WHAT IS CLAIMED IS:

Claim 1. An antibody-like binding protein comprising four polypeptide chains that form four antigen binding sites, wherein two polypeptide chains have a structure represented by the formula:

$$V_{L1}\text{-}L_1\text{-}V_{L2}\text{-}L_2\text{-}C_L \qquad [I]$$

and two polypeptide chains have a structure represented by the formula:

$$V_{H2}\text{-}L_3\text{-}V_{H1}\text{-}L_4\text{-}C_{H1}\text{-}Fc \qquad [II]$$

wherein:

V_{L1} is a first immunoglobulin light chain variable domain;

V_{L2} is a second immunoglobulin light chain variable domain;

V_{H1} is a first immunoglobulin heavy chain variable domain;

V_{H2} is a second immunoglobulin heavy chain variable domain;

C_L is an immunoglobulin light chain constant domain;

C_{H1} is the immunoglobulin C_{H1} heavy chain constant domain;

Fc is the immunoglobulin hinge region and C_{H2}, C_{H3} immunoglobulin heavy chain constant domains; and

L_1, L_2, L_3, and L_4 are amino acid linkers;

and wherein the polypeptides of formula I and the polypeptides of formula II form a cross-over light chain-heavy chain pair.

Claim 2. The antibody-like binding protein of claim 1, wherein:

L_1 is 3 to 12 amino acid residues in length;

L_2 is 3 to 14 amino acid residues in length;

L_3 is 1 to 8 amino acid residues in length; and

L_4 is 1 to 3 amino acid residues in length.

Claim 3. The antibody-like binding protein of either claim 1 or 2, wherein:

L_1 is 5 to 10 amino acid residues in length;

L_2 is 5 to 8 amino acid residues in length;

L_3 is 1 to 5 amino acid residues in length; and

L_4 is 1 to 2 amino acid residues in length.

Claim 4. The antibody-like binding protein of any one of claims 1-3, wherein:

L_1 is 7 amino acid residues in length;

L_2 is 5 amino acid residues in length;

L_3 is 1 amino acid residues in length; and

L_4 is 2 amino acid residues in length.

Claim 5. The antibody-like binding protein of claim 1, wherein:

L_1 is 1 to 3 amino acid residues in length;

L_2 is 1 to 4 amino acid residues in length;

L_3 is 2 to 15 amino acid residues in length; and

L_4 is 2 to 15 amino acid residues in length.

Claim 6. The antibody-like binding protein of either claim 1 or 5, wherein:

L_1 is 1 to 2 amino acid residues in length;

L_2 is 1 to 2 amino acid residues in length;

L_3 is 4 to 12 amino acid residues in length; and

L_4 is 2 to 12 amino acid residues in length.

Claim 7. The antibody-like binding protein of any one of claims 1, 5, or 6, wherein:

L_1 is 1 amino acid residue in length;

L_2 is 2 amino acid residues in length;

L_3 is 7 amino acid residues in length; and

L_4 is 5 amino acid residues in length.

Claim 8. The antibody-like binding protein of claim 1, wherein L_1 is 0 amino acid residues in length and L_3 is 2 or more amino acid residues in length.

Claim 9. The antibody-like binding protein of claim 1, wherein L_3 is 0 amino acid residues in length and L_1 is 1 or more amino acid residues in length.

Claim 10. The antibody-like binding protein of claim 1, wherein L_4 is 0 amino acid residues in length and L_2 is 3 or more amino acid residues in length.

Claim 11. The antibody-like binding protein of any one of claims 1-10, wherein the binding protein is capable of specifically binding one or more antigen targets.

Claim 12. The antibody-like binding protein of any one of claims 1-11, wherein the one or more antigen targets is selected from the group consisting of B7.1, B7.2, BAFF, BlyS, C3, C5, CCL11 (eotaxin), CCL15 (MIP-1d), CCL17 (TARC), CCL19 (MIP-3b), CCL2 (MCP-1), CCL20 (MIP-3a), CCL21 (MIP-2), SLC, CCL24 (MPIF-2/eotaxin-2), CCL25 (TECK), CCL26 (eotaxin-3), CCL3 (MIP-1a), CCL4 (MIP-1b), CCL5 (RANTES), CCL7 (MCP-3), CCL8 (mcp-2), CD3, CD19, CD20, CD24, CD40, CD40L, CD80, CD86, CDH1 (E-cadherin), Chitinase, CSF1 (M-CSF), CSF2 (GM-CSF), CSF3 (GCSF), CTLA4, CX3CL1 (SCYD1), CXCL12 (SDF1), CXCL13, EGFR, FCER1A, FCER2, HER2, IGF1R, IL-1, IL-12, IL13, IL15, IL17, IL18, IL1A, IL1B, IL1F10, IL1β, IL2, IL4, IL6, IL7, IL8, IL9, IL12/23, IL22, IL23, IL25, IL27, IL35, ITGB4 (b 4 integrin), LEP (leptin), MHC class II, TLR2, TLR4, TLR5, TNF, TNFα, TNFSF4 (OX40 ligand), TNFSF5 (CD40 ligand), Toll-like receptors, TREM1, TSLP, TWEAK, XCR1 (GPR5/CCXCR1), DNGR-1(CLEC91), and HMGB1.

