

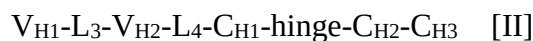
CLAIMS

What is claimed is:

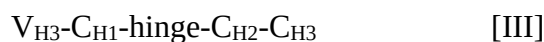
1. A trispecific binding protein comprising three antigen binding sites that each bind one or more target proteins, wherein at least one of the three antigen binding sites cross-reacts with an extracellular domain of a human CD38 polypeptide and an extracellular domain of a cynomolgus monkey CD38 polypeptide; wherein the binding protein comprises four polypeptide chains that form the three antigen binding sites, wherein a first polypeptide chain comprises a structure represented by the formula:



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



and a third polypeptide chain comprises a structure represented by the formula:



and a fourth polypeptide chain comprises a structure represented by the formula:



wherein:

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

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

V_{L3} is a third 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;

V_{H3} is a third immunoglobulin heavy chain variable domain;

C_L is an immunoglobulin light chain constant domain;

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

C_{H2} is an immunoglobulin C_{H2} heavy chain constant domain;

C_{H3} is an immunoglobulin C_{H3} heavy chain constant domain;

hinge is an immunoglobulin hinge region connecting the C_{H1} and C_{H2} domains;

and

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

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

wherein:

(a) the V_{H1} domain comprises a CDR-H1 sequence comprising the amino acid sequence of GYTFTSFN (SEQ ID NO:31), a CDR-H2 sequence comprising the amino acid sequence of IYPGNGGT (SEQ ID NO:32), and a CDR-H3 sequence comprising the amino acid sequence of ARTGGLRRAYFTY (SEQ ID NO:33), and the V_{L1} domain comprises a CDR-L1 sequence comprising the amino acid sequence of ESVDSYGNGF (SEQ ID NO:34), a CDR-L2 sequence comprising the amino acid sequence of LAS (SEQ ID NO:35), and a CDR-L3 sequence comprising the amino acid sequence of QQNKEDPWT (SEQ ID NO:36);

(b) the V_{H2} domain comprises a CDR-H1 sequence comprising the amino acid sequence of GYTFTSFN (SEQ ID NO:31), a CDR-H2 sequence comprising the amino acid sequence of IYPGNGGT (SEQ ID NO:32), and a CDR-H3 sequence comprising the amino acid sequence of ARTGGLRRAYFTY (SEQ ID NO:33), and the V_{L2} domain comprises a CDR-L1 sequence comprising the amino acid sequence of ESVDSYGNGF (SEQ ID NO:34), a CDR-L2 sequence comprising the amino acid sequence of LAS (SEQ ID NO:35), and a CDR-L3 sequence comprising the amino acid sequence of QQNKEDPWT (SEQ ID NO:36);

(c) the V_{H3} domain comprises a CDR-H1 sequence comprising the amino acid sequence of GYTFTSFN (SEQ ID NO:31), a CDR-H2 sequence comprising the amino acid sequence of IYPGNGGT (SEQ ID NO:32), and a CDR-H3 sequence comprising the amino acid sequence of ARTGGLRRAYFTY (SEQ ID NO:33), and the V_{L3} domain comprises a CDR-L1 sequence comprising the amino acid sequence of ESVDSYGNGF (SEQ ID NO:34), a CDR-L2 sequence comprising the amino acid sequence of LAS (SEQ ID NO:35), and a CDR-L3 sequence comprising the amino acid sequence of QQNKEDPWT (SEQ ID NO:36);

(d) the V_{H1} domain comprises a CDR-H1 sequence comprising the amino acid sequence of GYTFTSYA (SEQ ID NO:37), a CDR-H2 sequence comprising the amino acid sequence of IYPGQGGT (SEQ ID NO:38), and a CDR-H3 sequence comprising the amino acid sequence of ARTGGLRRAYFTY (SEQ ID NO:33), and the V_{L1} domain comprises a CDR-L1 sequence comprising the amino acid sequence of QSVSSYGQGF (SEQ ID NO:39), a CDR-L2 sequence comprising the amino acid sequence of GAS (SEQ ID NO:40), and a CDR-L3 sequence comprising the amino acid sequence of QQNKEDPWT (SEQ ID NO:36);

