen binding polypeptide binds to PD-1 or a fragment thereof.

[0397] Embodiment 147. The multispecific antigen binding polypeptide of embodiment 146, wherein the multispecific antigen binding polypeptide binds to PD-1 or a fragment thereof with an EC50 of about 60 picomolar or less.

[0398] Embodiment 148. The multispecific antigen binding polypeptide of any one of embodiments 144 to 147, wherein the first, second, third, or fourth antigen binding moiety comprises a first heavy chain variable region (VH), a heavy chain first constant region (CH1), a heavy chain second constant region (CH2), and/or a heavy chain third constant region (CH3).

[0399] Embodiment 149. The multispecific antigen binding polypeptide of any one of embodiments 144 to 148, wherein the multispecific antigen binding polypeptide comprises an amino acid sequence comprising at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 306.

[0400] Embodiment 150. The multispecific antigen binding polypeptide of any one of embodiments 144 to 149, wherein each of the first antigen binding moiety, the second antigen binding moiety, the third antigen binding moiety is paired to the common light chain polypeptide.

[0401] Embodiment 151. The multispecific antigen binding polypeptide of embodiment 150, wherein the common light chain polypeptide comprises an amino acid sequence at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 307.

[0402] Embodiment 152. A multispecific antigen binding polypeptide comprising:

- a. a first antigen binding moiety, comprising a first heavy chain variable region and a first heavy chain first constant region (CH1) paired with a first light chain; and
- b. a second antigen binding moiety, comprising a second heavy chain variable region and a second heavy chain first constant region (CH1) paired with a second light chain;

wherein a C terminus of the first CH1 is coupled to an N-terminus of the second heavy chain variable region wherein the first antigen binding moiety binds to a first target, the second antigen binding moiety binds to a second target.

[0403] Embodiment 153. The multispecific antigen binding polypeptide of embodiment 152, wherein the first light chain and the second light chain are a common light chain.

[0404] Embodiment 154. The multispecific antigen binding polypeptide of embodiment 152, wherein the first light chain and the second light chain are a surrogate light chain.

[0405] Embodiment 155. The multispecific antigen binding polypeptide of any one of embodiments 152 to 154, wherein the first antigen binding moiety and the second antigen binding moiety are directly coupled without a linker.

[0406] Embodiment 156. The multispecific antigen binding polypeptide of any one of embodiments 152 to 155, wherein the surrogate light chain polypeptide comprises a VpreB sequence conjugated to a $\lambda 5$ sequence.

[0407] Embodiment 157. The multispecific antigen binding polypeptide of embodiment 156, wherein the VpreB sequence comprises an amino acid sequence with at least 90%, at least 95%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to the amino acid sequence set forth in SEQ ID NO: 101.

[0408] Embodiment 158. The multispecific antigen binding polypeptide of embodiment 156, wherein the $\lambda 5$ sequence comprises an amino acid sequence with at least 90%, at least 95%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to the amino acid sequence set forth in SEQ ID NO: 106.

[0409] Embodiment 159. The multispecific antigen binding polypeptide of any one of embodiments 154 to 158, wherein the surrogate light chain polypeptide comprises:

- a. a light chain complementarity determining region 1 (LCDR1) comprising the amino acid sequence set forth in SEQ ID NO: 103;
- b. a light chain complementarity determining region 2 (LCDR2) comprising the amino acid sequence set forth in SEQ ID NO: 104; and/or
- c. a light chain complementarity determining region 3 (LCDR3) comprising the amino acid sequence set forth in SEQ ID NO: 105.

[0410] Embodiment 160. The multispecific antigen binding polypeptide of any one of embodiments 154 to 159, wherein the surrogate light chain polypeptide comprises an amino acid sequence at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 102.

[0411] Embodiment 161. The multispecific antigen binding polypeptide of any one of embodiments 154 to 160, wherein each of the first antigen binding moiety and/or the second antigen binding moiety is non-covalently paired to the surrogate light chain polypeptide.

[0412] Embodiment 162. The multispecific antigen binding polypeptide of any one of embodiments 154 to 160, wherein each of the first antigen binding moiety and/or the second antigen binding moiety is covalently paired to the surrogate light chain polypeptide.

[0413] Embodiment 163. The multispecific antigen binding polypeptide of any one of embodiments 154 to 162, wherein the first and second antigen binding moiety bind antigens on different polypeptides.

[0414] Embodiment 164. The multispecific antigen binding polypeptide of any one of embodiments 154 to 163, wherein the first and second antigen binding moiety bind antigens on the same polypeptide.

[0415] Embodiment 165. The multispecific antigen binding polypeptide of any one of embodiments 154 to 164, wherein the first target, and or the second target is VEGF-A or a fragment thereof.

[0416] Embodiment 166. The multispecific antigen binding polypeptide of embodiment 165, wherein the multispecific antigen binding polypeptide binds to VEGF-A or a fragment thereof with an EC₅₀ of about 5 picomolar or less.

[0417] Embodiment 167. The multispecific antigen binding polypeptide of embodiment 165 or 166, wherein the multispecific antigen binding polypeptide binds to VEGF-A or a fragment thereof at least 8-fold stronger than faricimab.

[0418] Embodiment 168. The multispecific antigen binding polypeptide of any one of embodiments 154 to 167, wherein the first target, and or the second target is ANG-2 or a fragment thereof.

[0419] Embodiment 169. The multispecific antigen binding polypeptide of embodiment 168, wherein the multispecific antigen binding polypeptide binds to ANG-2 or a fragment thereof with an EC₅₀ of about 11 picomolar or less.

[0420] Embodiment 170. The multispecific antigen binding polypeptide of embodiment 168 or 169, wherein the multispecific antigen binding polypeptide binds to ANG-2 or a fragment thereof at least 300-fold stronger than faricimab.

[0421] Embodiment 171. The multispecific antigen binding polypeptide of any one of embodiments 154 to 170, wherein the first target, and or the second target is VEGF-C or a fragment thereof.

[0422] Embodiment 172. The multispecific antigen binding polypeptide of embodiment 171, wherein the multispecific antigen binding polypeptide binds to VEGF-C or a fragment thereof with an EC₅₀ of about 19 picomolar or less.

[0423] Embodiment 173. The multispecific antigen binding polypeptide of any one of embodiments 171 to 172, wherein the first target and the second target are independently selected

from VEGF-A or fragment thereof, ANG-2 or a fragment thereof, and VEGF-C or a fragment thereof.

[0424] Embodiment 174. The multispecific antigen binding polypeptide of any one of embodiments 154 to 173, wherein the first and/or second antigen binding moiety bind antigens on different polypeptides.

[0425] Embodiment 175. The multispecific antigen binding polypeptide of any one of embodiments 154 to 174, wherein the first and/or second antigen binding moiety bind antigens on the same polypeptide.

[0426] Embodiment 176. The multispecific antigen binding polypeptide of any one of embodiments 154 to 175, wherein the first antigen binding moiety and/or the second antigen binding moiety binds to VEGF-A.

[0427] Embodiment 177. The multispecific antigen binding polypeptide of embodiment 176, wherein the first antigen binding moiety and/or the second antigen binding moiety binds to VEGF-A and comprises an immunoglobulin heavy chain variable region comprising:

- a. a heavy chain complementarity determining region 1 (HCDR1) comprising the amino acid sequence set forth in SEQ ID NO: 3;
- b. a heavy chain complementarity determining region 2 (HCDR2) comprising the amino acid sequence set forth in SEQ ID NO: 4; and/or
- c. a heavy chain complementarity determining region 3 (HCDR3) comprising the amino acid sequence set forth in SEQ ID NO: 5;

wherein the heavy chain variable region binds to VEGF-A upon pairing with the light chain polypeptide.

[0428] Embodiment 178. The multispecific antigen binding polypeptide of embodiment 176, wherein the first antigen binding moiety and/or the second antigen binding moiety comprises an immunoglobulin heavy chain variable region comprising an amino acid sequence comprising at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 1.

[0429] Embodiment 179. The multispecific antigen binding polypeptide of embodiment 176, wherein the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety comprises an amino acid sequence comprising at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 2.

[0430] Embodiment 180. The multispecific antigen binding polypeptide of any one of embodiments 152 to 178, wherein the first antigen binding moiety and/or the second antigen binding moiety binds to ANG-2.

[0431] Embodiment 181. The multispecific antigen binding polypeptide of embodiment 180, wherein the first antigen binding moiety and/or the second antigen binding moiety bind to ANG-2 and comprises an immunoglobulin heavy chain variable region comprising:

- a. a heavy chain complementarity determining region 1 (HCDR1) comprising the amino acid sequence set forth in SEQ ID NO: 13;
- b. a heavy chain complementarity determining region 2 (HCDR2) comprising the amino acid sequence set forth in SEQ ID NO: 14; and/or
- c. a heavy chain complementarity determining region 3 (HCDR3) comprising the amino acid sequence set forth in SEQ ID NO: 15;

wherein the heavy chain variable region binds to ANG-2 upon pairing with the light chain polypeptide.

[0432] Embodiment 182. The multispecific antigen binding polypeptide of embodiment 180, wherein the first antigen binding moiety and/or the second antigen binding moiety comprises an immunoglobulin heavy chain variable region comprises an amino acid sequence comprising at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 11.

[0433] Embodiment 183. The multispecific antigen binding polypeptide of embodiment 180, wherein the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety comprises an amino acid sequence comprising at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 12.

[0434] Embodiment 184. The multispecific antigen binding polypeptide of any one of embodiments 152 to 183, wherein the first antigen binding moiety binds to ANG-2 and the second antigen binding moiety binds to VEGF-A.

[0435] Embodiment 185. The multispecific antigen binding polypeptide of any one of embodiments 152 to 183, wherein the first antigen binding moiety binds to VEGF-A and the second antigen binding moiety binds to ANG-2.

[0436] Embodiment 186. The multispecific antigen binding polypeptide of any one of embodiments 152 to 185, wherein the multispecific antigen binding polypeptide comprises a first polypeptide chain comprising an amino acid sequence at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 401.

[0437] Embodiment 187. The multispecific antigen binding polypeptide of any one of embodiments 152 to 186, wherein the multispecific antigen binding polypeptide comprises a second polypeptide chain comprising an amino acid sequence at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 102.

[0438] Embodiment 188. The multispecific antigen binding polypeptide of any one of embodiments 152 to 185, wherein the first or second antigen binding moiety further comprises a heavy chain second constant region (CH2), and/or a heavy chain third constant region (CH3).

[0439] Embodiment 189. The multispecific antigen binding polypeptide of any one of embodiments 152 to 185 and 188, wherein the multispecific antigen binding polypeptide comprises a first polypeptide chain comprising an amino acid sequence at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 406.

[0440] Embodiment 190. The multispecific antigen binding polypeptide of any one of embodiments 152 to 186 and 188-189, wherein the multispecific antigen binding polypeptide comprises a second polypeptide chain comprising an amino acid sequence at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 102.

[0441] Embodiment 191. The multispecific antigen binding polypeptide of any one of embodiments 152 to 182, wherein the first antigen binding moiety and/or the second antigen binding moiety binds to VEGF-C.

[0442] Embodiment 192. The multispecific antigen binding polypeptide of embodiment 191, wherein the first antigen binding moiety and/or the second antigen binding moiety binds to VEGF-C and comprises an immunoglobulin heavy chain variable region comprising:

- a. a heavy chain complementarity determining region 1 (HCDR1) comprising the amino acid sequence set forth in SEQ ID NO: 23;
- b. a heavy chain complementarity determining region 2 (HCDR2) comprising the amino acid sequence set forth in SEQ ID NO: 24; and/or
- c. a heavy chain complementarity determining region 3 (HCDR3) comprising the amino acid sequence set forth in SEQ ID NO: 25;

wherein the heavy chain variable region binds to VEGF-C upon pairing with the light chain polypeptide.

[0443] Embodiment 193. The multispecific antigen binding polypeptide of embodiment 191, wherein the first antigen binding moiety and/or the second antigen binding moiety comprises an immunoglobulin heavy chain variable region comprising an amino acid sequence comprising at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 21.

[0444] Embodiment 194. The multispecific antigen binding polypeptide of embodiment 191, wherein the first antigen binding moiety, the second antigen binding moiety, and/or the third

antigen binding moiety comprises an amino acid sequence comprising at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 22.

[0445] Embodiment 195. The multispecific antigen binding polypeptide of any one of embodiments 152 to 193, wherein each of the first antigen binding moiety, and/or the second antigen binding moiety is non-covalently paired to the surrogate light chain polypeptide.

[0446] Embodiment 196. The multispecific antigen binding polypeptide of any one of embodiments 152 to 195, wherein each of the first antigen binding moiety, and/or the second antigen binding moiety is covalently paired to the surrogate light chain polypeptide.

[0447] Embodiment 197. The multispecific antigen binding polypeptide of any one of embodiments 152 to 196, wherein the first antigen binding moiety comprises a first heavy chain variable region (VH) and a heavy chain first constant region (CH1).

[0448] Embodiment 198. The multispecific antigen binding polypeptide of any one of embodiments 152 to 196, wherein the second antigen binding moiety comprises a second heavy chain variable region (VH) and a heavy chain first constant region (CH1).

[0449] Embodiment 199. The multispecific antigen binding polypeptide of any one of embodiments 152 to 196, wherein the heavy chain first constant region comprises an amino acid sequence with at least 80%, at least 90%, at least 95%, at least 97%, at least 98%, at least 99%, or at least 100% identity to the amino acid sequence set forth in SEQ ID NO: 141.

[0450] Embodiment 200. The multispecific antigen binding polypeptide of any one of embodiments 152 to 199, wherein the first antigen binding moiety comprises a first heavy chain variable region (VH), a heavy chain first constant region (CH1), a heavy chain second constant region (CH2), and/or a heavy chain third constant region (CH3).

[0451] Embodiment 201. The multispecific antigen binding polypeptide of any one of embodiments 152 to 199, wherein the second antigen binding moiety comprises a second heavy chain variable region (VH), a heavy chain first constant region (CH1), a heavy chain second constant region (CH2), and/or a heavy chain third constant region (CH3).

[0452] Embodiment 202. The multispecific antigen binding polypeptide of any one of embodiments 152 to 199, further comprising a third antigen binding moiety, wherein the third antigen binding moiety binds to a third target.

[0453] Embodiment 203. The multispecific antigen binding polypeptide of any one of embodiments 152 to 199, further comprising a third and a fourth antigen binding moiety, wherein the third antigen binding moiety binds to a third target and the fourth antigen binding moiety binds to a fourth target.

[0454] Embodiment 204. The multispecific antigen binding polypeptide of any one of embodiment 203, wherein the third target or fourth target comprises VEGF-A, VEGF-C, or ANG-2.

[0455] Embodiment 205. The multispecific antigen binding polypeptide of any one of embodiments 203 or 204, wherein the third antigen binding moiety comprises a third heavy chain variable region and a third heavy chain first constant region (CH1) paired with a third light chain.

[0456] Embodiment 206. The multispecific antigen binding polypeptide of any one of embodiments 203 or 204, wherein the fourth antigen binding moiety comprises a fourth heavy chain variable region and a fourth heavy chain first constant region (CH1) paired with a fourth light chain.

[0457] Embodiment 207. The multispecific antigen binding polypeptide of embodiment 205, wherein the third and/or fourth light chain is a common light chain.

[0458] Embodiment 208. The multispecific antigen binding polypeptide of embodiment 205, wherein the third and/or fourth light chain is a surrogate light chain.