Claim 13. The antibody-like binding protein of any one of claims 1-12, wherein the binding protein is bispecific and capable of binding two different antigen targets.

Claim 14. The antibody-like binding protein of any one of claims 1-13, wherein the two different antigen targets are selected from the group consisting of IL4 and IL13, IGF1R and HER2, IGF1R and EGFR, EGFR and HER2, BK and IL13, PDL-1 and CTLA-4, CTLA4 and MHC class II, IL-12 and IL-18, IL-1α and IL-1β, TNFα and IL12/23, TNFα and IL-12p40, TNFα and IL1β, TNFα and IL-23, and IL17 and IL23.

Claim 15. The antibody-like binding protein of any one of claims 1-14, wherein the binding protein is capable of inhibiting the function of one or more of the antigen targets.

Claim 16. The antibody-like binding protein of any one of claims 1-15, wherein at least one of the linkers selected from the group consisting of L_1, L_2, L_3, and L_4 contains at least one cysteine residue.

Claim 17. An antibody-like binding protein comprising two polypeptide chains that form two antigen binding sites, wherein a first polypeptide chain has a structure represented by the formula:

$$V_{L1}\text{-}L_1\text{-}V_{L2}\text{-}L_2\text{-}C_L \quad [I]$$

and a second polypeptide chain has a structure represented by the formula:

$$V_{H2}\text{-}L_3\text{-}V_{H1}\text{-}L_4\text{-}C_{H1} \quad [II]$$

wherein:

V_{L1} is a first immunoglobulin light chain variable domain;

V_{L2} is a second immunoglobulin light chain variable domain;

V_{H1} is a first immunoglobulin heavy chain variable domain;

V_{H2} is a second immunoglobulin heavy chain variable domain;

C_L is an immunoglobulin light chain constant domain;

C_{H1} is the immunoglobulin C_{H1} heavy chain constant domain; and

L_1, L_2, L_3, and L_4 are amino acid linkers;

and wherein the first and second polypeptides form a cross-over light chain-heavy chain pair.

Claim 18. The antibody-like binding protein of claim 17, wherein:

L_1 is 3 to 12 amino acid residues in length;

L_2 is 3 to 14 amino acid residues in length;

L_3 is 1 to 8 amino acid residues in length; and

L_4 is 1 to 3 amino acid residues in length.

Claim 19. The antibody-like binding protein of either claim 17 or 18, wherein:

L_1 is 5 to 10 amino acid residues in length;

L_2 is 5 to 8 amino acid residues in length;

L_3 is 1 to 5 amino acid residues in length; and

L_4 is 1 to 2 amino acid residues in length.

Claim 20. The antibody-like binding protein of any one of claims 17-19, wherein:

L_1 is 7 amino acid residues in length;

L_2 is 5 amino acid residues in length;

L_3 is 1 amino acid residues in length; and

L_4 is 2 amino acid residue in length.

Claim 21. The antibody-like binding protein of claim 17, wherein:

L_1 is 1 to 3 amino acid residues in length;

L_2 is 1 to 4 amino acid residues in length;

L_3 is 2 to 15 amino acid residues in length; and

L_4 is 2 to 15 amino acid residues in length.

Claim 22. The antibody-like binding protein of either claim 17 or 21, wherein:

L_1 is 1 to 2 amino acid residues in length;

L_2 is 1 to 2 amino acid residues in length;

L_3 is 4 to 12 amino acid residues in length; and

L_4 is 2 to 12 amino acid residues in length.

Claim 23. The antibody-like binding protein of any one of claims 17, 21, or 22, wherein:

L_1 is 1 amino acid residue in length;

L_2 is 2 amino acid residues in length;

L_3 is 7 amino acid residues in length; and

L_4 is 5 amino acid residues in length.

Claim 24. The antibody-like binding protein of claim 17, wherein L_1 is 0 amino acid residues in length and L_3 is 2 or more amino acid residues in length.

Claim 25. The antibody-like binding protein of claim 17, wherein L_3 is 0 amino acid residues in length and L_1 is 1 or more amino acid residues in length.

Claim 26. The antibody-like binding protein of claim 17, wherein L_4 is 0 amino acid residues in length and L_2 is 3 or more amino acid residues in length.