(e) the V_{H2} domain comprises a CDR-H1 sequence comprising the amino acid sequence of GYTFTSYA (SEQ ID NO:37), a CDR-H2 sequence comprising the amino acid sequence of IYPGQGGT (SEQ ID NO:38), and a CDR-H3 sequence comprising the amino acid sequence of ARTGGLRRAYFTY (SEQ ID NO:33), and the V_{L2} domain comprises a CDR-L1 sequence comprising the amino acid sequence of QSVSSYGQGF (SEQ ID NO:39), a CDR-L2 sequence comprising the amino acid sequence of GAS (SEQ ID NO:40), and a CDR-L3 sequence comprising the amino acid sequence of QQNKEDPWT (SEQ ID NO:36);

(f) the V_{H3} domain comprises a CDR-H1 sequence comprising the amino acid sequence of GYTFTSYA (SEQ ID NO:37), a CDR-H2 sequence comprising the amino acid sequence of IYPGQGGT (SEQ ID NO:38), and a CDR-H3 sequence comprising the amino acid sequence of ARTGGLRRAYFTY (SEQ ID NO:33), and the V_{L3} domain comprises a CDR-L1 sequence comprising the amino acid sequence of QSVSSYGQGF (SEQ ID NO:39), a CDR-L2 sequence comprising the amino acid sequence of GAS (SEQ ID NO:40), and a CDR-L3 sequence comprising the amino acid sequence of QQNKEDPWT (SEQ ID NO:36);

(g) the V_{H1} domain comprises a CDR-H1 sequence comprising the amino acid sequence of GFTFSSYG (SEQ ID NO:41), a CDR-H2 sequence comprising the amino acid sequence of IWYDGSNK (SEQ ID NO:42), and a CDR-H3 sequence comprising the amino acid sequence of ARMFRGAFDY (SEQ ID NO:43), and the V_{L1} domain comprises a CDR-L1 sequence comprising the amino acid sequence of QGIRND (SEQ ID NO:44), a CDR-L2 sequence comprising the amino acid sequence of AAS (SEQ ID NO:45), and a CDR-L3 sequence comprising the amino acid sequence of LQDYIYYPT (SEQ ID NO:46);

(h) the V_{H2} domain comprises a CDR-H1 sequence comprising the amino acid sequence of GFTFSSYG (SEQ ID NO:41), a CDR-H2 sequence comprising the amino acid sequence of IWYDGSNK (SEQ ID NO:42), and a CDR-H3 sequence comprising the amino acid sequence of ARMFRGAFDY (SEQ ID NO:43), and the V_{L2} domain comprises a CDR-L1 sequence comprising the amino acid sequence of QGIRND (SEQ ID NO:44), a CDR-L2 sequence comprising the amino acid sequence of AAS (SEQ ID NO:45), and a CDR-L3 sequence comprising the amino acid sequence of LQDYIYYPT (SEQ ID NO:46); or

(i) the V_{H3} domain comprises a CDR-H1 sequence comprising the amino acid sequence of GFTFSSYG (SEQ ID NO:41), a CDR-H2 sequence comprising the amino acid sequence of IWYDGSNK (SEQ ID NO:42), and a CDR-H3 sequence comprising the amino acid sequence of ARMFRGAFDY (SEQ ID NO:43), and the V_{L3} domain comprises a CDR-L1 sequence comprising the amino acid sequence of QGIRND (SEQ ID NO:44), a CDR-L2 sequence comprising the amino acid sequence of AAS (SEQ ID NO:45), and a CDR-L3 sequence comprising the amino acid sequence of LQDYIYYPT (SEQ ID NO:46).

2. The binding protein of claim 1, wherein the binding protein cross-reacts with a human CD38 polypeptide comprising the amino acid sequence of SEQ ID NO:1 or SEQ ID NO:105.

3. The binding protein of claim 1 or claim 2, wherein the binding protein cross-reacts with a cynomolgus monkey CD38 polypeptide comprising the amino acid sequence of SEQ ID NO:30.

4. The binding protein of any one of claims 1-3, wherein the binding protein comprises the antigen binding site that cross-reacts with an extracellular domain of a human CD38 polypeptide and an extracellular domain of a cynomolgus monkey CD38 polypeptide and two antigen binding sites that each bind a T-cell surface protein.