[0459] Embodiment 209. The multispecific antigen binding polypeptide of any one of embodiments 203 to 208, wherein the third antigen binding moiety is directly coupled to the first antigen binding moiety without a linker.

[0460] Embodiment 210. The multispecific antigen binding polypeptide of any one of embodiments 203 to 208, wherein the fourth antigen binding moiety is directly coupled to the second antigen binding moiety without a linker.

[0461] Embodiment 211. The multispecific antigen binding polypeptide of any one of embodiments 208 to 210, wherein the surrogate light chain polypeptide comprises a VpreB sequence conjugated to a $\lambda 5$ sequence.

[0462] Embodiment 212. The multispecific antigen binding polypeptide of embodiment 211, wherein the VpreB sequence comprises an amino acid sequence with at least 90%, at least 95%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to the amino acid sequence set forth in SEQ ID NO: 101.

[0463] Embodiment 213. The multispecific antigen binding polypeptide of embodiment 211, wherein the $\lambda 5$ sequence comprises an amino acid sequence with at least 90%, at least 95%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to the amino acid sequence set forth in SEQ ID NO: 106.

[0464] Embodiment 214. The multispecific antigen binding polypeptide of any one of embodiments 208 to 213, wherein the surrogate light chain polypeptide comprises:

- a. a light chain complementarity determining region 1 (LCDR1) comprising the amino acid sequence set forth in SEQ ID NO: 103;

- b. a light chain complementarity determining region 2 (LCDR2) comprising the amino acid sequence set forth in SEQ ID NO: 104; and/or
- c. a light chain complementarity determining region 3 (LCDR3) comprising the amino acid sequence set forth in SEQ ID NO: 105.

[0465] Embodiment 215. The multispecific antigen binding polypeptide of any one of embodiments 208 to 214, wherein the surrogate light chain polypeptide comprises an amino acid sequence at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 102.

[0466] Embodiment 216. The multispecific antigen binding polypeptide of any one of embodiments 152 to 215, wherein the multispecific antigen binding polypeptide comprises a first polypeptide chain comprising an amino acid sequence at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 402.

[0467] Embodiment 217. The multispecific antigen binding polypeptide of any one of embodiments 152 to 216, wherein the multispecific antigen binding polypeptide comprises a second polypeptide chain comprising an amino acid sequence at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 403.

[0468] Embodiment 218. The multispecific antigen binding polypeptide of any one of embodiments 152 to 215, wherein the multispecific antigen binding polypeptide comprises a first polypeptide chain comprising an amino acid sequence at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 404.

[0469] Embodiment 219. The multispecific antigen binding polypeptide of any one of embodiments 152 to 216, wherein the multispecific antigen binding polypeptide comprises a second polypeptide chain comprising an amino acid sequence at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 405.

[0470] Embodiment 220. A vascular endothelial growth factor A (VEGF-A) antigen binding polypeptide or antigen binding fragment thereof comprising:

- a. a heavy chain complementarity determining region 1 (HCDR1) comprising the amino acid sequence set forth in SEQ ID NO: 3;
- b. a heavy chain complementarity determining region 2 (HCDR2) comprising the amino acid sequence set forth in SEQ ID NO: 4; and/or
- c. a heavy chain complementarity determining region 3 (HCDR3) comprising the amino acid sequence set forth in SEQ ID NO: 5;

wherein the antigen binding polypeptide or antigen binding fragment thereof binds to VEGF-A.

[0471] Embodiment 221. The antigen binding or antigen binding fragment thereof of embodiment 220, comprising a heavy chain variable region comprising an amino acid sequence comprising at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 1.

[0472] Embodiment 222. The antigen binding or antigen binding fragment thereof of embodiment 220 or 221, comprising a heavy chain region comprising an amino acid sequence comprising at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 2.

[0473] Embodiment 223. The antigen binding or antigen binding fragment thereof of any one of embodiments 220 to 222, further comprising a surrogate light chain.

[0474] Embodiment 224. An angiopoietin 2 (ANG-2) antigen binding polypeptide or antigen binding fragment thereof comprising:

- a. a heavy chain complementarity determining region 1 (HCDR1) comprising the amino acid sequence set forth in SEQ ID NO: 13;
- b. a heavy chain complementarity determining region 2 (HCDR2) comprising the amino acid sequence set forth in SEQ ID NO: 14; and/or
- c. a heavy chain complementarity determining region 3 (HCDR3) comprising the amino acid sequence set forth in SEQ ID NO: 15,

wherein the antigen binding polypeptide or antigen binding fragment thereof binds to ANG-2.

[0475] Embodiment 225. The antigen binding polypeptide or antigen binding fragment thereof of embodiment 224, comprising a heavy chain variable region comprising an amino acid sequence comprising at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 11.

[0476] Embodiment 226. The antigen binding polypeptide or antigen binding fragment thereof of embodiment 224 or 225, comprising a heavy chain region comprising an amino acid sequence comprising at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 12.

[0477] Embodiment 227. The polypeptide or antigen binding fragment thereof of any one of embodiments 224 to 226, further comprising a surrogate light chain.

[0478] Embodiment 228. A vascular endothelial growth factor C (VEGF-C) antigen binding polypeptide or antigen binding fragment thereof comprising:

- a. a heavy chain complementarity determining region 1 (HCDR1) comprising the amino acid sequence set forth in SEQ ID NO: 23;
- b. a heavy chain complementarity determining region 2 (HCDR2) comprising the amino acid sequence set forth in SEQ ID NO: 24; and

- c. a heavy chain complementarity determining region 3 (HCDR3) comprising the amino acid sequence set forth in SEQ ID NO: 25;

wherein the antigen binding polypeptide or antigen binding fragment thereof binds to VEGF-C.

[0479] Embodiment 229. The antigen binding polypeptide or antigen binding fragment thereof of embodiment 228, comprising a heavy chain variable region comprising an amino acid sequence comprising at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 21.

[0480] Embodiment 230. The antigen binding polypeptide or antigen binding fragment thereof of embodiment 228 or 229, comprising a heavy chain region comprising an amino acid sequence comprising at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 22.

[0481] Embodiment 231. The antigen binding polypeptide or antigen binding fragment thereof of any one of embodiments 228 to 230, further comprising a surrogate light chain.

[0482] Embodiment 232. A pharmaceutical composition comprising the multispecific antigen binding polypeptide or the antigen binding polypeptide of any one of embodiments 1 to 231 and a pharmaceutically acceptable carrier, excipient, or diluent.

[0483] Embodiment 233. The pharmaceutical composition of embodiment 232 formulated for intravenous administration.

[0484] Embodiment 234. The pharmaceutical composition of embodiment 232 formulated for intravitreal administration.

[0485] Embodiment 235. A nucleic acid or plurality of nucleic acids encoding the multispecific antigen binding polypeptide or antigen binding polypeptide of any one of embodiments 1 to 231.

[0486] Embodiment 236. An expression vector comprising the nucleic acid of embodiment 235.

[0487] Embodiment 237. The expression vector of embodiment 236, wherein the expression vector is RNA.

[0488] Embodiment 238. The expression vector of embodiment 236, wherein the expression vector is plasmid or linearized DNA.

[0489] Embodiment 239. The expression vector of embodiment 236, wherein the expression vector is a viral vector.

[0490] Embodiment 240. The viral vector of embodiment 239, wherein the viral vector is an adenovirus.

[0491] Embodiment 241. The viral vector of embodiment 239, wherein the viral vector is an adeno-associated virus.

[0492] **Embodiment 242.** The viral vector of embodiment 239, wherein the viral vector is a lentivirus virus.

[0493] **Embodiment 243.** A pharmaceutical composition comprising the nucleic acid or plurality of nucleic acids encoding the multispecific antigen binding polypeptide of any one of embodiments 234 to 242 and a pharmaceutically acceptable carrier, excipient, or diluent.

[0494] **Embodiment 244.** The pharmaceutical composition of embodiment 243 formulated for intravenous administration.

[0495] **Embodiment 245.** The pharmaceutical composition of embodiment 243 formulated for intravitreal administration.

[0496] **Embodiment 246.** A method of treating a disease in an individual comprising administering to the individual the multispecific antigen binding polypeptide, the nucleic acid or plurality of nucleic acids encoding the multispecific antigen binding polypeptide, or pharmaceutical composition of any one of the preceding embodiments, thereby treating the disease.

[0497] **Embodiment 247.** The method of embodiment 246, wherein the disease is an ocular disease.

[0498] **Embodiment 248.** The method of embodiment 247, wherein the ocular disease comprises macular degeneration.

[0499] **Embodiment 249.** The method of embodiment 248, wherein the macular degeneration is neovascular age-related macular degeneration.

[0500] **Embodiment 250.** The method of embodiment 248, wherein the ocular disease comprises diabetic macular edema.

[0501] **Embodiment 251.** The method of embodiment 248, wherein the ocular disease comprises retinal vein occlusion.

[0502] **Embodiment 252.** The method of embodiment 246, wherein the disease is a cancer.

EXAMPLES

[0503] The following illustrative examples are representative of embodiments of compositions and methods described herein and are not meant to be limiting in any way.

Example 1-Production of VEGF-A/ANG-2/VEGF-C trispecific antigen binding polypeptides

[0504] Nucleic acid sequences encoding polypeptides corresponding to SEQ ID NO: 201, SEQ ID NO: 202, and SEQ ID NO: 203 were cloned into plasmid vectors to direct eukaryotic cell expression. Protein expression vectors were co-transfected into HEK293 cells.

[0505] Transfectants were isolated from supernatants by Protein A chromatography. Purified proteins were respectively analyzed for uniformity, purity, and quantity by SEC-HPLC, SDS-PAGE and UV spectrophotometric analysis.

[0506] For SDS-PAGE analysis, reduced and non-reduced samples of the RO-104 (RP-019; i.e., SEQ ID NO: 202) were electrophoresed. **FIG. 5A** confirms the presence of products and good levels of purity were observed. Under non-reducing conditions, protein bands around 150 kDa were seen. Under reducing conditions, bands corresponding to the molecular weight of light chain (~25 kDa) and heavy chains (~63 kDa) are observed. The purified RO-104 proteins were also analyzed in SE-HPLC. All three sample proteins showed 100% single peak, indicating 100% purity (*see FIG. 5B and 5C*).

Example 2-Binding of RO-104 VEGF-A/ ANG-2/ VEGF-C trispecific antigen polypeptide

[0507] Trispecific antigen polypeptides RO-104 prepared according to example 1 were tested for their binding affinity to target antigen.

[0508] **VEGF-A ELISA**- Recombinant human VEGF-A (Peprotech, Cat #100-20) was used to coat plates at 1 µg/mL. The products were diluted in blocking buffer at a starting concentration of 10 nM and then 1:3 serial dilutions were tested. The binding was detected by biotinylated anti-VpreB antibody and HRP-conjugated streptavidin. Faricimab and Aflibercept were run alongside RO-104 as reference material and its binding was detected by HRP-conjugated donkey anti-human IgG Fcγ antibody (Jackson ImmunoResearch Laboratories, Cat #709-035-098). OD450 nm readings were measured by Victor 3 (PerkinElmer 1420 Multilabel Counter). As illustrated in **FIGs. 6A, 6C, 6F and 6G**, the results showed the binding is similar to Faricimab and Aflibercept with picomolar affinity.

[0509] **ANG-2 ELISA** Recombinant human ANG-2 (Acro Biosystems, Cat #AN2-H52H4) was used to coat plates at 1 µg/mL. The products were diluted in blocking buffer at a starting concentration of 10 nM and then 1:3 serial dilutions were tested. The binding was detected by biotinylated anti-VpreB antibody and HRP-conjugated streptavidin. Faricimab and Aflibercept were run alongside RO-104 as reference material detected by HRP-conjugated donkey anti-human IgG Fcγ antibody (Jackson ImmunoResearch Laboratories, Cat # 709-035-098). OD450 nm readings were measured by Victor 3 (PerkinElmer 1420 Multilabel Counter). As illustrated in **FIGs. 6B, 6D, and 6H**, the results showed higher binding affinity for the product.

[0510] **VEGF-C ELISA** Recombinant human VEGF-C (Peprotech, Cat#100-20CD) was used to coat plates at 1 µg/mL. The products were diluted in blocking buffer at a starting concentration of 10 nM and then 1:3 serial dilutions were tested. The binding was detected by biotinylated anti-VpreB antibody and HRP-conjugated streptavidin. OD450 nm readings were measured by Victor

3 (PerkinElmer 1420 Multilabel Counter). As illustrated in **FIGs. 6E** and **6I**, the results showed high binding affinity for the products with EC50 value below 100pM.

[0511] Therefore, the tested trispecific RO-104 multispecific binding polypeptides showed a similar affinity to VEGF-A, higher affinity to ANG-2, and unique binding specificity to VEGF-C, when compared to the existing VEGF antigen binding agent and VEGF/ANG-2 bispecific antigen binding agent.

Example 3-Binding of different VEGF-A/ ANG-2/ VEGF-C trispecific antigen polypeptides

[0512] Three different constructs of VEGF-A/ANG-2/VEGF-C trispecific antigen polypeptides prepared according to methods in example 1 were tested for their binding capacity to target antigen. The three constructs were from N-terminus to C-terminus: a) VEGF-C/VEGF-A/ANG-2; b) VEGF-A/ANG-2/VEGF-C; and c) ANG-2/VEGF-C/VEGF-A.

[0513] VEGF-A ELISA- Recombinant human VEGF-A (Peprotech, Cat #100-20) was used to coat plates at 1 µg/mL. The products were diluted in blocking buffer at a starting concentration of 10 nM and then 1:3 dilutions were tested. The binding was detected by biotinylated anti-VpreB antibody and HRP-conjugated streptavidin. OD450 nm readings were measured by Victor 3 (PerkinElmer 1420 Multilabel Counter). As illustrated in **FIGs. 7A**, the results showed similar binding affinities for the three trispecific antigen polypeptides with EC50 value at 5.7pM, 5.0 pM, and 5.9pM, respectively.

[0514] ANG-2 ELISA Recombinant human ANG-2 (Acro Biosystems, Cat #AN2-H52H4) was used to coat plates at 1 µg/mL. The products were diluted in blocking buffer at a starting concentration of 10 nM and then 1:3 dilutions were tested. The binding was detected by biotinylated anti-VpreB antibody and HRP-conjugated streptavidin. OD450 nm readings were measured by Victor 3 (PerkinElmer 1420 Multilabel Counter). As illustrated in **FIGs. 7B**, the results showed similar binding affinity for the three constructs with EC50 value around 18.8pM, 10.7 pM, and 10.7pM, respectively.

[0515] VEGF-C ELISA Recombinant human VEGF-C (Peprotech, Cat #100-20CD) was used to coat plates at 1 µg/mL. The products were diluted in blocking buffer at a starting concentration of 10 nM and then 1:3 dilutions were tested. The binding was detected by biotinylated anti-VpreB antibody and HRP-conjugated streptavidin. OD450 nm readings were measured by Victor 3 (PerkinElmer 1420 Multilabel Counter). As illustrated in **FIGs. 7C**, the results showed that all three constructs bind to VEGF-C. The binding affinity of RO-104 (VEGF-A/ANG-2/VEGF-C) was stronger with EC50 value around 19.2 pM, which was 2-fold stronger than the other two trispecific constructs.

[0516] Overall, the binding affinity results suggested that changing positions of the antigen binding moieties within the multispecific antigen binding polypeptides did not affect their antigen binding affinity.

Example 4-in vivo anti-angiogenic efficacy of RO-104 in a rat model

[0517] Multispecific antigen binding polypeptides RO-104 were prepared according to example 1.