Claim 27. The antibody-like binding protein of any one of claims 17-26, wherein the binding protein is capable of specifically binding one or more antigen targets.

Claim 28. The antibody-like binding protein of any one of claims 17-27, wherein the one or more antigen targets is selected from the group consisting of B7.1, B7.2, BAFF, BlyS, C3, C5, CCL11 (eotaxin), CCL15 (MIP-1d), CCL17 (TARC), CCL19 (MIP-3b), CCL2 (MCP-1), CCL20 (MIP-3a), CCL21 (MIP-2), SLC, CCL24 (MPIF-2/eotaxin-2), CCL25 (TECK), CCL26 (eotaxin-3), CCL3 (MIP-1a), CCL4 (MIP-1b), CCL5 (RANTES), CCL7 (MCP-3), CCL8 (mcp-2), CD3, CD19, CD20, CD24, CD40, CD40L, CD80, CD86, CDH1 (E-cadherin), Chitinase, CSF1 (M-CSF), CSF2 (GM-CSF), CSF3 (GCSF), CTLA4, CX3CL1 (SCYD1), CXCL12 (SDF1), CXCL13, EGFR, FCER1A, FCER2, HER2, IGF1R, IL-1, IL-12, IL13, IL15, IL17, IL18, IL1A, IL1B, IL1F10, IL1β, IL2, IL4, IL6, IL7, IL8, IL9, IL12/23, IL22, IL23, IL25, IL27, IL35, ITGB4 (b 4 integrin), LEP (leptin), MHC class II, TLR2, TLR4, TLR5, TNF, TNFα, TNFSF4 (OX40 ligand), TNFSF5 (CD40 ligand), Toll-like receptors, TREM1, TSLP, TWEAK, XCR1 (GPR5/CCXCR1), DNGR-1(CLEC91), and HMGB1.

Claim 29. The antibody-like binding protein of any one of claims 17-28, wherein the binding protein is bispecific and capable of binding two different antigen targets.

Claim 30. The antibody-like binding protein of any one of claims 17-29, wherein the two different antigen targets are selected from the group consisting of IL4 and IL13,

IGF1R and HER2, IGF1R and EGFR, EGFR and HER2, BK and IL13, PDL-1 and CTLA-4, CTLA4 and MHC class II, IL-12 and IL-18, IL-1α and IL-1β, TNFα and IL12/23, TNFα and IL-12p40, TNFα and IL1β, TNFα and IL-23, and IL17 and IL23.

Claim 31. The antibody-like binding protein of any one of claims 17-30, wherein the binding protein is capable of inhibiting the function of one or more of the antigen targets.

Claim 32. The antibody-like binding protein of any one of claims 17-31, wherein at least one of the linkers selected from the group consisting of L_1, L_2, L_3, and L_4 contains at least one cysteine residue.

Claim 33. An isolated nucleic acid molecule comprising a nucleotide sequence encoding the antibody-like binding protein of any one of claims 1-32.

Claim 34. An expression vector comprising the nucleic acid molecule of claim 33.

Claim 35. An isolated host cell comprising the nucleic acid molecule of claim 33 or the expression vector of claim 34.

Claim 36. The host cell of claim 35, wherein the host cell is a mammalian cell or an insect cell.

Claim 37. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of the antibody-like binding protein of any one of claims 1-32.

Claim 38. A method for making the antibody-like binding protein of any one of claims 1-16, comprising expressing in a cell one or more nucleic acid molecules encoding polypeptides having structures represented by the formulas [I] and [II] below:

$$V_{L1}\text{-}L_1\text{-}V_{L2}\text{-}L_2\text{-}C_L \quad [I]$$

$$V_{H2}\text{-}L_3\text{-}V_{H1}\text{-}L_4\text{-}C_{H1}\text{-}Fc \quad [II]$$

wherein:

V_{L1} is a first immunoglobulin light chain variable domain;

V_{L2} is a second immunoglobulin light chain variable domain;

V_{H1} is a first immunoglobulin heavy chain variable domain;

V_{H2} is a second immunoglobulin heavy chain variable domain;

C_L is an immunoglobulin light chain constant domain;

C_{H1} is the immunoglobulin C_{H1} heavy chain constant domain;

Fc is the immunoglobulin hinge region and C_{H2}, C_{H3} immunoglobulin heavy chain constant domains; and

L_1, L_2, L_3, and L_4 are amino acid linkers;

and wherein the polypeptides of formula I and the polypeptides of formula II form a cross-over light chain-heavy chain pair.