5. The binding protein of claim 4, wherein the binding protein comprises the antigen binding site that cross-reacts with an extracellular domain of a human CD38 polypeptide and an extracellular domain of a cynomolgus monkey CD38 polypeptide, an antigen binding site that binds a human CD28 polypeptide, and an antigen binding site that binds a human CD3 polypeptide.

6. The binding protein of claim 1, wherein

(a) the V_{H1} domain comprises a CDR-H1 sequence comprising the amino acid sequence of GYTFTSFN (SEQ ID NO:31), a CDR-H2 sequence comprising the amino acid sequence of IYPGNGGT (SEQ ID NO:32), and a CDR-H3 sequence comprising the amino acid sequence of ARTGGLRRAYFTY (SEQ ID NO:33), and the V_{L1} domain comprises a CDR-L1 sequence comprising the amino acid sequence of ESVDSYGNGF (SEQ ID NO:34), a CDR-L2 sequence comprising the amino acid sequence of LAS (SEQ

ID NO:35), and a CDR-L3 sequence comprising the amino acid sequence of QQNKEDPWT (SEQ ID NO:36);

(b) the V_{H1} domain comprises a CDR-H1 sequence comprising the amino acid sequence of GYTFTSYA (SEQ ID NO:37), a CDR-H2 sequence comprising the amino acid sequence of IYPGQGGT (SEQ ID NO:38), and a CDR-H3 sequence comprising the amino acid sequence of ARTGGLRRAYFTY (SEQ ID NO:33), and the V_{L1} domain comprises a CDR-L1 sequence comprising the amino acid sequence of QSVSSYGQGF (SEQ ID NO:39), a CDR-L2 sequence comprising the amino acid sequence of GAS (SEQ ID NO:40), and a CDR-L3 sequence comprising the amino acid sequence of QQNKEDPWT (SEQ ID NO:36);

(c) the V_{H2} domain comprises a CDR-H1 sequence comprising the amino acid sequence of GYTFTSFN (SEQ ID NO:31), a CDR-H2 sequence comprising the amino acid sequence of IYPGNGGT (SEQ ID NO:32), and a CDR-H3 sequence comprising the amino acid sequence of ARTGGLRRAYFTY (SEQ ID NO:33), and the V_{L2} domain comprises a CDR-L1 sequence comprising the amino acid sequence of ESVDSYGNGF (SEQ ID NO:34), a CDR-L2 sequence comprising the amino acid sequence of LAS (SEQ ID NO:35), and a CDR-L3 sequence comprising the amino acid sequence of QQNKEDPWT (SEQ ID NO:36);

(d) the V_{H2} domain comprises a CDR-H1 sequence comprising the amino acid sequence of GYTFTSYA (SEQ ID NO:37), a CDR-H2 sequence comprising the amino acid sequence of IYPGQGGT (SEQ ID NO:38), and a CDR-H3 sequence comprising the amino acid sequence of ARTGGLRRAYFTY (SEQ ID NO:33), and the V_{L2} domain comprises a CDR-L1 sequence comprising the amino acid sequence of QSVSSYGQGF (SEQ ID NO:39), a CDR-L2 sequence comprising the amino acid sequence of GAS (SEQ ID NO:40), and a CDR-L3 sequence comprising the amino acid sequence of QQNKEDPWT (SEQ ID NO:36);

(e) the V_{H3} domain comprises a CDR-H1 sequence comprising the amino acid sequence of GYTFTSFN (SEQ ID NO:31), a CDR-H2 sequence comprising the amino acid sequence of IYPGNGGT (SEQ ID NO:32), and a CDR-H3 sequence comprising the amino acid sequence of ARTGGLRRAYFTY (SEQ ID NO:33), and the V_{L3} domain comprises a CDR-L1 sequence comprising the amino acid sequence of ESVDSYGNGF (SEQ ID NO:34), a CDR-L2 sequence comprising the amino acid sequence of LAS (SEQ

ID NO:35), and a CDR-L3 sequence comprising the amino acid sequence of QQNKEDPWT (SEQ ID NO:36); or

(h) the V_{H3} domain comprises a CDR-H1 sequence comprising the amino acid sequence of GYTFTSYA (SEQ ID NO:37), a CDR-H2 sequence comprising the amino acid sequence of IYPGQGGT (SEQ ID NO:38), and a CDR-H3 sequence comprising the amino acid sequence of ARTGGLRRAYFTY (SEQ ID NO:33), and the V_{L3} domain comprises a CDR-L1 sequence comprising the amino acid sequence of QSVSSYGQGF (SEQ ID NO:39), a CDR-L2 sequence comprising the amino acid sequence of GAS (SEQ ID NO:40), and a CDR-L3 sequence comprising the amino acid sequence of QQNKEDPWT (SEQ ID NO:36).