[0518] Rats were treated with laser to produce multiple Bruch's membrane injuries to induce neovascularized lesions. Following laser injury, rats were injected intravitreally with either vehicle or test article. After 8 days rats were intravenously injected with fluorescein and retinal vascular images were taken by fluoragraphical methods. The images were quantitatively analyzed for to determine resulting lesion areas, as shown in **FIG. 8A** and **FIG. 8B**. **Table 1** shows the area of choroidal neovascular lesion 8 days after treatment in arbitrary units (a.u.). The average lesion area was 2369 ± 184 arbitrary units (a.u.) in control, 1889 ± 184 a.u. in rats injected with faricimab), and significantly reduced to 1223 ± 97 a.u. in rats injected with the trispecific surrobody).

Table 1: Area of Choroidal Neovascular Lesion 8 Days After Treatment (a.u.)

	Mean	Standard Deviation	Standard error
Control	2369	1208	184
Faricimab	1889	1267	195
RO-104	1223	639	97

[0519] The two-sample t-test was used to determine statistical significance of lesion area between two group. As shown in **Table 2**, no statistical significance was shown when comparing the control lesion area mean to faricimab with a p-value of 0.08. Notably, the difference between the mean lesion area in the control group and the trispecific surrobody group exhibited strong statistical significance with a p-value of <0.001 . On the contrary, statistically significant difference was observed between the lesion area mean of the faricimab group and the trispecific surrobody group, with a p-value of 0.003.

Table 2: Two Sample T-Test Results Between Groups

	T stat	P value
Control v. Faricimab	1.79	0.08
Control v. RO-104	5.49	<0.0001
Faricimab v. RO-104	3.06	0.003

[0520] Rats were treated with laser to produce multiple Bruch's membrane injuries to induce neovascularized lesions. Following laser injury, rats were injected intravitreally with either

vehicle, 0.1 mg of Faricimab, 0.066mg of Aflibercept, or 0.1 mg of RO-104. After 8 days rats were intravenously injected with fluorescein and retinal vascular images were taken by fluoragraphical methods. The mean corrected total lesion fluorescence (CTLF) was 96054 arbitrary units (a.u.) in control, 92034 a.u. in rats injected with Faricimab, 67973 a.u. in rats injected with Aflibercept, and reduced 49726 a.u. in rats injected with the trispecific surrobody, as shown in **FIG. 8F** and **Table 3**. Compared to the control, the CTLF in rats injected with Faricimab was reduced by 4%, the CTLF in rats injected with Aflibercept was reduced by 29%, and the CTLF in rats injected with RO-104 was reduced by 48%.

Table 3: Percentage of Reduction of Fluorescence and P-value

	%reduction (vs. vehicle)	
Vehicle		
Faricimab	19%	p=0.2201
Aflibercept	29%	p=0.2036
RO-104	48%	p=0.0061

[0521] The result suggests that the trispecific RO-104 surpasses Faricimab and Aflibercept in effectively treating neovascular growth. The increased effect of RO-104 could be due to its ability to inhibit the VEGF-C pathway, in addition to VEGF-A and ANG-2.

Example 5-The half maximal inhibitory concentration (IC₅₀) of RO104 VEGF-A/ ANG-2/ VEGF-C trispecific antigen polypeptide

[0522] Trispecific antigen polypeptides RO-104 prepared according to example 1 were tested for their IC₅₀ of binding to target antigen. Inhibition of single target and receptor interaction binding ELISA was done using RO-104 and faricimab as the competitor, respectively.

[0523] **VEGF-A inhibition ELISA**- The trispecific RO-104 were diluted in blocking buffer at a starting concentration of 200 nM and then 1:3 serial dilutions were tested. This 2x RO-104 dilutions were mixed with 2x biotinylated VEGF R2/KDR receptor (Acro Biosystems, Cat # VE5-H82Q0). Then 1x mixtures of RO-104 and biotinylated VEGF R2/KDR were added to plate wells. The binding was detected through a biotinylated receptor VEGF R2/KDR and 1:5,000 dilution of HRP-conjugated streptavidin (Jackson ImmunoResearch Lab, Cat #016-030-084). Faricimab was run as an inhibitor using the same protocol. OD450 nm readings were measured by Victor 3 (PerkinElmer 1420 Multilabel Counter). As illustrated in **FIG. 9A**, IC₅₀ of RO-104 was 17.94nM, which was 1.46-fold lower compared to faricimab.

[0524] **ANG-2 inhibition ELISA**- Recombinant human ANG-2 (Acro Biosystems, Cat #AN2-H52H4) was used to coat plates at 1 µg/mL. The trispecific RO-104 were diluted in blocking buffer at a starting concentration of 200nM and then 1:3 serial dilutions were tested. This 2x RO-

104 dilutions were mixed with 2x biotinylated Tie2 receptor (R&D Systems, Cat #AVI10727). Then 1x mixtures of RO-104 and biotinylated Tie2 were added to plate wells. The binding was detected through a biotinylated receptor Tie2 and 1:5,000 dilution of HRP-conjugated streptavidin (Jackson ImmunoResearch Lab, Cat #016-030-084). Faricimab was run as an inhibitor using the same protocol. OD450 nm readings were measured by Victor 3 (PerkinElmer 1420 Multilabel Counter). As illustrated in **FIG. 9B**, IC₅₀ of RO-104 was 3.10nM, which was 12.42-fold lower compared to faricimab.

[0525] VEGF-C inhibition ELISA- Recombinant human VEGF-C (Peprotech, Cat#100-20CD) was used to coat plates at 1 µg/mL. The trispecific RO-104 were diluted in blocking buffer at a starting concentration of 200 nM and then 1:3 serial dilutions were tested. This 2x RO-104 dilutions were mixed with 2x biotinylated VEGF R2/KDR receptor (Acro Biosystems, Cat #VE5-H82Q0). Then 1x mixtures of RO-104 and biotinylated VEGF R2/KDR were added to plate wells. The binding was detected through a biotinylated receptor VEGF R2/KDR and 1:5,000 dilution of HRP-conjugated streptavidin (Jackson ImmunoResearch Lab, Cat #016-030-084). Faricimab was run as an inhibitor using the same protocol. OD450 nm readings were measured by Victor 3 (PerkinElmer 1420 Multilabel Counter). As illustrated in **FIG. 9C**, IC₅₀ of RO-104 was 3.775nM and the inhibition to VEGF-C was unique to RO-104.

[0526] TRISPEICIF TARGET RECEPTOR inhibition ELISA- The trispecific RO-104 inhibition of target-receptor binding was also tested at the presence of all three targets with the detection of one of the biotinylated targets or receptors at a time. Recombinant human ANG-2 was used to coat plates at 1 µg/mL. 2x RO-104 was diluted in blocking buffer at a starting concentration of 400 nM and then 1:3 serial dilutions were tested. The binding was detected through the 2nd or 3rd biotinylated target or a biotinylated Tie 2 in the presence of the other two targets. Faricimab was run as an inhibitor using same protocol. OD450 nm readings were measured by Victor 3 (PerkinElmer 1420 Multilabel Counter). As illustrated in **FIG. 9D**, for ANG-2, RO-104 showed 2.62 to 3.43-fold better IC₅₀ than faricimab, and the unique inhibition of RO-104 with VEGF-C was also again observed.

[0527] Overall, the results showed that RO-104 demonstrated improved IC₅₀ in single target-receptor and tri-specific target-receptor binding for the VEGF-C and ANG-2 arms as compared to faricimab with no notable differences in VEGF-A.

Example 6-Inhibition of VEGF-A induced endothelial cell migration

[0528] Trispecific antigen polypeptides RO-104 prepared according to example 1 were tested for their inhibition of endothelial cell migration.

[0529] VEGF-A inhibitor potency was determined via HUVEC scratch wound cell migration assay and analyzed by Incucyte Cell Migration Scratch Wound Analysis. Huvec cells (Lonza) were seeded at 50,000/well to achieve near 100% confluence in EBM-2 and incubated overnight. The next day, the Incucyte WoundMaker was used to create uniform scratch wounds in all wells, followed by three PBS washes. HUVEC cells were then treated with 4 nM VEGF-A (Peprotech) in the presence and absence of RO-104. The response and diminution of HUVEC migration by RO-104 was monitored using the IncuCyte live-cell analysis system. **FIG. 10A** showed the representative cell images of wound closure of HUVEC cells treated with 4nM VEGF and 30nM aflibercept versus RO-104. Percent confluence and relative wound density occupied by VEGF-A stimulated HUVEC migration were calculated.

[0530] Wound measurements at 8, 10, and 12 hours post-treatment were analyzed. At these timepoints, RO-104 and aflibercept both achieved similar relative inhibitory maximums, allowing for comparative analysis of wound density and wound confluence. As shown in **FIG. 10B**, wound density at these timepoints had an IC₅₀ of 5.65nM (SD = 1.52nM) for RO-104, comparing favorably to aflibercept's IC₅₀ of 14.97nM (SD = 4.57nM) (p=0.07). As shown in **FIG. 10C**, wound confluence inhibition via RO-104 yielded an IC₅₀ of 1.44nM (SD = 0.33nM), demonstrating comparable results to aflibercept's IC₅₀ of 1.37nM (SD = 0.57nM) (p=0.9).

[0531] The results suggested that the trispecific RO-104 is highly effective at inhibiting VEGF-A, and stimulated HUVEC wound closure by wound density was superior to that of aflibercept while wound confluence measured noninferior to aflibercept.

Example 7-Assessment of pre-existing anti-drug antibodies (ADAs) against RO-104 VEGF-A/ANG-2/ VEGF-C trispecific antigen polypeptide

[0532] Elevated levels of pre-existing anti-drug antibodies (ADAs) in patients may predict adverse outcomes in response to intravitreal injections with anti-vascular endothelial growth factor (anti-VEGF) agents. Higher levels of pre-existing ADAs detected against brolocizumab than ranibizumab may be correlated with a greater incidence of adverse events such as severe intraocular inflammation (IOI) including occlusive retinal vasculitis upon treatment with brolocizumab. Three versions of the trispecific antigen polypeptides (RP-018, RP-019, and RP-020) prepared according to methods in example 1 were tested against pre-existing ADAs to determine which version would be least likely to induce IOI in patients.

[0533] To detect ADAs, pooled human serum from Fisher Scientific (Cat #BP2657) was analyzed in an enzyme-linked immunosorbent assay (ELISA). For the first ELISA, plate wells were coated with 100 µL of 1 µg/mL or 5 µg/mL of the known most immunogenic agent (brolocizumab), the least immunogenic agent (ranibizumab), and three of our trispecific proteins

(RP-018, RP-019, and RP-020) made in 1x coating buffer (BioFfx/Surmodics, Cat# COAT-1000-01). Coating with 1 µg/mL and 5 µg/mL of brolucizumab showed similar results. Subsequent ELISAs used 1 µg/mL as the default coating. All plates were incubated overnight at room temperature. Wells were washed with PBS-Tween, blocked with 300 µL 1% BSA-PBST blocking buffer, washed three times again, and incubated with 100 µL of 1:3 serially diluted pooled human serum for 1 hour at room temperature. Samples were tested in duplicates. Wells were washed and then incubated with HRP-conjugated anti-human IgG-Fcγ secondary antibody (Jackson ImmunoResearch. Labs, Cat#709-035-098) for 1 hour at room temperature. After six washes, the TMB substrate and stop solution were added. ELISA results were visualized at OD450 nm by Victor 3 (PerkinElmer 1420 Multilabel Counter). The ADA titer was determined as three fold OD450 reading over background control.

[0534] Table 4 and FIG. 11 show the ADA titer in pooled human serum against the trispecific antigen polypeptides RP-018, RP-019 (RO-104), RP-020 as well as brolucizumab and ranibizumab. As shown in FIG. 11, the ADA titer in pooled human serum against RP-019 ranged from 1:2700-1:8100, and the ADA titers against RP-018 and RP-020 ranged from 1:900 to 1:2700, which was comparable to ranibizumab and 9-fold lower than brolucizumab. The result suggested that of the three equally efficacious proteins, RP-018 and RP-020 have the lowest amounts of pre-existing ADA in human serum, and are therefore least likely to induce adverse immunogenic responses in patients.

Table 4: The ADA titer in pooled human serum against the trispecific antigen polypeptides

Test Protein	ADA Titer (3-fold over background)
Brolucizumab	<1:24300
RP-019	<1:8,100
RP-018	<1:2,700
RP-020	<1:2,700
Ranibizumab	<1:2,700

Example 8-Pharmacokinetic analysis of RO-104 in rabbit eye vitreous

[0535] Trispecific antigen polypeptides RO-104 prepared according to example 1 were tested for their pharmacokinetic profile *in vivo*.

[0536] Eleven rabbits received 1 mg/eye intravitreal injections of RO-104 in both eyes as their treatment, and two rabbits received no treatment. The concentration of RO-104 was measured across a 29-day period. To determine the concentration of RO-104 bound to the three targets in the vitreous humor, rabbits were sacrificed on days 1, 3, 8, 15, and 29. The concentration of RO-104 in the left eye of one sacrificed rabbit was measured in target-specific binding ELISA at these time points. Half-life for binding to each target was calculated by using the highest and

lowest concentration across the 29-day study. All experiments were performed in accordance with the ARVO statement for Use of Animals in Ophthalmic and Vision research.

[0537] For all three targets, the measured maximum concentration of RO-104 bound in the vitreous was measured and reported as $C_{\max}$. **Table 5** shows the specific values for $C_{\max}$ in ng/mL. The time for RO-104 to reach the max concentration for each target was reported as $T_{\max}$ and occurred on day 3 for all targets, meaning it took about 72 hours for RO-104 to reach its max concentration in the vitreous. The half-life beginning at $T_{\max}$ for RO-104 bound to VEGF-A, ANG-2, and VEGF-C were 3.66, 3.82, and 3.68 days, respectively. **FIG. 12** showed the concentration of RO-104 bound to each target in the eye across the 29-day period. The result suggested that RO-104 has a relatively similar half-life across target, and it is absorbed and eliminated from the eye at an appropriate rate.

Table 5: pharmacokinetics for RO-104 to reach the max concentration in the vitreous

Rabbit (Dutch Belted)	Target binding	Dose (mg/eye)	$C_{\max}$ (ng/mL)	$T_{\max}$ (days)	AUClast (days*ng/mL)	AUCinf (days*ng/mL)	Clast (ng/mL)	Tlast (days)	$T_{1/2}$ (Days)
M	Ang-2	1	70400	3	621000	62500	698	29	3.82
M	VEGF-A	1	68300	3	586000	58900	583	29	3.66
M	VEGF-C	1	69200	3	598000	60100	598	29	3.68

Example 9-Production of ErbB3/VEGF-A/ANG-2/VEGF-C tetraspecific surrobody

[0538] Nucleic acid sequences encoding sequences corresponding to SEQ ID NO: 301 and SEQ ID NO: 102 were cloned into plasmid vectors to direct eukaryotic cell expression. Protein expression vectors were co-transfected into HEK293 cells.

[0539] Transfectants were isolated from supernatants by Protein A chromatography. Purified proteins were respectively analyzed for uniformity, purity, and quantity by SEC-HPLC, SDS-PAGE and UV spectrophotometric analysis.

Example 10-Binding of ErbB3/VEGF-A/ANG-2/VEGF-C tetraspecific surrobody

[0540] Test articles were prepared according to example 9 were tested for binding to target antigen by ELISA.