Claim 39. A method for making the antibody-like binding protein of any one of claims 17-32, comprising expressing in a cell one or more nucleic acid molecules encoding polypeptides having structures represented by the formulas [I] and [II] below:

$$V_{L1}\text{-}L_1\text{-}V_{L2}\text{-}L_2\text{-}C_L \quad [I]$$

$$V_{H2}\text{-}L_3\text{-}V_{H1}\text{-}L_4\text{-}C_{H1} \quad [II]$$

wherein:

V_{L1} is a first immunoglobulin light chain variable domain;

V_{L2} is a second immunoglobulin light chain variable domain;

V_{H1} is a first immunoglobulin heavy chain variable domain;

V_{H2} is a second immunoglobulin heavy chain variable domain;

C_L is an immunoglobulin light chain constant domain;

C_{H1} is the immunoglobulin C_{H1} heavy chain constant domain; and

L_1, L_2, L_3, and L_4 are amino acid linkers;

and wherein the polypeptide of formula I and the polypeptide of formula II form a cross-over light chain-heavy chain pair.

Claim 40. A method of making an antibody-like binding protein comprising four polypeptide chains that form four antigen binding sites, comprising:

(a) identifying a first antibody variable domain that binds a first target antigen and a second antibody variable domain that binds a second target antigen, each containing a V_L, and a V_H;

(b) assigning either the light chain or the heavy chain as template chain;

(c) assigning the V_L of the first antibody variable domain or the second antibody variable domain as V_{L1};

(d) assigning a V_{L2}, a V_{H1}, and a V_{H2} according to formulas [I] and [II] below:

$$V_{L1}\text{-}L_1\text{-}V_{L2}\text{-}L_2\text{-}C_L \quad [I]$$

$$V_{H2}\text{-}L_3\text{-}V_{H1}\text{-}L_4\text{-}C_{H1}\text{-}Fc \quad [II]$$

(e) determining maximum and minimum lengths for L_1, L_2, L_3, and L_4;

(f) generating polypeptide structures of formulas I and II;

(g) selecting polypeptide structures of formulas I and II that bind the first target antigen and the second target antigen when combined to form the antibody-like binding protein;

wherein:

V_{L1} is a first immunoglobulin light chain variable domain;

V_{L2} is a second immunoglobulin light chain variable domain;

V_{H1} is a first immunoglobulin heavy chain variable domain;

V_{H2} is a second immunoglobulin heavy chain variable domain;

C_L is an immunoglobulin light chain constant domain;

C_{H1} is the immunoglobulin C_{H1} heavy chain constant domain;

Fc is the immunoglobulin hinge region and C_{H2}, C_{H3} immunoglobulin heavy chain constant domains; and

L_1, L_2, L_3, and L_4 are amino acid linkers;

and wherein the polypeptides of formula I and the polypeptides of formula II form a cross-over light chain-heavy chain pair.

Claim 41. The method of claim 40, wherein the first antibody variable domain and the second antibody variable domain are the same.

Claim 42. A method of making an antibody-like binding protein comprising four polypeptide chains that form four antigen binding sites, comprising:

(a) identifying a first antibody variable domain that binds a first target antigen and a second antibody variable domain that binds a second target antigen, each containing a V_L, and a V_H;

(b) assigning either the light chain or the heavy chain as template chain;

(c) assigning the V_L of the first antibody variable domain or the second antibody variable domain as V_{L1};

(d) assigning a V_{L2}, a V_{H1}, and a V_{H2} according to formulas [I] and [II] below:

$$V_{L1}\text{-}L_1\text{-}V_{L2}\text{-}L_2\text{-}C_L \quad [I]$$

$$V_{H2}\text{-}L_3\text{-}V_{H1}\text{-}L_4\text{-}C_{H1} \quad [II]$$

(e) determining maximum and minimum lengths for L_1, L_2, L_3, and L_4;

(f) generating polypeptide structures of formulas I and II;

(g) selecting polypeptide structures of formulas I and II that bind the first target antigen and the second target antigen when combined to form the antibody-like binding protein;

wherein:

V_{L1} is a first immunoglobulin light chain variable domain;

V_{L2} is a second immunoglobulin light chain variable domain;

V_{H1} is a first immunoglobulin heavy chain variable domain;

V_{H2} is a second immunoglobulin heavy chain variable domain;

C_L is an immunoglobulin light chain constant domain;

C_{H1} is the immunoglobulin C_{H1} heavy chain constant domain; and

L_1, L_2, L_3, and L_4 are amino acid linkers;

and wherein the polypeptides of formula I and the polypeptides of formula II form a cross-over light chain-heavy chain pair.

Claim 43. The method of claim 42, wherein the first antibody variable domain and the second antibody variable domain are the same.