7. The binding protein of claim 6, wherein

(a) the V_{H3} domain comprises a CDR-H1 sequence comprising the amino acid sequence of GYTFTSFN (SEQ ID NO:31), a CDR-H2 sequence comprising the amino acid sequence of IYPGNGGT (SEQ ID NO:32), and a CDR-H3 sequence comprising the amino acid sequence of ARTGGLRRAYFTY (SEQ ID NO:33), and the V_{L3} domain comprises a CDR-L1 sequence comprising the amino acid sequence of ESVDSYGNGF (SEQ ID NO:34), a CDR-L2 sequence comprising the amino acid sequence of LAS (SEQ ID NO:35), and a CDR-L3 sequence comprising the amino acid sequence of QQNKEDPWT (SEQ ID NO:36); or

(b) the V_{H3} domain comprises a CDR-H1 sequence comprising the amino acid sequence of GYTFTSYA (SEQ ID NO:37), a CDR-H2 sequence comprising the amino acid sequence of IYPGQGGT (SEQ ID NO:38), and a CDR-H3 sequence comprising the amino acid sequence of ARTGGLRRAYFTY (SEQ ID NO:33), and the V_{L3} domain comprises a CDR-L1 sequence comprising the amino acid sequence of QSVSSYGQGF (SEQ ID NO:39), a CDR-L2 sequence comprising the amino acid sequence of GAS (SEQ ID NO:40), and a CDR-L3 sequence comprising the amino acid sequence of QQNKEDPWT (SEQ ID NO:36).

8. The binding protein of claim 7, wherein

(a) the V_{H3} domain comprises the amino acid sequence of SEQ ID NO:5, and the V_{L3} domain comprises the amino acid sequence of SEQ ID NO:6;

(b) the V_{H3} domain comprises the amino acid sequence of SEQ ID NO:17, and the V_{L3} domain comprises the amino acid sequence of SEQ ID NO:18;

(c) the V_{H3} domain comprises the amino acid sequence of SEQ ID NO:21, and the V_{L3} domain comprises the amino acid sequence of SEQ ID NO:18;

(d) the V_{H3} domain comprises the amino acid sequence of SEQ ID NO:23, and the V_{L3} domain comprises the amino acid sequence of SEQ ID NO:18; or

(e) the V_{H3} domain comprises the amino acid sequence of SEQ ID NO:13, and the V_{L3} domain comprises the amino acid sequence of SEQ ID NO:14.

9. The binding protein of claim 1, wherein the V_{H3} domain comprises a CDR-H1 sequence comprising the amino acid sequence of GFTFSSYG (SEQ ID NO:41), a CDR-H2 sequence comprising the amino acid sequence of IWYDGSNK (SEQ ID NO:42), and a CDR-H3 sequence comprising the amino acid sequence of ARMFRGAFDY (SEQ ID NO:43), and the V_{L3} domain comprises a CDR-L1 sequence comprising the amino acid sequence of QGIRND (SEQ ID NO:44), a CDR-L2 sequence comprising the amino acid sequence of AAS (SEQ ID NO:45), and a CDR-L3 sequence comprising the amino acid sequence of LQDYIYYPT (SEQ ID NO:46).

10. The binding protein of claim 9, wherein the V_{H3} domain comprises the amino acid sequence of SEQ ID NO:9, and the V_{L3} domain comprises the amino acid sequence of SEQ ID NO:10.