[0541] VEGF-A ELISA- Human VEGF-A (VEGF165) was used to coat plates at 1 μ g/mL. The products were diluted in blocking buffer at a starting concentration of 10nM and then 1:3 dilutions were tested. Binding to target was detected by 1:10,000 dilution of CaptureSelect™ Biotin Anti-IgG-CH1 Conjugate (ThermoFisher, Cat #7103202500) followed by 1:5,000 dilution of HRP-conjugated streptavidin. As illustrated in **FIG. 13**, the ErbB3/VEGF-A/ANG-2/VEGF-C tetraspecific surrobody binds to VEGF-A with EC50 value around 23.7pM.

[0542] **ANG-2 ELISA**- Human ANG-2 (Angiopoietin-2) was used to coat plates at 1 µg/mL. The products were diluted in blocking buffer at a starting concentration of 10nM and then 1:3 dilutions were tested. Binding to target was detected by 1:10,000 dilution of CaptureSelect™ Biotin Anti-IgG-CH1 Conjugate (ThermoFisher, Cat #7103202500) followed by 1:5,000 dilution of HRP-conjugated streptavidin. As illustrated in **FIG. 13**, the ErbB3/VEGF-A/ANG-2/VEGF-C tetraspecific surrobody binds to ANG-2 with EC50 value around 32.1pM.

[0543] **VEGF-C ELISA**- Human VEGF-C was used to coat plates at 1 µg/mL. The products were diluted in blocking buffer at a starting concentration of 10nM and then 1:3 dilutions were tested. Binding to target was detected by 1:10,000 dilution of CaptureSelect™ Biotin Anti-IgG-CH1 Conjugate (ThermoFisher, Cat #7103202500) followed by 1:5,000 dilution of HRP-conjugated streptavidin. As illustrated in **FIG. 13**, the ErbB3/VEGF-A/ANG-2/VEGF-C tetraspecific surrobody binds to VEGF-C with EC50 value around 4.23nM.

[0544] **ErbB3 ELISA**- Human ErbB3 was used to coat plates at 1 µg/mL. The products were diluted in blocking buffer at a starting concentration of 10nM and then 1:3 dilutions were tested. Binding to target was detected by 1:10,000 dilution of CaptureSelect™ Biotin Anti-IgG-CH1 Conjugate (ThermoFisher, Cat #7103202500) followed by 1:5,000 dilution of HRP-conjugated streptavidin. As illustrated in **FIG. 13**, the ErbB3/VEGF-A/ANG-2/VEGF-C tetraspecific surrobody binds to ErbB3 with EC50 value around 0.57nM.

Example 11-Production of EGFr/ErbB2/ErbB3 trispecific antibody

[0545] Nucleic acid sequences encoding sequences corresponding to SEQ ID NO: 302 and SEQ ID NO: 303 were cloned into plasmid vectors to direct eukaryotic cell expression. Protein expression vectors were co-transfected into HEK293 cells.

[0546] Transfectants were isolated from supernatants by CaptureSelect IgG-CH1 chromatography. Purified proteins were respectively analyzed for uniformity, purity, and quantity by SEC-HPLC, SDS-PAGE and UV spectrophotometric analysis.

Example 12-Binding of EGFr/ErbB2/ErbB3 trispecific antibody

[0547] Test articles were prepared according to example 11 were tested for binding to target antigen by ELISA.

[0548] **EGFr ELISA**- Human EGFr (Acro Biosystems) was used to coat plates at 1 µg/mL. The products were diluted in blocking buffer at a starting concentration indicated in corresponding figures and then 1:3 dilutions were tested. Binding to target was detected by 1:10,000 dilution of CaptureSelect™ Biotin Anti-IgG-CH1 Conjugate (ThermoFisher, Cat #7103202500) followed

by 1:5,000 dilution of HRP-conjugated streptavidin. As illustrated in **FIG. 14**, the EGFr/ErbB2/ErbB3 trispecific antibody binds to EGFr with EC50 value around 0.21nM.

[0549] ErbB2 ELISA- Human ErbB2 (Acro Biosystems) was used to coat plates at 1 µg/mL. The products were diluted in blocking buffer at a starting concentration indicated in corresponding figures and then 1:3 dilutions were tested. Binding to target was detected by 1:10,000 dilution of CaptureSelect™ Biotin Anti-IgG-CH1 Conjugate (ThermoFisher, Cat #7103202500) followed by 1:5,000 dilution of HRP-conjugated streptavidin. As illustrated in **FIG. 14**, the EGFr/ErbB2/ErbB3 trispecific antibody binds to ErbB2 with EC50 value around 50.8pM.

[0550] ErbB3 ELISA- Human ErbB3 (Acro Biosystems) was used to coat plates at 1 µg/mL. The products were diluted in blocking buffer at a starting concentration indicated in corresponding figures and then 1:3 dilutions were tested. Binding to target was detected by 1:10,000 dilution of CaptureSelect™ Biotin Anti-IgG-CH1 Conjugate (ThermoFisher, Cat #7103202500) followed by 1:5,000 dilution of HRP-conjugated streptavidin. As illustrated in **FIG. 14**, the EGFr/ErbB2/ErbB3 trispecific antibody binds to ErbB3 with EC50 value around 2.8nM.

Example 13-Production of EGFr/ErbB2/ErbB3/cMet tetraspecific antibody

[0551] Nucleic acid sequences encoding sequences corresponding to SEQ ID NO: 304 and SEQ ID NO: 303 were cloned into plasmid vectors to direct eukaryotic cell expression. Protein expression vectors were co-transfected into HEK293 cells.

[0552] Transfectants were isolated from supernatants by CaptureSelect IgG-CH1 chromatography. Purified proteins were respectively analyzed for uniformity, purity, and quantity by SEC-HPLC, SDS-PAGE and UV spectrophotometric analysis.

Example 14-Binding of cMet/EGFr/ErbB2/ErbB3 tetraspecific antibody

[0553] Test articles were prepared according to example 13 were tested for binding to target antigen by ELISA.

[0554] EGFr ELISA- Human EGFr was used to coat plates at 1 µg/mL. The products were diluted in blocking buffer at a starting concentration indicated in corresponding figures and then 1:3 dilutions were tested. Binding to target was detected by 1:10,000 dilution of CaptureSelect™ Biotin Anti-IgG-CH1 Conjugate (ThermoFisher, Cat #7103202500) followed by 1:5,000 dilution of HRP-conjugated streptavidin. As illustrated in **FIG. 15**, the cMet/EGFr/ErbB2/ErbB3 tetraspecific antibody binds to EGFr with EC50 value around 0.33nM.

[0555] **ErbB2 ELISA**- Human ErbB2 was used to coat plates at 1 µg/mL. The products were diluted in blocking buffer at a starting concentration indicated in corresponding figures and then 1:3 dilutions were tested. Binding to target was detected by 1:10,000 dilution of CaptureSelect™ Biotin Anti-IgG-CH1 Conjugate (ThermoFisher, Cat #7103202500) followed by 1:5,000 dilution of HRP-conjugated streptavidin. As illustrated in **FIG. 15**, the cMet/EGFr/ErbB2/ErbB3 tetraspecific antibody binds to ErbB2 with EC50 value around 50.8pM.

[0556] **ErbB3 ELISA**- Human ErbB3 was used to coat plates at 1 µg/mL. The products were diluted in blocking buffer at a starting concentration indicated in corresponding figures and then 1:3 dilutions were tested. Binding to target was detected by 1:10,000 dilution of CaptureSelect™ Biotin Anti-IgG-CH1 Conjugate (ThermoFisher, Cat #7103202500) followed by 1:5,000 dilution of HRP-conjugated streptavidin. As illustrated in **FIG. 15**, the cMet/EGFr/ErbB2/ErbB3 tetraspecific antibody binds to ErbB3 with EC50 value around 2.78nM.

[0557] **c-Met ELISA**- Human c-Met (Acro Biosystems) was used to coat plates at 1 µg/mL. The products were diluted in blocking buffer at a starting concentration indicated in corresponding figures and then 1:3 dilutions were tested. Binding to target was detected by 1:10,000 dilution of CaptureSelect™ Biotin Anti-IgG-CH1 Conjugate (ThermoFisher, Cat #7103202500) followed by 1:5,000 dilution of HRP-conjugated streptavidin. As illustrated in **FIG. 15**, the cMet/EGFr/ErbB2/ErbB3 tetraspecific antibody binds to c-Met with EC50 value around 0.21nM.

Example 15-Production of EGFr/ErbB2/ErbB3/cMet surrobody cross domain tetraspecific

[0558] Nucleic acid sequences encoding sequences corresponding to SEQ ID NO: 308, SEQ ID NO: 309 and SEQ ID NO: 132 are cloned into plasmid vectors to direct eukaryotic cell expression. Protein expression vectors were co-transfected into HEK293 cells.

[0559] Transfectants are isolated from supernatants by CaptureSelect IgG-CH1 chromatography. Purified proteins are respectively analyzed for uniformity, purity, and quantity by SEC-HPLC, SDS-PAGE and UV spectrophotometric analysis.

Example 16-Binding of EGFr/ErbB2/ErbB3/cMet surrobody cross domain tetraspecific

[0560] Test articles prepared according to example 15 are tested for binding to target antigen by ELISA.

[0561] **EGFr ELISA**- Human EGFr is used to coat plates at 1 µg/mL. The products are diluted in blocking buffer at a starting concentration and then 1:3 dilutions are tested. Binding to target is detected by 1:10,000 dilution of CaptureSelect™ Biotin Anti-IgG-CH1 Conjugate (ThermoFisher, Cat #7103202500) followed by 1:5,000 dilution of HRP-conjugated streptavidin.

[0562] ErbB2 ELISA- Human ErbB2 is used to coat plates at 1 µg/mL. The products are diluted in blocking buffer at a starting concentration and then 1:3 dilutions are tested. Binding to target is detected by 1:10,000 dilution of CaptureSelect™ Biotin Anti-IgG-CH1 Conjugate

(ThermoFisher, Cat #7103202500) followed by 1:5,000 dilution of HRP-conjugated streptavidin.

[0563] ErbB3 ELISA- Human ErbB3 is used to coat plates at 1 µg/mL. The products are diluted in blocking buffer at a starting concentration and then 1:3 dilutions are tested. Binding to target is detected by 1:10,000 dilution of CaptureSelect™ Biotin Anti-IgG-CH1 Conjugate

(ThermoFisher, Cat #7103202500) followed by 1:5,000 dilution of HRP-conjugated streptavidin.

c-Met ELISA- Human c-Met is used to coat plates at 1 µg/mL. The products are diluted in blocking buffer at a starting concentration and then 1:3 dilutions are tested. Binding to target is detected by 1:10,000 dilution of CaptureSelect™ Biotin Anti-IgG-CH1 Conjugate (ThermoFisher, Cat #7103202500) followed by 1:5,000 dilution of HRP-conjugated streptavidin.

Example 17-Production of EGFr/ErbB2/ErbB3/cMet antibody cross domain tetraspecific

[0564] Nucleic acid sequences encoding sequences corresponding to SEQ ID NO: 310, SEQ ID NO: 311, and SEQ ID NO: 102 are cloned into plasmid vectors to direct eukaryotic cell expression. Protein expression vectors were co-transfected into HEK293 cells.

[0565] Transfectants are isolated from supernatants by CaptureSelect IgG-CH1 chromatography. Purified proteins were respectively analyzed for uniformity, purity, and quantity by SEC-HPLC, SDS-PAGE and UV spectrophotometric analysis.

Example 18-Binding of EGFr/ErbB2/ErbB3/cMet antibody cross domain tetraspecific

[0566] Test articles prepared according to example 17 are tested for binding to target antigen by ELISA

[0567] EGFr ELISA- Human EGFr is used to coat plates at 1 µg/mL. The products are diluted in blocking buffer at a starting concentration and then 1:3 dilutions are tested. Binding to target is detected by 1:10,000 dilution of CaptureSelect™ Biotin Anti-IgG-CH1 Conjugate

(ThermoFisher, Cat #7103202500) followed by 1:5,000 dilution of HRP-conjugated streptavidin.

[0568] ErbB2 ELISA- Human ErbB2 is used to coat plates at 1 µg/mL. The products are diluted in blocking buffer at a starting concentration and then 1:3 dilutions are tested. Binding to target is detected by 1:10,000 dilution of CaptureSelect™ Biotin Anti-IgG-CH1 Conjugate

(ThermoFisher, Cat #7103202500) followed by 1:5,000 dilution of HRP-conjugated streptavidin.

[0569] ErbB3 ELISA- Human ErbB3 is used to coat plates at 1 µg/mL. The products are diluted in blocking buffer at a starting concentration and then 1:3 dilutions are tested. Binding to target is

detected by 1:10,000 dilution of CaptureSelect™ Biotin Anti-IgG-CH1 Conjugate (ThermoFisher, Cat #7103202500) followed by 1:5,000 dilution of HRP-conjugated streptavidin.

[0570] c-Met ELISA- Human c-Met is used to coat plates at 1 µg/mL. The products are diluted in blocking buffer at a starting concentration and then 1:3 dilutions are tested. Binding to target is detected by 1:10,000 dilution of CaptureSelect™ Biotin Anti-IgG-CH1 Conjugate (ThermoFisher, Cat #7103202500) followed by 1:5,000 dilution of HRP-conjugated streptavidin.

Example 19-Production of anti-PD-1 trivalent and tetravalent antibodies

[0571] Nucleic acid sequences encoding sequences corresponding to SEQ ID NO: 305 and SEQ ID NO: 307 were cloned into plasmid vectors to direct eukaryotic cell expression. Protein expression vectors were co-transfected into HEK293 cells.

[0572] HEK293 Freestyle cells were cultured in Hyclone SFM4Transfx-293 media supplemented with 4mM Glutamine. Cells were incubated in a shaking incubator to densities between 0.25e6 – 2.0e6 cells/mL. Proper inoculation was performed to produce cells between 1e6 – 1.5e6/mL for day of transfection.

[0573] For transfection DNA-PEI complexes for transfection were prepared according to standard practices. Plasmids were mixed in equal amounts for a total of 125 mcg into 6 mL media. Separately 6mL of media was combined with 0.25mg PEI solution (Polyethylenimine - linear, 25 kDa, Polysciences #23966, prepared as stock 1mg/mL). The PEI and DNA solutions were then mixed and incubated at room temperature for 15 minutes. After incubation the complexes were added to cells that were then returned to grow in shake incubator. The next day the transfected cells were supplemented by the addition of 3.1 mL of 20% stock tryptone solution (final concentration 0.5%). Protein harvest from cell supernatants were typically performed at day 6.

[0574] Transfectants were isolated from supernatants by Protein A or CaptureSelect IgG-CH1 chromatography. Purified proteins were respectively analyzed for uniformity, purity, and quantity by SEC-HPLC, SDS-PAGE and UV spectrophotometric analysis.

Example 20-Binding of anti-PD-1 trivalent and tetravalent antibodies

[0575] Test articles were prepared according to example 19 were tested for binding to target antigen by ELISA. The structures of the anti-PD-1 trivalent antibody and tetravalent antibody are shown in **FIGs. 16A** and **16B**.

[0576] PD-1 ELISA- Human PD-1 (Acro Biosystems) was used to coat plates at 1 µg/mL. The products were diluted in blocking buffer at a starting concentration of 10nM and then 1:3 dilutions were tested. Binding to target was detected by 1:10,000 dilution of CaptureSelect™

Biotin Anti-IgG-CH1 Conjugate (ThermoFisher, Cat #7103202500) followed by 1:5,000 dilution of HRP-conjugated streptavidin. As illustrated in **FIG. 17**, the results showed that both trivalent antibody and tetravalent bind to PD-1 much stronger than the anti-PD-1 Nivolumab Fab binding domain. The EC₅₀ of anti-PD-1 trivalent antibody was 90.6pM and the EC₅₀ of anti-PD-1 tetravalent antibody was 59.1pM, whereas the EC₅₀ of anti-PD-1 Fab domain was 0.53nM.