CLAIMS

Claim 1. An antibody-like binding protein comprising four polypeptide chains that form four antigen binding sites, wherein two polypeptide chains have a structure represented by the formula:

$$V_{L1}\text{-}L_1\text{-}V_{L2}\text{-}L_2\text{-}C_L \qquad [I]$$

and two polypeptide chains have a structure represented by the formula:

$$V_{H2}\text{-}L_3\text{-}V_{H1}\text{-}L_4\text{-}C_{H1}\text{-}Fc \qquad [II]$$

wherein:

V_{L1} is a first immunoglobulin light chain variable domain;

V_{L2} is a second immunoglobulin light chain variable domain;

V_{H1} is a first immunoglobulin heavy chain variable domain;

V_{H2} is a second immunoglobulin heavy chain variable domain;

C_L is an immunoglobulin light chain constant domain;

C_{H1} is the immunoglobulin C_{H1} heavy chain constant domain;

Fc is the immunoglobulin hinge region and C_{H2}, C_{H3} immunoglobulin heavy chain constant domains; and

L_1, L_2, L_3, and L_4 are amino acid linkers;

and wherein the polypeptides of formula I and the polypeptides of formula II form a cross-over light chain-heavy chain pair.

Claim 2. The antibody-like binding protein of claim 1, wherein:

L_1 is 3 to 12 amino acid residues in length;

L_2 is 3 to 14 amino acid residues in length;

L_3 is 1 to 8 amino acid residues in length; and

L_4 is 1 to 3 amino acid residues in length.

Claim 3. The antibody-like binding protein of either claim 1 or 2, wherein:

L_1 is 5 to 10 amino acid residues in length;

L_2 is 5 to 8 amino acid residues in length;

L_3 is 1 to 5 amino acid residues in length; and

L_4 is 1 to 2 amino acid residues in length.

Claim 4. The antibody-like binding protein of any one of claims 1-3, wherein:

L_1 is 7 amino acid residues in length;

L_2 is 5 amino acid residues in length;

L_3 is 1 amino acid residues in length; and

L_4 is 2 amino acid residues in length.

Claim 5. The antibody-like binding protein of claim 1, wherein:

L_1 is 1 to 3 amino acid residues in length;

L_2 is 1 to 4 amino acid residues in length;

L_3 is 2 to 15 amino acid residues in length; and

L_4 is 2 to 15 amino acid residues in length.

Claim 6. The antibody-like binding protein of either claim 1 or 5, wherein:

L_1 is 1 to 2 amino acid residues in length;

L_2 is 1 to 2 amino acid residues in length;

L_3 is 4 to 12 amino acid residues in length; and

L_4 is 2 to 12 amino acid residues in length.

Claim 7. The antibody-like binding protein of any one of claims 1, 5, or 6, wherein:

L_1 is 1 amino acid residue in length;

L_2 is 2 amino acid residues in length;

L_3 is 7 amino acid residues in length; and

L_4 is 5 amino acid residues in length.

Claim 8. The antibody-like binding protein of claim 1, wherein L_1 is 0 amino acid residues in length and L_3 is 2 or more amino acid residues in length.

Claim 9. The antibody-like binding protein of claim 1, wherein L_3 is 0 amino acid residues in length and L_1 is 1 or more amino acid residues in length.

Claim 10. The antibody-like binding protein of claim 1, wherein L_4 is 0 amino acid residues in length and L_2 is 3 or more amino acid residues in length.

Claim 11. The antibody-like binding protein of any one of claims 1-10, wherein the binding protein is capable of specifically binding one or more antigen targets.

Claim 12. The antibody-like binding protein of any one of claims 1-11, wherein the one or more antigen targets is selected from the group consisting of B7.1, B7.2, BAFF, BlyS, C3, C5, CCL11 (eotaxin), CCL15 (MIP-1d), CCL17 (TARC), CCL19 (MIP-3b), CCL2 (MCP-1), CCL20 (MIP-3a), CCL21 (MIP-2), SLC, CCL24 (MPIF-2/eotaxin-2), CCL25 (TECK), CCL26 (eotaxin-3), CCL3 (MIP-1a), CCL4 (MIP-1b), CCL5 (RANTES), CCL7 (MCP-3), CCL8 (mcp-2), CD3, CD19, CD20, CD24, CD40, CD40L, CD80, CD86, CDH1 (E-cadherin), Chitinase, CSF1 (M-CSF), CSF2 (GM-CSF), CSF3 (GCSF), CTLA4, CX3CL1 (SCYD1), CXCL12 (SDF1), CXCL13, EGFR, FCER1A, FCER2, HER2, IGF1R, IL-1, IL-12, IL13, IL15, IL17, IL18, IL1A, IL1B, IL1F10, IL1β, IL2, IL4, IL6, IL7, IL8, IL9, IL12/23, IL22, IL23, IL25, IL27, IL35, ITGB4 (b 4 integrin), LEP (leptin), MHC class II, TLR2, TLR4, TLR5, TNF, TNFα, TNFSF4 (OX40 ligand), TNFSF5 (CD40 ligand), Toll-like receptors, TREM1, TSLP, TWEAK, XCR1 (GPR5/CCXCR1), DNGR-1(CLEC91), and HMGB1.