11. The binding protein of any one of claims 1, 9, and 10, wherein

(a) the V_{H1} domain comprises the amino acid sequence of SEQ ID NO:49, the V_{L1} domain comprises the amino acid sequence of SEQ ID NO:50, the V_{H2} domain comprises the amino acid sequence of SEQ ID NO:53, and the V_{L2} domain comprises the amino acid sequence of SEQ ID NO:54;

(b) the V_{H2} domain comprises the amino acid sequence of SEQ ID NO:49, the V_{L2} domain comprises the amino acid sequence of SEQ ID NO:50, the V_{H1} domain comprises the amino acid sequence of SEQ ID NO:53, and the V_{L1} domain comprises the amino acid sequence of SEQ ID NO:54;

(c) the V_{H1} domain comprises the amino acid sequence of SEQ ID NO:51, the V_{L1} domain comprises the amino acid sequence of SEQ ID NO:52, the V_{H2} domain comprises the amino acid sequence of SEQ ID NO:53, and the V_{L2} domain comprises the amino acid sequence of SEQ ID NO:54;

(d) the V_{H2} domain comprises the amino acid sequence of SEQ ID NO:51, the V_{L2} domain comprises the amino acid sequence of SEQ ID NO:52, the V_{H1} domain comprises the amino acid sequence of SEQ ID NO:53, and the V_{L1} domain comprises the amino acid sequence of SEQ ID NO:54

(e) the V_{H1} domain comprises the amino acid sequence of SEQ ID NO:49, the V_{L1} domain comprises the amino acid sequence of SEQ ID NO:50, the V_{H2} domain comprises the amino acid sequence of SEQ ID NO:84, and the V_{L2} domain comprises the amino acid sequence of SEQ ID NO:85;

(f) the V_{H2} domain comprises the amino acid sequence of SEQ ID NO:49, the V_{L2} domain comprises the amino acid sequence of SEQ ID NO:50, the V_{H1} domain comprises the amino acid sequence of SEQ ID NO:84, and the V_{L1} domain comprises the amino acid sequence of SEQ ID NO:85;

(g) the V_{H1} domain comprises the amino acid sequence of SEQ ID NO:51, the V_{L1} domain comprises the amino acid sequence of SEQ ID NO:52, the V_{H2} domain comprises the amino acid sequence of SEQ ID NO:84, and the V_{L2} domain comprises the amino acid sequence of SEQ ID NO:85; or

(h) the V_{H2} domain comprises the amino acid sequence of SEQ ID NO:51, the V_{L2} domain comprises the amino acid sequence of SEQ ID NO:52, the V_{H1} domain comprises the amino acid sequence of SEQ ID NO:84, and the V_{L1} domain comprises the amino acid sequence of SEQ ID NO:85.

12. The binding protein of claim 11, wherein

(a) the V_{H1} domain comprises the amino acid sequence of SEQ ID NO:49, the V_{L1} domain comprises the amino acid sequence of SEQ ID NO:50, the V_{H2} domain comprises the amino acid sequence of SEQ ID NO:53, the V_{L2} domain comprises the amino acid sequence of SEQ ID NO:54, the V_{H3} domain comprises the amino acid sequence of SEQ ID NO:13, and the V_{L3} domain comprises the amino acid sequence of SEQ ID NO:14; or

(b) the V_{H1} domain comprises the amino acid sequence of SEQ ID NO:49, the V_{L1} domain comprises the amino acid sequence of SEQ ID NO:50, the V_{H2} domain comprises the amino acid sequence of SEQ ID NO:53, the V_{L2} domain comprises the amino acid sequence of SEQ ID NO:54, the V_{H3} domain comprises the amino acid sequence of SEQ ID NO:9, and the V_{L3} domain comprises the amino acid sequence of SEQ ID NO:10.

13. The binding protein of any one of claims 1-12, wherein at least one of L_1 , L_2 , L_3 or L_4 is independently 0 amino acids in length.

14. The binding protein of any one of claims 1-12, wherein L_1 , L_2 , L_3 or L_4 are each independently at least one amino acid in length.

15. The binding protein of any one of claims 1-12, wherein (a) L_1 , L_2 , L_3 and L_4 each independently are zero amino acids in length or comprise a sequence selected from the group consisting of GGGGSGGGGS (SEQ ID NO:55), GGGGSGGGGSGGGGS (SEQ ID NO:56), S, RT, TKGPS (SEQ ID NO:57), GQPKAAP (SEQ ID NO: 58), and GGS GSSGSGG (SEQ ID NO:59); or (b) L_1 , L_2 , L_3 and L_4 each independently comprise a sequence selected from the group consisting of GGGGSGGGGS (SEQ ID NO:55), GGGGSGGGGSGGGGS (SEQ ID NO:56), S, RT, TKGPS (SEQ ID NO:57), GQPKAAP (SEQ ID NO: 58), and GGS GSSGSGG (SEQ ID NO:59).