Example 21-Production of VEGF-A/ANG-2/VEGF-C trispecific antigen binding polypeptides RP-010 and RP-015

[0577] Nucleic acid sequences encoding polypeptides corresponding to SEQ ID NO: 402, SEQ ID NO: 403, and SEQ ID NO: 102 were cloned into plasmid vectors to direct eukaryotic cell expression of RP-015. Nucleic acid sequences encoding polypeptides corresponding to SEQ ID NO: 404, SEQ ID NO: 405, and SEQ ID NO: 102 were cloned into plasmid vectors to direct eukaryotic cell expression of RP-010. Protein expression vectors were co-transfected into HEK293 cells.

[0578] Transfectants were isolated from supernatants by Protein A chromatography. Purified proteins were respectively analyzed for uniformity, purity, and quantity by SEC-HPLC, SDS-PAGE and UV spectrophotometric analysis.

[0579] For SDS-PAGE analysis, reduced and non-reduced samples of the RP-010 and RP-015 were electrophoresed. As shown in **FIG. 18A**, under non-reducing conditions, multiple protein bands corresponding to RP-010 (~226 kDa) were seen. Under reducing conditions, bands corresponding to the molecular weight of light chain (~23 kDa) and heavy chains (~74 kDa) were observed. As shown in **FIG. 18C**, under non-reducing conditions, multiple protein bands corresponding to RP-015 (~285 kDa) were seen. Under reducing conditions, bands corresponding to the molecular weight of light chain (~27 kDa) and heavy chains (~76 kDa) were observed.

[0580] The purified proteins were also analyzed in SE-HPLC. Only ~60% of the purified proteins for RP-010 showed at the expected main peak, indicating ~60% purity of RP-010 (see **FIG. 18B**). On the contrary, 99.5% of the purified proteins for RP-015 showed at the expected main peak, indicating ~99.5% purify of RP-015 (see **Fig. 18D**). The results suggest that the production method can achieve high purity of RP-015 with only one purification step.

Example 22-Binding of RP-015 VEGF-A/ ANG-2/ VEGF-C trispecific antigen polypeptide

[0581] Trispecific antigen polypeptides RP-015 prepared according to example 21 were tested for their binding affinity to target antigen.

[0582] VEGF-A ELISA- Recombinant human VEGF-A (PeproTech, Cat #100-20) was used to coat plates at 1 µg/mL. The products were diluted in blocking buffer at a starting concentration of 10 nM and then 1:3 serial dilutions were tested. The binding was detected by biotinylated anti-VpreB antibody and HRP-conjugated streptavidin. OD450 nm readings were measured by Victor 3 (PerkinElmer 1420 Multilabel Counter). As illustrated in **FIG. 19A**, the binding of RP-015 is similar to RO-104 with an EC₅₀ of ~5.1 picomolar.

[0583] ANG-2 ELISA Recombinant human ANG-2 (Acro Biosystems, Cat #AN2-H52H4) was used to coat plates at 1 µg/mL. The products were diluted in blocking buffer at a starting concentration of 10 nM and then 1:3 serial dilutions were tested. The binding was detected by biotinylated anti-VpreB antibody and HRP-conjugated streptavidin. OD450 nm readings were measured by Victor 3 (PerkinElmer 1420 Multilabel Counter). As illustrated in **FIG. 19B**, RP-015 binds to ANG-2 with an EC₅₀ of 22.7 picomolar.

[0584] VEGF-C ELISA Recombinant human VEGF-C (PeproTech, Cat#100-20CD) was used to coat plates at 1 µg/mL. The products were diluted in blocking buffer at a starting concentration of 10 nM and then 1:3 serial dilutions were tested. The binding was detected by biotinylated anti-VpreB antibody and HRP-conjugated streptavidin. OD450 nm readings were measured by Victor 3 (PerkinElmer 1420 Multilabel Counter). As illustrated in **FIG. 19C**, RP-015 binds to VEGF-C with an EC₅₀ of ~5.8pM.

[0585] Therefore, the tested trispecific RP-015 multispecific binding polypeptides showed a similar affinity to VEGF-A, ANG-2, and VEGF-C as RO-104.

Example 23-Production of VEGF-A/ANG-2 bispecific multispecific antigen binding polypeptides RP-028 and RP-029

[0586] Nucleic acid sequences encoding polypeptides corresponding to SEQ ID NO: 406 and SEQ ID NO: 102 were cloned into plasmid vectors to direct eukaryotic cell expression of RP-028. Nucleic acid sequences encoding polypeptides corresponding to SEQ ID NO: 401 and SEQ ID NO: 102 were cloned into plasmid vectors to direct eukaryotic cell expression of RP-029. Protein expression vectors were co-transfected into HEK293 cells.

[0587] Transfectants were isolated from supernatants by Protein A chromatography for RP-028. Transfectants were isolated from supernatants by CaptureSelect IgG-CH1 chromatography for RP-029. Purified proteins were respectively analyzed for uniformity, purity, and quantity by SEC-HPLC, SDS-PAGE and UV spectrophotometric analysis.

[0588] For SDS-PAGE analysis, reduced and non-reduced samples of the RP-028 and RP-029 were electrophoresed. As shown in **FIG. 20A**, under non-reducing conditions, multiple protein bands corresponding to RP-028 (~219 kDa) were seen. Under reducing conditions, bands

corresponding to the molecular weight of light chain (~26 kDa) and heavy chains (~73 kDa) were observed. As shown in **FIG. 20C**, under non-reducing conditions, multiple protein bands corresponding to RP-029 (~97 kDa) were seen. Under reducing conditions, bands corresponding to the molecular weight of light chain (~26 kDa) and heavy chains (~42 kDa) were observed.

[0589] The purified proteins were also analyzed in SE-HPLC. About ~100% of the purified proteins for RP-028 showed at the expected main peak, indicating ~100% purity of RP-028 after a single step of purification (*see FIG. 20B*). Similarly, 97.4% of the purified proteins for RP-029 showed at the expected main peak, indicating ~97.4% purify of RP-029 (*see Fig. 20D*).

Example 24-Binding of RP-028 and RP-029 VEGF-A/ ANG-2 bispecific antigen polypeptide

[0590] Bispecific antigen polypeptides RP-028 and RP-029 prepared according to example 23 were tested for their binding affinity to target antigen.

[0591] VEGF-A ELISA- Recombinant human VEGF-A (PeproTech, Cat #100-20) was used to coat plates at 1 µg/mL. The products were diluted in blocking buffer at a starting concentration of 10 nM and then 1:3 serial dilutions were tested. The binding was detected by biotinylated anti-VpreB antibody and HRP-conjugated streptavidin. OD450 nm readings were measured by Victor 3 (PerkinElmer 1420 Multilabel Counter). As illustrated in **FIG. 21A**, the binding of RP-028 has an EC₅₀ of ~4.6 picomolar and the binding of RP-029 has an EC₅₀ of ~7.7 picomolar.

[0592] ANG-2 ELISA Recombinant human ANG-2 (Acro Biosystems, Cat #AN2-H52H4) was used to coat plates at 1 µg/mL. The products were diluted in blocking buffer at a starting concentration of 10 nM and then 1:3 serial dilutions were tested. The binding was detected by biotinylated anti-VpreB antibody and HRP-conjugated streptavidin. OD450 nm readings were measured by Victor 3 (PerkinElmer 1420 Multilabel Counter). As illustrated in **FIG. 21B**, the binding of RP-028 has an EC₅₀ of ~5.8 picomolar and the binding of RP-029 has an EC₅₀ of ~29.7 picomolar.

Example 25-The half maximal inhibitory concentration (IC₅₀) of RP-028 and RP-029 VEGF-A/ ANG-2 bispecific antigen polypeptide for target-receptor binding

[0593] Bispecific antigen polypeptides RP-028 and RP-029 prepared according to example 23 were tested for their IC₅₀ of binding to target antigen. Inhibition of single target and receptor interaction binding ELISA was done using faricimab as the competitor, respectively.

[0594] VEGF-A inhibition ELISA- The bispecific RP-028 and RP-029 were diluted in blocking buffer at a starting concentration of 100 nM and then 1:3 serial dilutions were tested. This 2x bispecific antigen polypeptides dilutions were mixed with 2x biotinylated VEGF R2/KDR receptor (Acro Biosystems, Cat # VE5-H82Q0). Then 1x mixtures of bispecific antigen

polypeptides and biotinylated VEGF R2/KDR were added to plate wells. The binding was detected through a biotinylated receptor VEGF R2/KDR and 1:5,000 dilution of HRP-conjugated streptavidin (Jackson ImmunoResearch Lab, Cat #016-030-084). Faricimab was run as an inhibitor using the same protocol. OD450 nm readings were measured by Victor 3 (PerkinElmer 1420 Multilabel Counter). As illustrated in **FIG. 22A**, IC₅₀ of RP-028 was 8.97nM, which was 3-fold lower compared to faricimab. As illustrated in **FIG. 22C**, IC₅₀ of RP-029 was 11.14nM, which was 2.34-fold lower compared to faricimab.

[0595] ANG-2 inhibition ELISA- Recombinant human ANG-2 (Acro Biosystems, Cat #AN2-H52H4) was used to coat plates at 1 µg/mL. The bispecific antigen polypeptides were diluted in blocking buffer at a starting concentration of 100nM and then 1:3 serial dilutions were tested. This 2x bispecific antigen polypeptide dilutions were mixed with 2x biotinylated Tie2 receptor (R&D Systems, Cat #AVI10727). Then 1x mixtures of bispecific antigen polypeptide and biotinylated Tie2 were added to plate wells. The binding was detected through a biotinylated receptor Tie2 and 1:5,000 dilution of HRP-conjugated streptavidin (Jackson ImmunoResearch Lab, Cat #016-030-084). Faricimab was run as an inhibitor using the same protocol. OD450 nm readings were measured by Victor 3 (PerkinElmer 1420 Multilabel Counter). As illustrated in **FIG. 22B**, IC₅₀ of RP-028 was 1.84nM, which was 82.8-fold lower compared to faricimab. As illustrated in **FIG. 22D**, IC₅₀ of RP-029 was 4.01nM, which was 9.59-fold lower compared to faricimab.

[0596] Overall, the results showed that RO-104 demonstrated improved IC₅₀ in single target-receptor and tri-specific target-receptor binding for the VEGF-C and ANG-2 arms as compared to faricimab with no notable differences in VEGF-A.

Example 26-exemplary multispecific antigen binding polypeptide sequences

[0597] Exemplary sequences of the multispecific antigen binding polypeptides and its components are listed in Table 6.

Table 6: Exemplary sequences of the multispecific antigen binding polypeptides and its components

SEQ ID NO.	Sequence	Construct
1	QVQLVQSGAEVKKPGASVKVSCKASGYTFSIYTIHWVR QAPGQGLEWMGGINPYNGNTKYAQKFQGRVTMTRDT SISTAYMELSRLRSDDTAVYYCAKAPAVFWWTGLDYW GQGTLLTVSS	anti-VEGFA-VH

2	QVQLVQSGAEVKKPGASVKVSCKASGYTFSIYTIHWVR QAPGQGLEWMGGINPYNGNTKYAQKFQGRVTMTRDT SISTAYMELSRLSDDTAVYYCAKAPAVFWWTGLDYW GQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLV KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSV VTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC	anti-VEGFA- HC
3	SIYTIH	anti-VEGFA- CDR1
4	WMGGINPYNGNTK	anti-VEGFA- CDR2
5	AKAPAVFWWTGLD	anti-VEGFA- CDR3
11	EVQLVESGGGLVKPGGSLRLSCAASGFTFSSYGMHWV RQAPGKGLEWVAGISADSGDKNYADSVKGRFTISRDN AKNSLYLQMNSLRAEDTAVYYCAKEFISWIYTFDYLDY WGQGTLLTVSS	anti-ANG-2- VH
12	EVQLVESGGGLVKPGGSLRLSCAASGFTFSSYGMHWV RQAPGKGLEWVAGISADSGDKNYADSVKGRFTISRDN AKNSLYLQMNSLRAEDTAVYYCAKEFISWIYTFDYLDY WGQGTLLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCL VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSS VTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC	anti-ANG-2-HC
13	SSYGMH	anti-ANG-2- CDR1
14	WVAGISADSGDKN	anti-ANG-2- CDR1
15	AKEFISWIYTFDYLD	anti-ANG-2- CDR1
21	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYGMWSVR QAPGKGLEWVARINGDGGYKNYADSVKGRFTISRDN KNTLYLQMNSLRAEDTAVYYCARELWAFINDSFGLD YWGQGTLLTVSS	anti-VEGFC- VH
22	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYGMWSVR QAPGKGLEWVARINGDGGYKNYADSVKGRFTISRDN KNTLYLQMNSLRAEDTAVYYCARELWAFINDSFGLD YWGQGTLLTVSSASTKGPSVFPLAPSSKSTSGGTAALG CLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYS LSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC	anti-VEGFC- HC
23	SSYGMS	anti-VEGFC- CDR1
24	WVARINGDGGYKN	anti-VEGFC- CDR2
25	ARELWAFINDSFGLD	anti-VEGFC- CDR3
101	QPVLHQPPAMSSALGTTIRLTCTLRNDHDIGVYSVYWY QQRPGHPPRFLRLRYFSQSDKSQGPQVPPRFSGSKDVARN RGYLSISELQPEDEAMYYCAMGARSSVTHVFGSGTQLT VL	VpreB

102	QPVLHQPPAMSSALGTTIRLTCTLRNDHDIGVYSVYWY QQRPGHPPRFLRLRYFSQSDKSQGPQVPPRFSGSKDVARN RGYLSISELQPEDEAMYYCAMGARSSVTHVFGSGTQLT VLSQPKATPSVTLFPPSSEELQANKATLVCLMNDFYPGI LTVTWKADGTPITQGVEMTTTPSKQSNNKYAASSYLSLT PEQWRSRRSYSCQVMHEGSTVEKTVAPAECS	SLC-Fus1
103	NDHDIGVYS	SLC-Fus1 CDR1
104	YFSQSDK	SLC-Fus1 CDR2
105	AMGARSSVTH	SLC-Fus1 CDR3
106	SQPKATPSVTLFPPSSEELQANKATLVCLMNDFYPGILT VTWKADGTPITQGVEMTTTPSKQSNNKYAASSYLSLTPE QWRSRRSYSCQVMHEGSTVEKTVAPAECS	
111	DIQLTQSPSSLSASVGDRVTITCSASQDISNYLNWYQQK PGKAPKVLIYFTSSLHSGVPSRFSGSGSGTDFTLTISLQP EDFATYYCQQYSTVPWTFGQGTKVEIK	Fab_Vk-CH1- X_LC-VH
112	DIQLTQSPSSLSASVGDRVTITCSASQDISNYLNWYQQK PGKAPKVLIYFTSSLHSGVPSRFSGSGSGTDFTLTISLQP EDFATYYCQQYSTVPWTFGQGTKVEIKSSASTKGPSVF LAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTS GVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNH KPSNTKVDKKVEPKSC	Fab_Vk-CH1- X_LC-VH full
121	DIQLTQSPSSLSASVGDRVTITCSASQDISNYLNWYQQK PGKAPKVLIYFTSSLHSGVPSRFSGSGSGTDFTLTISLQP EDFATYYCQQYSTVPWTFGQGTKVEIK	VA-Fab_LC- VH
122	DIQLTQSPSSLSASVGDRVTITCSASQDISNYLNWYQQK PGKAPKVLIYFTSSLHSGVPSRFSGSGSGTDFTLTISLQP EDFATYYCQQYSTVPWTFGQGTKVEIKRTVAAPSVFIFP PSDEQLKSGTASVCLLNNFYPREAKVQWKVDNALQS GNSQESVTEQDSKDYSLSTLTLSKADYEEKHKVYAC EVTHQGLSSPVTKSFNRGEC	VA-Fab_LC- Full
131	QPVLHQPPAMSSALGTTIRLTCTLRNDHDIGVYSVYWY QQRPGHPPRFLRLRYFSQSDKSQGPQVPPRFSGSKDVARN RGYLSISELQPEDEAMYYCAMGARSSVTHVFGSGTQLT VL	VpreB-CH1- swap-VH
132	QPVLHQPPAMSSALGTTIRLTCTLRNDHDIGVYSVYWY QQRPGHPPRFLRLRYFSQSDKSQGPQVPPRFSGSKDVARN RGYLSISELQPEDEAMYYCAMGARSSVTHVFGSGTQLT VLSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPE PVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSS SLGTQTYICNVNHKPSNTKVDKKVEPKSC	VpreB-CH1- swap-full
141	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGT QTYICNVNHKPSNTKVDKKVEPKSC	CH1
151	GGGGS	linker