Claim 13. The antibody-like binding protein of any one of claims 1-12, wherein the binding protein is bispecific and capable of binding two different antigen targets.

Claim 14. The antibody-like binding protein of any one of claims 1-13, wherein the two different antigen targets are selected from the group consisting of IL4 and IL13, IGF1R and HER2, IGF1R and EGFR, EGFR and HER2, BK and IL13, PDL-1 and CTLA-4, CTLA4 and MHC class II, IL-12 and IL-18, IL-1α and IL-1β, TNFα and IL12/23, TNFα and IL-12p40, TNFα and IL1β, TNFα and IL-23, and IL17 and IL23.

Claim 15. The antibody-like binding protein of any one of claims 1-14, wherein the binding protein is capable of inhibiting the function of one or more of the antigen targets.

Claim 16. The antibody-like binding protein of any one of claims 1-15, wherein at least one of the linkers selected from the group consisting of L_1, L_2, L_3, and L_4 contains at least one cysteine residue.

Claim 17. An antibody-like binding protein comprising two polypeptide chains that form two antigen binding sites, wherein a first polypeptide chain has a structure represented by the formula:

$$V_{L1}\text{-}L_1\text{-}V_{L2}\text{-}L_2\text{-}C_L \qquad [I]$$

and a second polypeptide chain has a structure represented by the formula:

$$V_{H2}\text{-}L_3\text{-}V_{H1}\text{-}L_4\text{-}C_{H1} \qquad [II]$$

wherein:

V_{L1} is a first immunoglobulin light chain variable domain;

V_{L2} is a second immunoglobulin light chain variable domain;

V_{H1} is a first immunoglobulin heavy chain variable domain;

V_{H2} is a second immunoglobulin heavy chain variable domain;

C_L is an immunoglobulin light chain constant domain;

C_{H1} is the immunoglobulin C_{H1} heavy chain constant domain; and

L_1, L_2, L_3, and L_4 are amino acid linkers;

and wherein the first and second polypeptides form a cross-over light chain-heavy chain pair.

Claim 18. The antibody-like binding protein of claim 17, wherein:

L_1 is 3 to 12 amino acid residues in length;

L_2 is 3 to 14 amino acid residues in length;

L_3 is 1 to 8 amino acid residues in length; and

L_4 is 1 to 3 amino acid residues in length.

Claim 19. The antibody-like binding protein of either claim 17 or 18, wherein:

L_1 is 5 to 10 amino acid residues in length;

L_2 is 5 to 8 amino acid residues in length;

L_3 is 1 to 5 amino acid residues in length; and

L_4 is 1 to 2 amino acid residues in length.

Claim 20. The antibody-like binding protein of any one of claims 17-19, wherein:

L_1 is 7 amino acid residues in length;

L_2 is 5 amino acid residues in length;

L_3 is 1 amino acid residues in length; and

L_4 is 2 amino acid residue in length.

Claim 21. The antibody-like binding protein of claim 17, wherein:

L_1 is 1 to 3 amino acid residues in length;

L_2 is 1 to 4 amino acid residues in length;

L_3 is 2 to 15 amino acid residues in length; and

L_4 is 2 to 15 amino acid residues in length.

Claim 22. The antibody-like binding protein of either claim 17 or 21, wherein:

L_1 is 1 to 2 amino acid residues in length;

L_2 is 1 to 2 amino acid residues in length;

L_3 is 4 to 12 amino acid residues in length; and

L_4 is 2 to 12 amino acid residues in length.

Claim 23. The antibody-like binding protein of any one of claims 17, 21, or 22, wherein:

L_1 is 1 amino acid residue in length;

L_2 is 2 amino acid residues in length;

L_3 is 7 amino acid residues in length; and

L_4 is 5 amino acid residues in length.

Claim 24. The antibody-like binding protein of claim 17, wherein L_1 is 0 amino acid residues in length and L_3 is 2 or more amino acid residues in length.

Claim 25. The antibody-like binding protein of claim 17, wherein L_3 is 0 amino acid residues in length and L_1 is 1 or more amino acid residues in length.

Claim 26. The antibody-like binding protein of claim 17, wherein L_4 is 0 amino acid residues in length and L_2 is 3 or more amino acid residues in length.

Claim 27. The antibody-like binding protein of any one of claims 17-26, wherein the binding protein is capable of specifically binding one or more antigen targets.