16. The binding protein of any one of claims 1-12, wherein

(a) L_1 comprises the sequence GQPKAAP (SEQ ID NO: 58), L_2 comprises the sequence TKGPS (SEQ ID NO:57), L_3 comprises the sequence S, and L_4 comprises the sequence RT;

(b) L_1 comprises the sequence GGGGSGGGGS (SEQ ID NO:55), L_2 comprises the sequence GGGGSGGGGS (SEQ ID NO:55), L_3 is 0 amino acids in length, and L_4 is 0 amino acids in length;

(c) L_1 comprises the sequence GGS GSSGSGG (SEQ ID NO:59), L_2 comprises the sequence GGS GSSGSGG (SEQ ID NO:59), L_3 is 0 amino acids in length, and L_4 is 0 amino acids in length; or

(d) L_1 comprises the sequence GGGGSGGGGSGGGGS (SEQ ID NO:56), L_2 is 0 amino acids in length, L_3 comprises the sequence GGGGSGGGGSGGGGS (SEQ ID NO:56), and L_4 is 0 amino acids in length.

17. The binding protein of any one of claims 1-16, wherein the hinge- C_{H2} - C_{H3} domains of the second and the third polypeptide chains are human IgG4 hinge- C_{H2} - C_{H3} domains, and wherein the hinge- C_{H2} - C_{H3} domains each comprise amino acid substitutions at positions corresponding to positions 234 and 235 of human IgG4 according to EU Index, wherein the amino acid substitutions are F234A and L235A.
18. The binding protein of any one of claims 1-16, wherein the hinge- C_{H2} - C_{H3} domains of the second and the third polypeptide chains are human IgG4 hinge- C_{H2} - C_{H3} domains, and wherein the hinge- C_{H2} - C_{H3} domains each comprise amino acid substitutions at positions corresponding to positions 233-236 of human IgG4 according to EU Index, wherein the amino acid substitutions are E233P, F234V, L235A, and a deletion at 236.
19. The binding protein of any one of claims 1-18, wherein the hinge- C_{H2} - C_{H3} domains of the second and the third polypeptide chains are human IgG4 hinge- C_{H2} - C_{H3} domains, and wherein the hinge- C_{H2} - C_{H3} domains each comprise amino acid substitutions at positions corresponding to positions 228 and 409 of human IgG4 according to EU Index, wherein the amino acid substitutions are S228P and R409K.
20. The binding protein of any one of claims 1-16, wherein the hinge- C_{H2} - C_{H3} domains of the second and the third polypeptide chains are human IgG1 hinge- C_{H2} - C_{H3} domains, and wherein the hinge- C_{H2} - C_{H3} domains each comprise amino acid substitutions at positions corresponding to positions 234, 235, and 329 of human IgG1 according to EU Index, wherein the amino acid substitutions are L234A, L235A, and P329A.
21. The binding protein of any one of claims 1-16, wherein the hinge- C_{H2} - C_{H3} domains of the second and the third polypeptide chains are human IgG1 hinge- C_{H2} - C_{H3} domains, and wherein the hinge- C_{H2} - C_{H3} domains each comprise amino acid substitutions at positions corresponding to positions 298, 299, and 300 of human IgG1 according to EU Index, wherein the amino acid substitutions are S298N, T299A, and Y300S.
22. The binding protein of any one of claims 1-21, wherein the hinge- C_{H2} - C_{H3} domain of the second polypeptide chain comprises amino acid substitutions at positions corresponding to positions 349, 366, 368, and 407 of human IgG1 or IgG4 according to EU Index, wherein the amino acid substitutions are Y349C, T366S, L368A, and Y407V; and wherein the hinge- C_{H2} - C_{H3} domain of the third polypeptide chain comprises amino acid substitutions at positions corresponding to positions 354 and 366 of human IgG1 or

IgG4 according to EU Index, wherein the amino acid substitutions are S354C and T366W.

23. The binding protein of any one of claims 1-21, wherein the hinge- C_{H2} - C_{H3} domain of the second polypeptide chain comprises amino acid substitutions at positions corresponding to positions 354 and 366 of human IgG1 or IgG4 according to EU Index, wherein the amino acid substitutions are S354C and T366W; and wherein the hinge- C_{H2} - C_{H3} domain of the third polypeptide chain comprises amino acid substitutions at positions corresponding to positions 349, 366, 368, and 407 of human IgG1 or IgG4 according to EU Index, wherein the amino acid substitutions are Y349C, T366S, L368A, and Y407V.