201	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYGMSWVR QAPGKGLEWVARINGDGGYKNYADSVKGRFTISRDN KNTLYLQMNSLRAEDTAVYYCARELWAFINDFSFGLD YWGQGTLLTVSSASTKGPSVFPLAPSSKSTSGGTAALG CLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYS LSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC QVQLVQSGAEVKKPGASVKVSCKASGYTFSIYTIHWVR QAPGQGLEWMGGINPYNGNTKYAQKFQGRVTMTRDT SISTAYMELSRLRSDDTAVYYCAKAPAVFWWTGLDYW GQGTLLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLV KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSV VTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCEVQ LVESGGGLVKPGGSLRLSCAASGFTFSSYGMHWVRQAP GKGLEWVAGISADSGDKNYADSVKGRFTISRDNKNSL YLQMNSLRAEDTAVYYCAKEFISWIYTFDYLDYWGQG TLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDY FPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTV PSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC	Trispecific VC- VA-A2_HC (RP-018)
202	QVQLVQSGAEVKKPGASVKVSCKASGYTFSIYTIHWVR QAPGQGLEWMGGINPYNGNTKYAQKFQGRVTMTRDT SISTAYMELSRLRSDDTAVYYCAKAPAVFWWTGLDYW GQGTLLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLV KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSV VTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCEVQ LVESGGGLVKPGGSLRLSCAASGFTFSSYGMHWVRQAP GKGLEWVAGISADSGDKNYADSVKGRFTISRDNKNSL YLQMNSLRAEDTAVYYCAKEFISWIYTFDYLDYWGQG TLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDY FPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTV PSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCEVQLLES GGGLVQPGGSLRLSCAASGFTFSSYGMSWVRQAPGKG LEWVARINGDGGYKNYADSVKGRFTISRDNKNTLYL QMNSLRAEDTAVYYCARELWAFINDFSFGLDYWGQGT LTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYF PEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTV SSSLGTQTYICNVNHKPSNTKVDKKVEPKSC	Trispecific VA- Ang2-VC_HC (RP-019)

203	EVQLVESGGGLVKPGGSLRLSCAASGFTFSSYGMHWV RQAPGKGLEWVAGISADSGDKNYADSVKGRFTISRDN AKNSLYLQMNSLRAEDTAVYYCAKEFISWIYTFDYLDY WGQGTLLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCL VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSS VVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCEV QLLES GGGLVQPGGSLRLSCAASGFTFSSYGMSWVRQA PGKGLEWVARINGDGGYKNYADSVKGRFTISRDN SKN TLYLQMNSLRAEDTAVYYCARELWAFINDFSFGLDYW GQGTLLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLV KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSV VTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCQVQ LVQSGAEVKKPGASVKVSCKASGYTFSIYTIHWVRQAP GQGLEWMGGINPYNGNTKYAQKFQGRVTMTRDTSIST AYMELSRLRSDDTAVYYCAKAPAVFWWTGLDYWGQG TLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDY FPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTV PSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC	Trispecific Ang2-VC- VA_HC (RP- 020)
204	EVQLVESGGGLVQPGGSLRLSCAASGYDFTHYGMNHWV RQAPGKGLEWVGWINTYTGEPTYAADFKRRFTFSLDTS KSTAYLQMNSLRAEDTAVYYCAKYPYYYGTSHWYFD VWGQGTLLTVSSASVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDS TYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSF NRGECEVQLVESGGGLVKPGGSLRLSCAASGFTFSSYG MHWVRQAPGKGLEWVAGISADSGDKNYADSVKGRFTI SRDNAKNSLYLQMNSLRAEDTAVYYCAKEFISWIYTFD YLDYWGQGTLLTVSSASTKGPSVFPLAPSSKSTSGGTA ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSG LYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEP KSCEVQLLES GGGLVQPGGSLRLSCAASGFTFSSYGMS WVRQAPGKGLEWVARINGDGGYKNYADSVKGRFTISR DNSKNTLYLQMNSLRAEDTAVYYCARELWAFINDFSF GLDYWGQGTLLTVSSASTKGPSVFPLAPSSKSTSGGTA ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSG LYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEP KSC	Trispecific VA-Vh-Ck- Ang2-VC_HC

205	EVQLVESGGGLVQPGGSLRLSCAASGYDFTHYGMNWV RQAPGKGLEWVGWINTYTGEPTYAADFKRRFTFSLDTS KSTAYLQMNSLRAEDTAVYYCAKYPYYYGTSHWYFD VWGQGTLLTVSSASTKGPSVFPLAPSSKSTSGGTAALG CLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYS LSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC EVQLVESGGGLVKPGGSLRLSCAASGFTFSSYGMHWV RQAPGKGLEWVAGISADSGDKNYADSVKGRFTISRDN AKNSLYLQMNSLRAEDTAVYYCAKEFISWIYTFDYLDY WGQGTLLTVSSASKATPSVTLFPPSSEELQANKATLVCL MNDFYPGILTVTWKADGTPITQGVEMTTPSKQSNKYA ASSYLSLTPEQWRSRRSYSCQVMHEGSTVEKTVAPAEC SEVQLLESGGGLVQPGGSLRLSCAASGFTFSSYGMHWV RQAPGKGLEWVARINGDGGYKNYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARELWAFINDSFGLD YWGQGTLLTVSSASKATPSVTLFPPSSEELQANKATLV CLMNDFYPGILTVTWKADGTPITQGVEMTTPSKQSNK YAASSYLSLTPEQWRSRRSYSCQVMHEGSTVEKTVAPA ECS	Trispecific VA_Fab-Ang2- VC_L5- CH1_swap-HC
301	EVQLLESGGGLVQPGGSLRLSCAASGFTFSNYWMHWV RQAPGKGLEWVALISGGGGNTYYADSVKGRFTISRDN KNTLYLQMNSLRAEDTAVYYCAKDNEKNLYTWLDYW GQGTLLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLV KDYFPEPVITVSWNSGALTSGVHTFPAVLQSSGLYSLSS VVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCQV QLVQSGAEVKKPGASVKVSCKASGYTFSIYTIHWVRQA PGQGLEWMGGINPYNGNTKYAQKFQGRVTMTRDTSIS TAYMELSRLRSDDTAVYYCAKAPAVFWWTGLDYWGQ GTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKD YFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT VPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCEVQLV ESGGGLVKPGGSLRLSCAASGFTFSSYGMHWVRQAPG KGLEWVAGISADSGDKNYADSVKGRFTISRDNKNSLY LQMNSLRAEDTAVYYCAKEFISWIYTFDYLDYWGQGT LTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYF PEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVP SSSLGTQTYICNVNHKPSNTKVDKKVEPKSCEVQLLES GGGLVQPGGSLRLSCAASGFTFSSYGMHWVRQAPGKGLE WVARINGDGGYKNYADSVKGRFTISRDNKNTLYLQM NSLRAEDTAVYYCARELWAFINDSFGLDYWGQGTLLV TVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPE PVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSS SLGTQTYICNVNHKPSNTKVDKKVEPKSC	ErbB3-VA- Ang2- VC_tetraspecifi c_Sab

302	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYGISWV RQAPGQGLEWMGWISAYNANTNYAQKLQGRVTMTTD TSTSTAYMELRSLRSDDTAVYYCAKDRHWHWWLDAF DYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAAL GCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLY SLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKS CQVQLVQSGAEVKKPGASVKVSCKASGYTFTGYMH WVRQAPGQGLEWMGWINPNSGGTNYAQKFQGRVTMT RDTSTAYMELRSLRSDDTAVYYCARDHGSRHFWSY WGFDYWQGTLVTVSSASTKGPSVFPLAPSSKSTSGGT AALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVE PKSCQVQLVQSGAEVKKPGASVKLSCKASGYTFTAYYI NWVRQAPGQGLEWIGRIYPGSGYTSYAQKFQGRATLT ADESTSTAYMELSSLRSEDVAVYFCARPPVYYDSAWFA YWQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALG CLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYS LSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC	EGFR-ErbB2- ErbB3_Trispeci fic_Fab-HC
303	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQK PGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISLQP EDFATYYCQQSYSTPPTFGQGTKVEIKRTVAAPSVFIFPP SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSG NSQESVTEQDSKSTYLSSTLTLSKADYEKHKVYACE VTHQGLSPVTKSFNRGEC	Common Light Chain
304	QVQLVQSGSELKKPGASVKVSCKASGYTFTTYSMNWV RQAPGQGLEWMGWINTYTGDPTYAQGFTGRFVFSLDT SVSTAYLQISSLKAEDTAVYYCARETYFYDRGGYPFDPW GQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLV KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSV VTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCQVQ LVQSGAEVKKPGASVKVSCKASGYTFTSYGISWVRQAP GQGLEWMGWISAYNANTNYAQKLQGRVTMTTDTSTST AYMELRSLRSDDTAVYYCAKDRHWHWWLDAFDYW QGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLV DYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSV VTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCQVQ LVQSGAEVKKPGASVKVSCKASGYTFTGYMHWVRQA PGQGLEWMGWINPNSGGTNYAQKFQGRVTMTTRDTSIS TAYMELRSLRSDDTAVYYCARDHGSRHFWSYWGFDYW GQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLV KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSV VTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCQVQ LVQSGAEVKKPGASVKLSCKASGYTFTAYYINWVRQAP GQGLEWIGRIYPGSGYTSYAQKFQGRATLTADESTSTAY MELSSLRSEDVAVYFCARPPVYYDSAWFAYWGQGTTLT VSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEP VTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSS LGTQTYICNVNHKPSNTKVDKKVEPKSC	cMet-EGFR- ErbB2- ErbB3_Tetraspe cific Fab

305	QVQLVESGGGVVQPGRSLRLDCKASGITFSNSGMHWV RQAPGKGLEWVAVIWIYDGSKRYYADSVKGRFTISRDN KNTLFLQMNSLRAEDTAVYYCATNDDYWGGQGLTVTS SASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLG TQTYICNVNHKPSNTKVDKKVEPKSCQVQLVESGGGV VQPGRSLRLDCKASGITFSNSGMHWVRQAPGKGLEWV AVIWIYDGSKRYYADSVKGRFTISRDNKNTLFLQMNSL RAEDTAVYYCATNDDYWGGQGLTVTVSSASTKGPSVFPL APSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSG VHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHK PSNTKVDKKVEPKSCQVQLVESGGGVVQPGRSLRLDCK ASGITFSNSGMHWVRQAPGKGLEWVAVIWIYDGSKRYY ADSVKGRFTISRDNKNTLFLQMNSLRAEDTAVYYCAT NDDYWGGQGLTVTVSSASTKGPSVFPLAPSSKSTSGGTA ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGL YSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPK SC	anti-PD-1-VH- G1CH1 cross fabX3
306	QVQLVESGGGVVQPGRSLRLDCKASGITFSNSGMHWV RQAPGKGLEWVAVIWIYDGSKRYYADSVKGRFTISRDN KNTLFLQMNSLRAEDTAVYYCATNDDYWGGQGLTVTS SASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLG TQTYICNVNHKPSNTKVDKKVEPKSCQVQLVESGGGV VQPGRSLRLDCKASGITFSNSGMHWVRQAPGKGLEWV AVIWIYDGSKRYYADSVKGRFTISRDNKNTLFLQMNSL RAEDTAVYYCATNDDYWGGQGLTVTVSSASTKGPSVFPL APSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSG VHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHK PSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPP KPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGV EVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEY KCKVSNKALPAPIEKISKAKGQPREPQVYTLPPSRDEL TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPV LDSGDSFFLYSKLTVDKSRWQQGNVSCFVSVMHEALHNH YTQKSLSLSPG	anti-PD-1-VH- G1CH1- NivoVH-IgG1
307	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQK PQQAPRLLIYDASNRATGIPARFSGSGTDFTLTISLEPE DFAVYYCQQSSNWPRFTGQGTKVEIKRTVAAPSVFIFPP SDEQLKSGTASVCLLNNFYPREAKVQWKVDNALQSGN SQESVTEQDSKSTYSLSSLTLSKADYEKHKVYACEVT HQGLSSPVTKSFNRGEC	anti-PD-1- Vk_Ck
308	QVQLVQSGAEVKKPGASVKLSCKASGYTFTAYYINWVR QAPGQGLEWIGRIYPGSGYTSYAQKFQGRATLTADSTS TAYMELSSLRSEDVAVYFCARPPVYYDSAWFAYWGQGT LTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDY FPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT VPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCEVQLLE SGGGLVQPGGSLRLSCAASGFTFSNYWMHWVRQAPGKGL EWVALISGGGGNTYYADSVKGRFTISRDNKNTLYLQM NSLRAEDTAVYYCAKDNEKNLYTWLDYWGGQGLTVTS	Tetraspecific ErbB2-ErbB3- Vh-L5-EGFR- C-Met_HC