Claim 28. The antibody-like binding protein of any one of claims 17-27, wherein the one or more antigen targets is selected from the group consisting of B7.1, B7.2, BAFF, BlyS, C3, C5, CCL11 (eotaxin), CCL15 (MIP-1d), CCL17 (TARC), CCL19 (MIP-3b), CCL2 (MCP-1), CCL20 (MIP-3a), CCL21 (MIP-2), SLC, CCL24 (MPIF-2/eotaxin-2), CCL25 (TECK), CCL26 (eotaxin-3), CCL3 (MIP-1a), CCL4 (MIP-1b), CCL5 (RANTES), CCL7 (MCP-3), CCL8 (mcp-2), CD3, CD19, CD20, CD24, CD40, CD40L, CD80, CD86, CDH1 (E-cadherin), Chitinase, CSF1 (M-CSF), CSF2 (GM-CSF), CSF3 (GCSF), CTLA4, CX3CL1 (SCYD1), CXCL12 (SDF1), CXCL13, EGFR, FCER1A, FCER2, HER2, IGF1R, IL-1, IL-12, IL13, IL15, IL17, IL18, IL1A, IL1B, IL1F10, IL1β, IL2, IL4, IL6, IL7, IL8, IL9, IL12/23, IL22, IL23, IL25, IL27, IL35, ITGB4 (b 4 integrin), LEP (leptin), MHC class II, TLR2, TLR4, TLR5, TNF, TNFα, TNFSF4 (OX40 ligand), TNFSF5 (CD40 ligand), Toll-like receptors, TREM1, TSLP, TWEAK, XCR1 (GPR5/CCXCR1), DNGR-1(CLEC91), and HMGB1.

Claim 29. The antibody-like binding protein of any one of claims 17-28, wherein the binding protein is bispecific and capable of binding two different antigen targets.

Claim 30. The antibody-like binding protein of any one of claims 17-29, wherein the two different antigen targets are selected from the group consisting of IL4 and IL13, IGF1R and HER2, IGF1R and EGFR, EGFR and HER2, BK and IL13, PDL-1 and CTLA-4, CTLA4 and MHC class II, IL-12 and IL-18, IL-1α and IL-1β, TNFα and IL12/23, TNFα and IL-12p40, TNFα and IL1β, TNFα and IL-23, and IL17 and IL23.

Claim 31. The antibody-like binding protein of any one of claims 17-30, wherein the binding protein is capable of inhibiting the function of one or more of the antigen targets.

Claim 32. The antibody-like binding protein of any one of claims 17-31, wherein at least one of the linkers selected from the group consisting of L_1, L_2, L_3, and L_4 contains at least one cysteine residue.

Claim 33. An isolated nucleic acid molecule comprising a nucleotide sequence encoding the antibody-like binding protein of any one of claims 1-32.

Claim 34. An expression vector comprising the nucleic acid molecule of claim 33.

Claim 35. An isolated host cell comprising the nucleic acid molecule of claim 33 or the expression vector of claim 34.

Claim 36. The host cell of claim 35, wherein the host cell is a mammalian cell or an insect cell.

Claim 37. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of the antibody-like binding protein of any one of claims 1-32.

Claim 38. A method for making the antibody-like binding protein of any one of claims 1-16, comprising expressing in a cell one or more nucleic acid molecules encoding polypeptides having structures represented by the formulas [I] and [II] below:

$$V_{L1}\text{-}L_1\text{-}V_{L2}\text{-}L_2\text{-}C_L \qquad [I]$$

$$V_{H2}\text{-}L_3\text{-}V_{H1}\text{-}L_4\text{-}C_{H1}\text{-}Fc \qquad [II]$$

wherein:

V_{L1} is a first immunoglobulin light chain variable domain;

V_{L2} is a second immunoglobulin light chain variable domain;

V_{H1} is a first immunoglobulin heavy chain variable domain;

V_{H2} is a second immunoglobulin heavy chain variable domain;

C_L is an immunoglobulin light chain constant domain;

C_{H1} is the immunoglobulin C_{H1} heavy chain constant domain;

Fc is the immunoglobulin hinge region and C_{H2}, C_{H3} immunoglobulin heavy chain constant domains; and

L_1, L_2, L_3, and L_4 are amino acid linkers;

and wherein the polypeptides of formula I and the polypeptides of formula II form a cross-over light chain-heavy chain pair.