24. The binding protein of claim 1, wherein the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:61, the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:60, the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:62, and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:63.

25. The binding protein of claim 1, wherein the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:61, the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:64, the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:65, and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:63.

26. The binding protein of claim 1, wherein the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:61, the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:66, the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:67, and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:63.

27. The binding protein of claim 1, wherein the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:61, the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:60, the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:68, and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:69.

28. The binding protein of claim 1, wherein the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:61, the second polypeptide chain comprises the

amino acid sequence of SEQ ID NO:64, the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:70, and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:69.

29. The binding protein of claim 1, wherein the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:61, the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:66, the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:71, and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:69.

30. A kit of polynucleotides, comprising:

(a) a first polynucleotide comprising the sequence of SEQ ID NO:73, a second polynucleotide comprising the sequence of SEQ ID NO:72, a third polynucleotide comprising the sequence of SEQ ID NO:74, and a fourth polynucleotide comprising the sequence of SEQ ID NO:75;

(b) a first polynucleotide comprising the sequence of SEQ ID NO:73, a second polynucleotide comprising the sequence of SEQ ID NO:76, a third polynucleotide comprising the sequence of SEQ ID NO:77, and a fourth polynucleotide comprising the sequence of SEQ ID NO:75;

(c) a first polynucleotide comprising the sequence of SEQ ID NO:73, a second polynucleotide comprising the sequence of SEQ ID NO:78, a third polynucleotide comprising the sequence of SEQ ID NO:79, and a fourth polynucleotide comprising the sequence of SEQ ID NO:75;

(d) a first polynucleotide comprising the sequence of SEQ ID NO:73, a second polynucleotide comprising the sequence of SEQ ID NO:72, a third polynucleotide comprising the sequence of SEQ ID NO:80, and a fourth polynucleotide comprising the sequence of SEQ ID NO:81;

(e) a first polynucleotide comprising the sequence of SEQ ID NO:73, a second polynucleotide comprising the sequence of SEQ ID NO:76, a third polynucleotide comprising the sequence of SEQ ID NO:82, and a fourth polynucleotide comprising the sequence of SEQ ID NO:81; or

(f) a first polynucleotide comprising the sequence of SEQ ID NO:73, a second polynucleotide comprising the sequence of SEQ ID NO:78, a third polynucleotide comprising the sequence of SEQ ID NO:83, and a fourth polynucleotide comprising the sequence of SEQ ID NO:81.

31. A polynucleotide encoding the binding protein of any one of claims 1-29.
32. A vector comprising the polynucleotide of claim 31.
33. A host cell comprising the kit of polynucleotides of claim 30, the polynucleotide of claim 31, or the vector of claim 32.
34. A method of producing a binding protein, the method comprising culturing the host cell of claim 33 such that the binding protein is produced.
35. The method of claim 34, further comprising recovering the binding protein from the host cell.
36. A pharmaceutical composition comprising the binding protein of any one of claims 1-29 and a pharmaceutically acceptable carrier.
37. The binding protein of any one of claims 1-29 or the pharmaceutical composition of claim 36 for use in preventing and/or treating cancer in a patient.
38. The binding protein or composition for use of claim 37, wherein the binding protein comprises one antigen binding site that binds a T-cell surface protein and another antigen binding site that binds the extracellular domain of a human CD38 polypeptide.
39. The binding protein or composition for use of claim 38, wherein the binding protein is a trispecific binding protein comprising a first antigen binding site that binds CD3, a second antigen binding site that binds CD28, and a third antigen binding site that binds the extracellular domain of a human CD38 polypeptide.
40. The binding protein or composition for use of any one of claims 37-39, wherein the binding protein or composition is to be co-administered with a chemotherapeutic agent.
41. The binding protein or composition for use of any one of claims 37-40, wherein the cancer is multiple myeloma.

42. The binding protein or composition for use of any one of claims 37-41, wherein the cancer is acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia (CLL), or a B cell lymphoma.

43. The binding protein or composition for use of any one of claims 37-42, wherein the patient is a human.

44. The binding protein or composition for use of any one of claims 37-43, wherein cells of the cancer from the patient express a human CD38 isoform E polypeptide on their cell surface.