	SASKATPSVTLFPPSSEELQANKATLVCLMNDFYPGILTV TWKADGTPITQGVEMTTTPSKQSNNKYAASSYLSLTPEQ WRSRRSYSCQVMHEGSTVEKTVAPAEC SQVQLVQSGAE VKKPGASVKV SCKASGYTFTSYGISWVRQAPGQGLEW MGWISAYNGNTNYAQKLQGRVTMTTDTSTSTAYMELR SLRSDDTAVYYCAKDRHWHWWLDAFDYWGQGTLVTV SSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLG TQTYICNVNHKPSNTKVDKKVEPKSCQVQLVQSGSELK KPGASVKV SCKASGYTFTSYSMNWVRQAPGQGLEWM GWINTYTGDPITYAQGFTGRYVFSLDTSVNTAYLQISSLK AEDTAVYYCARETYYYDRGGYPFDPWGQGTLVTVSSA STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQ TYICNVNHKPSNTKVDKKVEPKSC	
309	DIQMTQSPSSLSASVGDRVITITCRASQSISSYLNWYQQK PGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISLQ EDFATYYCQQSISTPPITFGQGRLEIKRTVAAPSVFIFPP SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSG NSQESVTEQDSKSTYSLSSLTLSKADYEKHKVYACE VTHQGLSSPVTKSFNRGEC	Fab_LC (Vk 1- 39)
310	QVQLVQSGAEVKKPGASVKLSCKASGYTFTAYYINWVR QAPGQGLEWIGRIYPGSGYTSYAQKFQGRATLTADSTS TAYMELSSLRSED TAVYFCARPPVYYDSAWFAYWGQGT LVTVSSASVAAPSVFIFPPSDEQLKSGTASVVCLLNNFY REAKVQWKVDNALQSGNSQESVTEQDSKSTYSLSSLT TLKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC EVQL LLESGGGLVQPGGSLRLSCAASGFTFSNYWMHWVRQA PGKGLEWVALISGGGGNTYYADSVKGRFTISRDN SKNT LYLQMNSLR AEDTAVYYCAKDNEKNLYTWLDYWGQG TLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDY FPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT VPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCQVQLVQ SGAEVKKPGASVKV SCKASGYTFTSYGISWVRQAPGQ LEWMGWISAYNGNTNYAQKLQGRVTMTTDTSTSTAYM ELRSLRSDDTAVYYCAKDRHWHWWLDAFDYWGQGT LVTVSSASVAAPSVFIFPPSDEQLKSGTASVVCLLNNFY PREAKVQWKVDNALQSGNSQESVTEQDSKSTYSLSSLT LTKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC EVQL VQSGSELKKPGASVKV SCKASGYTFTSYSMNWVRQAP GQGLEWMGWINTYTGDPITYAQGFTGRYVFSLDTSVNT AYLQISSLK AEDTAVYYCARETYYYDRGGYPFDPWGQ TLVTVSSASVAAPSVFIFPPSDEQLKSGTASVVCLLNNFY PREAKVQWKVDNALQSGNSQESVTEQDSKSTYSLSSLT LTKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	Tetraspecific ErbB2-Vh-Ck- ErbB3_Sab- EGFR-Vh-Ck- C-Met-Vh- Ck_HC
311	DIQMTQSPSSLSASVGDRVITITCRASQSISSYLNWYQQK PGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISLQ EDFATYYCQQSISTPPITFGQGRLEIKSSASTKGPSVFP LAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSG VHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHK PSNTKVDKKVEPKSC	Fab-Vk-CH1- LC

401	EVQLVESGGGLVKPGGSLRLSCAASGFTFSSYGMLHWVR QAPGKGLEWVAGISADSGDKNYADSVKGRFTISRDNK NSLYLQMNSLRAEDTAVYYCAKEFISWIYTFDYLDYWG QGTLTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVV TVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCQVQL VQSGAEVKKPGASVKVSCKASGYTFSIYTIHWVRQAPG QGLEWMGGINPYNGNTKYAQKFQGRVTMTRDTSISTAY MELSRRLSDDTAVYYCAKAPAVFWWTGLDYWGQGTLV TVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEP VTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSS LGTQTYICNVNHKPSNTKVDKKVEPKSC	RP-029_ANG- 2-Sab-X-VA- Sab
402	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYGMSWVR QAPGKGLEWVARINGDGGYKNYADSVKGRFTISRDNK NTLYLQMNSLRAEDTAVYYCARELWAFINDFSFGLDYW GQGTLTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLV KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSV VTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCQVQ LVQSGAEVKKPGASVKVSCKASGYTFSIYTIHWVRQAP GQGLEWMGGINPYNGNTKYAQKFQGRVTMTRDTSIST AYMELSRRLSDDTAVYYCAKAPAVFWWTGLDYWGQG TLTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDY FPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT PSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCP PCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDV SHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVV SVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKG QPREPQVYTLPPCRDELTKNQVSLWCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQ QGNVFSCSVMHEALHNHYTQKSLSLSPG	RP- 015_1013A01- HC-RO101- VA-HC
403	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYGMSWVR QAPGKGLEWVARINGDGGYKNYADSVKGRFTISRDNK NTLYLQMNSLRAEDTAVYYCARELWAFINDFSFGLDYW GQGTLTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLV KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSV VTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCEVQ LVESGGGLVKPGGSLRLSCAASGFTFSSYGMLHWVRQAP GKGLEWVAGISADSGDKNYADSVKGRFTISRDNKNSL YLQMNSLRAEDTAVYYCAKEFISWIYTFDYLDYWGQG TLTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDY FPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT PSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCP PCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDV SHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVV SVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKG QPREPQVCTLPPSRDELTKNQVSLSCAVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSFFLVSKLTVDKSRWQ QGNVFSCSVMHEALHNHYTQKSLSLSPG	RP- 015_1013A01- HC-RO101- Ang2-HC

404	QPV LHQPPAMSSALGTTIRLTCTLRNDHDIGVYSVYWY QQRPGHPPRFLRLRYFSQSDKSQGPQVPPRFSGSKDVARN RGYLSISELQPEDEAMYYCAMGARSSVTHVFGSGTQLT VLSQPKATPSVTLFPPSSEELQANKATLVCLMNDFYPGIL TVTWKADGTPITQGVEMTTTPSKQSNNKYAASSYLSLTP EQWRSRRSYSCQVMHEGSTVEKTVAPAEC SQVQLVQSG AEVKKPGASVKV SCKASGYTFSIYTIHWVRQAPGQGLE WMGGINPYNGNTKYAQKFQGRVTMTRDTSISTAYMELS RLRSDDTAVYYCAKAPAVFWWTGLDYWGQGT LVTVSS ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVT SWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGT QTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE AAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPE VKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQ VYTLPPCRDELTKNQVSLWCLVKGFYPSDIAVEWESNG QPENNYKTTTPVLDS DGSFFLYSKLTVDKSRWQQGNVF SCSVMHEALHNHYTQKSLSLSPG	RP-010_SLC- RO101-VA-HC
405	QPV LHQPPAMSSALGTTIRLTCTLRNDHDIGVYSVYWY QQRPGHPPRFLRLRYFSQSDKSQGPQVPPRFSGSKDVARN RGYLSISELQPEDEAMYYCAMGARSSVTHVFGSGTQLT VLSQPKATPSVTLFPPSSEELQANKATLVCLMNDFYPGIL TVTWKADGTPITQGVEMTTTPSKQSNNKYAASSYLSLTP EQWRSRRSYSCQVMHEGSTVEKTVAPAECSEVQLVESG GGLVKPGGSLRLSCAASGFTFSSYGMHWVRQAPGKGL EWVAGISADSGDKNYADSVKGRFTISRDN AKNSLYLQM NSLRAEDTAVYYCAKEFISWIYTFDYLDYWGQGT LVT SSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLG TQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAP EAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREP QVCTLPPSRDELTKNQVSLSCAVKGFYPSDIAVEWESNG QPENNYKTTTPVLDS DGSFFLVSKLTVDKSRWQQGNVF SCSVMHEALHNHYTQKSLSLSPG	RP-010_SLC- RO101-Ang2- HC
406	QVQLVQSGAEVKKPGASVKV SCKASGYTFSIYTIHWVR QAPGQGLEWMGGINPYNGNTKYAQKFQGRVTMTRDTS ISTAYMELSRLRSDDTAVYYCAKAPAVFWWTGLDYWG QGT LVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVK DYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSV TVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCEVQL VESGGGLVKPGGSLRLSCAASGFTFSSYGMHWVRQAP GKGLEWVAGISADSGDKNYADSVKGRFTISRDN AKNSL YLQMNSLRAEDTAVYYCAKEFISWIYTFDYLDYWGQ TLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDY FPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSVTV PSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCP PCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDV SHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVV SVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKG	RP- 028_VA_Sab- X-Ang2_SgG

	QPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQ QGNVFSCSVMHEALHNHYTQKSLSLSPG	
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[0598] While preferred embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention.

[0599] All publications, patent applications, issued patents, and other documents referred to in this specification are herein incorporated by reference as if each individual publication, patent application, issued patent, or other document was specifically and individually indicated to be incorporated by reference in its entirety. Definitions that are contained in text incorporated by reference are excluded to the extent that they contradict definitions in this disclosure.

CLAIMSWHAT IS CLAIMED IS:

1. A multispecific antigen binding polypeptide comprising:
 - a. a first antigen binding moiety, comprising a first heavy chain variable region;
 - b. a second antigen binding moiety, comprising a second heavy chain variable region; and
 - c. a third antigen binding moiety, comprising a third heavy chain variable region;wherein the first antigen binding moiety binds to a first target, the second antigen binding moiety binds to a second target, and the third antigen binding moiety binds to a third target, wherein the first antigen binding moiety, the second antigen binding moiety, and the third antigen binding moiety are paired to a light chain polypeptide.
2. The multispecific antigen binding polypeptide of claim 1, wherein the first antigen binding moiety, the second antigen binding moiety, and the third antigen binding moiety are directly connected without a linker.
3. The multispecific antigen binding polypeptide of claim 2, wherein a C-terminus of the first heavy chain variable region or the first antigen binding moiety is directly connected to an N-terminus of the second heavy chain variable region.
4. The multispecific antigen binding polypeptide of claim 2, wherein a C-terminus of the second heavy chain variable region or the second antigen binding moiety is directly connected to an N-terminus of the third heavy chain variable region.
5. The multispecific antigen binding polypeptide of any one of claims 2 to 4, wherein a C-terminus of the first heavy chain variable region or the first antigen binding moiety is directly connected to an N-terminus of the second heavy chain variable region, and wherein a C-terminus of the second heavy chain variable region or the second antigen binding moiety is directly connected to an N-terminus of the third heavy chain variable region.
6. The multispecific antigen binding polypeptide of claim 1, wherein the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety are linked via a linker.
7. The multispecific antigen binding polypeptide of claim 6, wherein the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety are covalently linked via the linker.
8. The multispecific antigen binding polypeptide of claim 6, wherein the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety are non-covalently linked via the linker.

9. The multispecific antigen binding polypeptide of any one of claims 2 to 8, wherein the linker couples the C-terminus of the first antigen binding moiety to the N-terminus of the second antigen binding moiety.
10. The multispecific antigen binding polypeptide of any one of claims 2 to 8, wherein the linker couples the C-terminus of the second antigen binding moiety to the N-terminus of the third antigen binding moiety.
11. The multispecific antigen binding polypeptide of any one of claims 1 to 10, further comprising a fourth antigen binding moiety, wherein the fourth antigen binding moiety comprises a fourth heavy chain variable region, wherein the fourth antigen binding moiety binds to a fourth target, wherein the fourth antigen binding moiety is paired to a light chain polypeptide.
12. The multispecific antigen binding polypeptide of claim 11, wherein the first antigen binding moiety, the second antigen binding moiety, the third antigen binding moiety, and the fourth antigen binding moiety are directly connected without a linker.
13. The multispecific antigen binding polypeptide of claim 12, wherein a C-terminus of the third heavy chain variable region is directly connected to an N-terminus of the fourth heavy chain variable region.
14. The multispecific antigen binding polypeptide of claim 11, wherein the first antigen binding moiety, the second antigen binding moiety, the third antigen binding moiety, and/or the fourth antigen binding moiety are linked via a linker.
15. The multispecific antigen binding polypeptide of claim 14, wherein the linker couples the C-terminus of the third antigen binding moiety to the N-terminus of the fourth antigen binding moiety.
16. The multispecific antigen binding polypeptide of any one of claims 6 to 15, wherein the linker comprises the amino acid sequence of SEQ ID NO: 151.
17. The multispecific antigen binding polypeptide of any one of claims 1 to 16, wherein the first antigen binding moiety, the second antigen binding moiety, the third antigen binding moiety, and/or the fourth antigen binding moiety comprises a crossed domain.
18. The multispecific antigen binding polypeptide of any one of claims 1 to 16, wherein the first antigen binding moiety, the second antigen binding moiety, the third antigen binding moiety, and/or the fourth antigen binding moiety comprises at least two crossed domains, wherein the at least two crossed domains are comprised in at least two different antigen binding moieties.
19. The multispecific antigen binding polypeptide of any one of claims 1 to 16, wherein the first antigen binding moiety, the second antigen binding moiety, the third antigen binding moiety,

and/or the fourth antigen binding moiety comprises at least three crossed domains wherein the at least three crossed domains are comprised in at least three different antigen binding moieties.

20. The multispecific antigen binding polypeptide of any one of claims 1 to 19, wherein the light chain polypeptide paired to the first antigen binding moiety, the second antigen binding moiety, and the third antigen binding moiety comprise the same amino acid sequence.

21. The multispecific antigen binding polypeptide of any one of claims 1 to 19, wherein the light chain polypeptide paired to the first antigen binding moiety, the second antigen binding moiety, and the third antigen binding moiety comprise different amino acid sequences.

22. The multispecific antigen binding polypeptide of any one of claims 1 to 19, wherein the light chain polypeptide paired to the first antigen binding moiety, the second antigen binding moiety, the third antigen binding moiety, and the fourth antigen binding moiety comprise the same amino acid sequence.

23. The multispecific antigen binding polypeptide of any one of claims 1 to 19, wherein the light chain polypeptide paired to the first antigen binding moiety, the second antigen binding moiety, the third antigen binding moiety, and the fourth antigen binding moiety comprise different amino acid sequences.

24. The multispecific antigen binding polypeptide of any one of claims 1 to 23, wherein the light chain polypeptide comprises a light chain constant region comprising one or more amino acid substitutions from a heavy chain first constant region (CH1).

25. The multispecific antigen binding polypeptide of claim 24, wherein the light chain polypeptide comprises a light chain constant region comprising one or more amino acid substitutions from a heavy chain first constant region (CH1) and the light chain comprises an amino acid sequence comprising at least 90%, at least 95%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to the amino acid sequence set forth in SEQ ID NO: 111 or 112.

26. The multispecific antigen binding polypeptide of claim 24, wherein the light chain polypeptide comprises a light chain constant region comprising one or more amino acid substitutions from a heavy chain first constant region (CH1) and the light chain comprises an amino acid sequence comprising at least 90%, at least 95%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to the amino acid sequence set forth in SEQ ID NO: 121 or 122.

27. The multispecific antigen binding polypeptide of claim 24, wherein the light chain polypeptide comprises a light chain constant region comprising one or more amino acid substitutions from a heavy chain first constant region (CH1) and the light chain comprises an amino acid sequence comprising at least 90%, at least 95%, at least 97%, at least 98%, at least

99%, or at least 100% sequence identity to the amino acid sequence set forth in SEQ ID NO: 131 or 132.

28. The multispecific antigen binding polypeptide of any one of claims 1 to 23, wherein the light chain polypeptide is a universal light chain polypeptide.

29. The multispecific antigen binding polypeptide of claim 28, wherein the universal light chain polypeptide is a common light chain polypeptide.

30. The multispecific antigen binding polypeptide of claim 28, wherein the universal light chain polypeptide is a surrogate light chain polypeptide.

31. The multispecific antigen binding polypeptide of claim 30, wherein the surrogate light chain polypeptide comprises a VpreB sequence fused to a λ 5 sequence.

32. The multispecific antigen binding polypeptide of claim 31, wherein the VpreB sequence comprises an amino acid sequence comprising at least 90%, at least 95%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to the amino acid sequence set forth in SEQ ID NO: 101.

33. The multispecific antigen binding polypeptide of claim 31, wherein the λ 5 sequence comprises an amino acid sequence comprising at least 90%, at least 95%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to the amino acid sequence set forth in SEQ ID NO: 106.

34. The multispecific antigen binding polypeptide of any one of claims 30 to 33, wherein the surrogate light chain polypeptide comprises:

- a. a light chain complementarity determining region 1 (LCDR1) comprising the amino acid sequence set forth in SEQ ID NO: 103;
- b. a light chain complementarity determining region 2 (LCDR2) comprising the amino acid sequence set forth in SEQ ID NO: 104; and/or
- c. a light chain complementarity determining region 3 (LCDR3) comprising the amino acid sequence set forth in SEQ ID NO: 105.