Claim 39. A method for making the antibody-like binding protein of any one of claims 17-32, comprising expressing in a cell one or more nucleic acid molecules encoding polypeptides having structures represented by the formulas [I] and [II] below:

$$V_{L1}\text{-}L_1\text{-}V_{L2}\text{-}L_2\text{-}C_L \quad [I]$$

$$V_{H2}\text{-}L_3\text{-}V_{H1}\text{-}L_4\text{-}C_{H1} \quad [II]$$

wherein:

V_{L1} is a first immunoglobulin light chain variable domain;

V_{L2} is a second immunoglobulin light chain variable domain;

V_{H1} is a first immunoglobulin heavy chain variable domain;

V_{H2} is a second immunoglobulin heavy chain variable domain;

C_L is an immunoglobulin light chain constant domain;

C_{H1} is the immunoglobulin C_{H1} heavy chain constant domain; and

L_1, L_2, L_3, and L_4 are amino acid linkers;

and wherein the polypeptide of formula I and the polypeptide of formula II form a cross-over light chain-heavy chain pair.

Claim 40. A method of making an antibody-like binding protein comprising four polypeptide chains that form four antigen binding sites, comprising:

(a) identifying a first antibody variable domain that binds a first target antigen and a second antibody variable domain that binds a second target antigen, each containing a V_L, and a V_H;

(b) assigning either the light chain or the heavy chain as template chain;

(c) assigning the V_L of the first antibody variable domain or the second antibody variable domain as V_{L1};

(d) assigning a V_{L2}, a V_{H1}, and a V_{H2} according to formulas [I] and [II] below:

$$V_{L1}\text{-}L_1\text{-}V_{L2}\text{-}L_2\text{-}C_L \qquad [I]$$

$$V_{H2}\text{-}L_3\text{-}V_{H1}\text{-}L_4\text{-}C_{H1}\text{-}Fc \qquad [II]$$

(e) determining maximum and minimum lengths for L_1, L_2, L_3, and L_4;

(f) generating polypeptide structures of formulas I and II;

(g) selecting polypeptide structures of formulas I and II that bind the first target antigen and the second target antigen when combined to form the antibody-like binding protein;

wherein:

V_{L1} is a first immunoglobulin light chain variable domain;

V_{L2} is a second immunoglobulin light chain variable domain;

V_{H1} is a first immunoglobulin heavy chain variable domain;

V_{H2} is a second immunoglobulin heavy chain variable domain;

C_L is an immunoglobulin light chain constant domain;

C_{H1} is the immunoglobulin C_{H1} heavy chain constant domain;

Fc is the immunoglobulin hinge region and C_{H2}, C_{H3} immunoglobulin heavy chain constant domains; and

L_1, L_2, L_3, and L_4 are amino acid linkers;

and wherein the polypeptides of formula I and the polypeptides of formula II form a cross-over light chain-heavy chain pair.

Claim 41. The method of claim 40, wherein the first antibody variable domain and the second antibody variable domain are the same.

Claim 42. A method of making an antibody-like binding protein comprising four polypeptide chains that form four antigen binding sites, comprising:

(a) identifying a first antibody variable domain that binds a first target antigen and a second antibody variable domain that binds a second target antigen, each containing a V_L, and a V_H;

(b) assigning either the light chain or the heavy chain as template chain;

(c) assigning the V_L of the first antibody variable domain or the second antibody variable domain as V_{L1};

(d) assigning a V_{L2}, a V_{H1}, and a V_{H2} according to formulas [I] and [II] below:

$$V_{L1}\text{-}L_1\text{-}V_{L2}\text{-}L_2\text{-}C_L \quad [I]$$

$$V_{H2}\text{-}L_3\text{-}V_{H1}\text{-}L_4\text{-}C_{H1} \quad [II]$$

(e) determining maximum and minimum lengths for L_1, L_2, L_3, and L_4;

(f) generating polypeptide structures of formulas I and II;

(g) selecting polypeptide structures of formulas I and II that bind the first target antigen and the second target antigen when combined to form the antibody-like binding protein;

wherein:

V_{L1} is a first immunoglobulin light chain variable domain;

V_{L2} is a second immunoglobulin light chain variable domain;

V_{H1} is a first immunoglobulin heavy chain variable domain;

V_{H2} is a second immunoglobulin heavy chain variable domain;

C_L is an immunoglobulin light chain constant domain;

C_{H1} is the immunoglobulin C_{H1} heavy chain constant domain; and

L_1, L_2, L_3, and L_4 are amino acid linkers;

and wherein the polypeptides of formula I and the polypeptides of formula II form a cross-over light chain-heavy chain pair.

Claim 43. The method of claim 42, wherein the first antibody variable domain and the second antibody variable domain are the same.

Claim 44. The antibody-like binding protein of either claim 1 or 17, wherein L_2 and L_4 are both at least one amino acid in length, and

(a) the length of L_2 is at least twice the length of L_4; or

(b) the length of L_4 is at least twice the length of L_2.

Claim 45. An antibody-like binding protein or method thereof according to any one of claims 1-44 as substantially described herein with reference to the figures and examples.