35. The multispecific antigen binding polypeptide of any one of claims 30 to 34, wherein the surrogate light chain polypeptide comprises an amino acid sequence comprising at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 102.

36. The multispecific antigen binding polypeptide of claim 29, wherein the common light chain polypeptide comprises an amino acid sequence comprising at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 303.

37. The multispecific antigen binding polypeptide of any one of claims 1 to 36, wherein the first target, the second target and/or the third target is VEGF-A or a fragment thereof.

38. The multispecific antigen binding polypeptide of claim 37, wherein the multispecific antigen binding polypeptide binds to VEGF-A or a fragment thereof with an EC₅₀ of about 5 picomolar or less.
39. The multispecific antigen binding polypeptide of claim 37 or 38, wherein the multispecific antigen binding polypeptide binds with an affinity to VEGF-A or a fragment thereof at least 8-fold stronger than faricimab.
40. The multispecific antigen binding polypeptide of any one of claims 37-39, wherein the multispecific antigen binding polypeptide inhibits the interaction of VEGF-A and the VEGF-A receptor.
41. The multispecific antigen binding polypeptide of claim 40, wherein the multispecific antigen binding polypeptide inhibits the interaction of VEGF-A and the VEGF-A receptor with an IC₅₀ of about 18 nanomolar or less.
42. The multispecific antigen binding polypeptide of claim 40, wherein the multispecific antigen binding polypeptide inhibits the interaction of VEGF-A and the VEGF-A receptor at least 1.3-fold stronger than faricimab.
43. The multispecific antigen binding polypeptide of any one of claims 1 to 42, wherein the first target, the second target, and/or the third target is ANG-2 or a fragment thereof.
44. The multispecific antigen binding polypeptide of claim 43, wherein the multispecific antigen binding polypeptide binds to ANG-2 or a fragment thereof with an EC₅₀ of about 11 picomolar or less.
45. The multispecific antigen binding polypeptide of claim 43 or 44, wherein the multispecific antigen binding polypeptide binds with an affinity to ANG-2 or a fragment thereof at least 300-fold stronger than faricimab.
46. The multispecific antigen binding polypeptide of any one of claims 43-45, wherein the multispecific antigen binding polypeptide inhibits the interaction of ANG-2 and the ANG-2 receptor.
47. The multispecific antigen binding polypeptide of claim 46, wherein the multispecific antigen binding polypeptide inhibits the interaction of ANG-2 and the ANG-2 receptor with an IC₅₀ of about 3.1 nanomolar or less.
48. The multispecific antigen binding polypeptide of claim 46, wherein the multispecific antigen binding polypeptide inhibits the interaction of ANG-2 and the ANG-2 receptor at least 12-fold stronger than faricimab.
49. The multispecific antigen binding polypeptide of any one of claims 1 to 48, wherein the first target, the second target and/or the third target is VEGF-C or a fragment thereof.

50. The multispecific antigen binding polypeptide of claim 49, wherein the multispecific antigen binding polypeptide binds to VEGF-C or a fragment thereof with an EC50 of about 19 picomolar or less.
51. The multispecific antigen binding polypeptide of any one of claims 49-50, wherein the multispecific antigen binding polypeptide inhibits the interaction of VEGF-C and the VEGF-C receptor.
52. The multispecific antigen binding polypeptide of claim 40, wherein the multispecific antigen binding polypeptide inhibits the interaction of VEGF-C and the VEGF-C receptor with an IC50 of about 3.8 nanomolar or less.
53. The multispecific antigen binding polypeptide of any one of claims 1 to 52, wherein the first target is VEGF-A or fragment thereof, the second target is ANG-2 or a fragment thereof, and the third target is VEGF-C or a fragment thereof.
54. The multispecific antigen binding polypeptide of any one of claims 1 to 53, wherein the first, second, and third antigen binding moiety bind different polypeptide antigens.
55. The multispecific antigen binding polypeptide of any one of claims 1 to 53, wherein the first, second, and third antigen binding moiety bind the same polypeptide antigens.
56. The multispecific antigen binding polypeptide of any one of claims 1 to 55, wherein the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety binds to VEGF-A.
57. The multispecific antigen binding polypeptide of claim 56, wherein the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety binds to VEGF-A and comprises an immunoglobulin heavy chain variable region comprising:
- a. a heavy chain complementarity determining region 1 (HCDR1) comprising the amino acid sequence set forth in SEQ ID NO: 3;
 - b. a heavy chain complementarity determining region 2 (HCDR2) comprising the amino acid sequence set forth in SEQ ID NO: 4; and/or
 - c. a heavy chain complementarity determining region 3 (HCDR3) comprising the amino acid sequence set forth in SEQ ID NO: 5;
- wherein the heavy chain variable region binds to VEGF-A upon pairing with the light chain polypeptide.
58. The multispecific antigen binding polypeptide of claim 56, wherein the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety comprises an immunoglobulin heavy chain variable region comprising an amino acid sequence comprising at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 1.

59. The multispecific antigen binding polypeptide of claim 56, wherein the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety comprises an amino acid sequence comprising at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 2.

60. The multispecific antigen binding polypeptide of any one of claims 1 to 55, wherein the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety binds to ANG-2.

61. The multispecific antigen binding polypeptide of claim 60, wherein the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety binds to ANG-2 and comprises an immunoglobulin heavy chain variable region comprising:

- a. a heavy chain complementarity determining region 1 (HCDR1) comprising the amino acid sequence set forth in SEQ ID NO: 13;
- b. a heavy chain complementarity determining region 2 (HCDR2) comprising the amino acid sequence set forth in SEQ ID NO: 14; and/or
- c. a heavy chain complementarity determining region 3 (HCDR3) comprising the amino acid sequence set forth in SEQ ID NO: 15;

wherein the heavy chain variable region binds to ANG-2 upon pairing with the light chain polypeptide.

62. The multispecific antigen binding polypeptide of claim 60, wherein the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety comprises an immunoglobulin heavy chain variable region comprising an amino acid sequence comprising at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 11.

63. The multispecific antigen binding polypeptide of claim 60, wherein the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety comprises an amino acid sequence comprising at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 12.

64. The multispecific antigen binding polypeptide of any one of claims 1 to 55, wherein the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety binds to VEGF-C.

65. The multispecific antigen binding polypeptide of claim 64, wherein the first antigen binding moiety, the second antigen binding moiety, or the third antigen binding moiety binds to VEGF-C and comprises an immunoglobulin heavy chain variable region comprising:

- a. a heavy chain complementarity determining region 1 (HCDR1) comprising the amino acid sequence set forth in SEQ ID NO: 23;

- b. a heavy chain complementarity determining region 2 (HCDR2) comprising the amino acid sequence set forth in SEQ ID NO: 24; and/or
- c. a heavy chain complementarity determining region 3 (HCDR3) comprising the amino acid sequence set forth in SEQ ID NO: 25;

wherein the heavy chain variable region binds to VEGF-C upon pairing with the light chain polypeptide.

66. The multispecific antigen binding polypeptide of claim 64, wherein the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety comprises an immunoglobulin heavy chain variable region comprising an amino acid sequence comprising at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 21.

67. The multispecific antigen binding polypeptide of claim 60, wherein the first antigen binding moiety, the second antigen binding moiety, and/or the third antigen binding moiety comprises an amino acid sequence comprising at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 22.

68. The multispecific antigen binding polypeptide of any one of claims 1 to 67, wherein each of the first antigen binding moiety, the second antigen binding moiety and the third antigen binding moiety is non-covalently paired to the surrogate light chain polypeptide.

69. The multispecific antigen binding polypeptide of any one of claims 1 to 67, wherein each of the first antigen binding moiety, the second antigen binding moiety and the third antigen binding moiety is covalently paired to the surrogate light chain polypeptide.

70. The multispecific antigen binding polypeptide of any one of claims 1 to 69, wherein the first, second, and/or third antigen binding moiety comprise a heavy chain first constant region (CH1) comprising one or more amino acid substitutions from a light chain constant region.

71. The multispecific antigen binding polypeptide of any one of claims 1 to 70, wherein the first antigen binding moiety comprises a first heavy chain variable region (VH) and a first heavy chain first constant region (CH1).

72. The multispecific antigen binding polypeptide of any one of claims 1 to 71, wherein the second antigen binding moiety comprises a second heavy chain variable region (VH) and a second heavy chain first constant region (CH1).

73. The multispecific antigen binding polypeptide of any one of claims 1 to 72, wherein the third antigen binding moiety comprises a third heavy chain variable region (VH) and a third heavy chain first constant region (CH1).

74. The multispecific antigen binding polypeptide of any one of claims 71 to 73, wherein the first, second, or third heavy chain first constant region comprises an amino acid sequence with at

least 80%, at least 90%, at least 95%, at least 97%, at least 98%, at least 99%, or at least 100% identity to the amino acid sequence set forth in SEQ ID NO: 141.

75. The multispecific antigen binding polypeptide of any one of claims 1 to 74, wherein the multispecific antigen binding polypeptide comprises an amino acid sequence comprising at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in any one of SEQ ID NOs: 201 to 205.

76. The multispecific antigen binding polypeptide of any one of claims 1 to 74, wherein the multispecific antigen binding polypeptide comprises an amino acid sequence comprising at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 201.

77. The multispecific antigen binding polypeptide of any one of claims 1 to 74, wherein the multispecific antigen binding polypeptide comprises an amino acid sequence comprising at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 202.

78. The multispecific antigen binding polypeptide of any one of claims 1 to 74, wherein the multispecific antigen binding polypeptide comprises at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 203.

79. The multispecific antigen binding polypeptide of any one of claims 76 to 78, wherein the first, second, and third antigen binding moiety comprise or consist of the amino acid sequence set forth in any one of SEQ ID NOs: 201 to 203.

80. The multispecific antigen binding polypeptide of any one of claims 76 to 78, wherein the first, second, and third antigen binding moiety comprise or consist of the amino acid sequence set forth in SEQ ID NO: 201.

81. The multispecific antigen binding polypeptide of any one of claims 76 to 78, wherein the first, second, and third antigen binding moiety comprise or consist of the amino acid sequence set forth in SEQ ID NO: 202.

82. The multispecific antigen binding polypeptide of any one of claims 76 to 78, wherein the first, second, and third antigen binding moiety comprise or consist of the amino acid sequence set forth in SEQ ID NO: 203.

83. A multispecific antigen binding polypeptide comprising:

- a. a first antigen binding moiety, comprising a first heavy chain variable region and a first heavy chain first constant region (CH1) paired with a first light chain; and
- b. a second antigen binding moiety, comprising a second heavy chain variable region and a second heavy chain first constant region (CH1) paired with a second light chain;

wherein a C terminus of the first CH1 is coupled to an N-terminus of the second heavy chain variable region wherein the first antigen binding moiety binds to a first target, and wherein the second antigen binding moiety binds to a second target.

84. The multispecific antigen binding polypeptide of claim 83, wherein the first light chain and the second light chain are a common light chain.
85. The multispecific antigen binding polypeptide of claim 83, wherein the first light chain and the second light chain are a surrogate light chain.
86. The multispecific antigen binding polypeptide of any one of claims 83 to 85, wherein the first antigen binding moiety and the second antigen binding moiety are directly coupled without a linker.
87. The multispecific antigen binding polypeptide of any one of claims 83 to 86, wherein the surrogate light chain polypeptide comprises a VpreB sequence conjugated to a $\lambda 5$ sequence.
88. The multispecific antigen binding polypeptide of claim 87, wherein the VpreB sequence comprises an amino acid sequence with at least 90%, at least 95%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to the amino acid sequence set forth in SEQ ID NO: 101.
89. The multispecific antigen binding polypeptide of claim 87, wherein the $\lambda 5$ sequence comprises an amino acid sequence with at least 90%, at least 95%, at least 97%, at least 98%, at least 99%, or at least 100% sequence identity to the amino acid sequence set forth in SEQ ID NO: 106.
90. The multispecific antigen binding polypeptide of any one of claims 85 to 89, wherein the surrogate light chain polypeptide comprises:
- a light chain complementarity determining region 1 (LCDR1) comprising the amino acid sequence set forth in SEQ ID NO: 103;
 - a light chain complementarity determining region 2 (LCDR2) comprising the amino acid sequence set forth in SEQ ID NO: 104; and/or
 - a light chain complementarity determining region 3 (LCDR3) comprising the amino acid sequence set forth in SEQ ID NO: 105.
91. The multispecific antigen binding polypeptide of any one of claims 85 to 90, wherein the surrogate light chain polypeptide comprises an amino acid sequence at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 102.
92. The multispecific antigen binding polypeptide of any one of claims 85 to 91, wherein each of the first antigen binding moiety and/or the second antigen binding moiety is non-covalently paired to the surrogate light chain polypeptide.

93. The multispecific antigen binding polypeptide of any one of claims 85 to 91, wherein each of the first antigen binding moiety and/or the second antigen binding moiety is covalently paired to the surrogate light chain polypeptide.
94. The multispecific antigen binding polypeptide of any one of claims 85 to 93, wherein the first and second antigen binding moiety bind antigens on different polypeptides.
95. The multispecific antigen binding polypeptide of any one of claims 85 to 94, wherein the first and second antigen binding moiety bind antigens on the same polypeptide.
96. A pharmaceutical composition comprising the multispecific antigen binding polypeptide or the antigen binding polypeptide of any one of claims 1 to 95 and a pharmaceutically acceptable carrier, excipient, or diluent.
97. The pharmaceutical composition of claim 96 formulated for intravenous administration.
98. The pharmaceutical composition of claim 96 formulated for intravitreal administration.
99. A nucleic acid or plurality of nucleic acids encoding the multispecific antigen binding polypeptide or antigen binding polypeptide of any one of claims 1 to 95.
100. An expression vector comprising the nucleic acid of claim 99.
101. The expression vector of claim 100, wherein the expression vector is RNA.
102. The expression vector of claim 100, wherein the expression vector is plasmid or linearized DNA.
103. The expression vector of claim 100, wherein the expression vector is a viral vector.
104. The viral vector of claim 103, wherein the viral vector is an adenovirus.
105. The viral vector of claim 103, wherein the viral vector is an adeno-associated virus.
106. The viral vector of claim 103, wherein the viral vector is a lentivirus virus.
107. A pharmaceutical composition comprising the nucleic acid or plurality of nucleic acids encoding the multispecific antigen binding polypeptide of any one of claims 99 to 106 and a pharmaceutically acceptable carrier, excipient, or diluent.
108. The pharmaceutical composition of claim 107 formulated for intravenous administration.
109. The pharmaceutical composition of claim 107 formulated for intravitreal administration.
110. A method of treating a disease in an individual comprising administering to the individual the multispecific antigen binding polypeptide, the nucleic acid or plurality of nucleic acids encoding the multispecific antigen binding polypeptide, or pharmaceutical composition of any one of the preceding claims, thereby treating the disease.
111. The method of claim 110, wherein the disease is an ocular disease.
112. The method of claim 111, wherein the ocular disease comprises macular degeneration.
113. The method of claim 112, wherein the macular degeneration is neovascular age-related macular degeneration.

- 114. The method of claim 112, wherein the ocular disease comprises diabetic macular edema.
- 115. The method of claim 112, wherein the ocular disease comprises retinal vein occlusion.
- 116. The method of claim 110, wherein the disease is a cancer.