

WHAT IS CLAIMED IS:

1. Isolated polypeptides comprising a light chain variable region having three complementary determining regions (CDRs) having sequences L1, L2, and L3, wherein
the L1 sequence is RAX₁QX₂IX₃NYLN (SEQ ID NO: 1),
the L2 sequence is YTSSLX₄X₅ (SEQ ID NO: 2),
the L3 sequence is QQYIKLPWT (SEQ ID NO: 3); and
a heavy chain variable region having three complementary determining regions (CDRs) having sequences H1, H2, and H3, wherein
the H1 sequence is GGSVSSYDIS (SEQ ID NO: 8);
the H2 sequence is VIWTDGGTNYNSAFMS (SEQ ID NO: 9); and
the H3 sequence is VYDGYWPFAY (SEQ ID NO: 10);
wherein X₁ is S or L; X₂ is G or W; X₃ is S or A; X₄ is H or F, X₅ is S or E; with the proviso that X₁, X₂, X₃, X₄ and X₅ cannot be S, G, S, H and S, respectively, at the same time.
2. The polypeptides of claim 1, wherein the L1 sequence is selected from an amino acid sequence of RASQWISNYLN (SEQ ID NO: 12), RASQGIANYLN (SEQ ID NO: 15) and RALQGISNYLN (SEQ ID NO: 22).
3. The polypeptides of claim 1, wherein the L2 sequence is selected from an amino acid sequence of YTSSLFS (SEQ ID NO: 17) and YTSSLHE (SEQ ID NO: 19).
4. The polypeptides of claim 1 comprising a set of 6 CDRs selected from the follow sets of 6 CDRs:
SEQ ID NO: 12, SEQ ID NO: 6, SEQ ID NO: 3, SEQ ID NO: 8, SEQ ID NO: 9, and SEQ ID NO: 10;
SEQ ID NO: 15, SEQ ID NO: 6, SEQ ID NO: 3, SEQ ID NO: 8, SEQ ID NO: 9, and SEQ ID NO: 10;
SEQ ID NO: 5, SEQ ID NO: 17, SEQ ID NO: 3, SEQ ID NO: 8, SEQ ID NO: 9, and SEQ ID NO: 10;
SEQ ID NO: 5, SEQ ID NO: 19, SEQ ID NO: 3, SEQ ID NO: 8, SEQ ID NO: 9, and SEQ ID NO: 10; and
SEQ ID NO: 22, SEQ ID NO: 6, SEQ ID NO: 3, SEQ ID NO: 8, SEQ ID NO: 9, and SEQ ID NO: 10.

5. Isolated polypeptides comprising a light chain variable region and a heavy chain variable region, each said light chain variable region and each said heavy chain variable region independently having at least 80%, 85%, 90%, 95%, 98% or 99% identity to a pair of amino acid sequences selected from: SEQ ID NOS: 11 and 13, SEQ ID NOS: 14 and 13, SEQ ID NOS: 16 and 13, SEQ ID NOS: 18 and 13, SEQ ID NOS: 20 and 13, and SEQ ID NOS: 21 and 13; and said isolated polypeptides specifically bind to human CD46 protein.
6. The isolated polypeptides of claim 5, comprising a light chain variable region and a heavy chain variable region having a pair of sequences selected from: SEQ ID NOS: 11 and 13, SEQ ID NOS: 14 and 13, SEQ ID NOS: 16 and 13, SEQ ID NOS: 18 and 13, SEQ ID NOS: 20 and 13, or SEQ ID NOS: 21 and 13.
7. An isolated antibody or antibody fragment comprising a light chain variable region having three complementary determining regions (CDRs) having sequences L1, L2, and L3, wherein
the L1 sequence is RAX₁QX₂IX₃NYLN (SEQ ID NO: 1),
the L2 sequence is YTSSLX₄X₅ (SEQ ID NO: 2),
the L3 sequence is QQYIKLPWT (SEQ ID NO: 3); and
a heavy chain variable region having three complementary determining regions (CDRs) having sequences H1, H2, and H3, wherein
the H1 sequence is GGSVSSYDIS (SEQ ID NO: 8);
the H2 sequence is VIWTDGGTNYNSAFMS (SEQ ID NO: 9); and
the H3 sequence is VYDGYPWFAFAY (SEQ ID NO: 10);
wherein X₁ is S or L; X₂ is G or W; X₃ is S or A; X₄ is H or F, X₅ is S or E; with the proviso that X₁, X₂, X₃, X₄ and X₅ cannot be S, G, S, H and S, respectively, at the same time.
8. The antibody or antibody fragment of claim 7, wherein the L1 sequence is selected from an amino acid sequence of RASQWISNYLN (SEQ ID NO: 12), RASQGIANYLN (SEQ ID NO: 15), and RALQGISNYLN (SEQ ID NO: 22).
9. The antibody or antibody fragment of claim 7 wherein the L2 sequence is selected from an amino acid sequence of YTSSLFS (SEQ ID NO: 17) and YTSSLHE (SEQ ID NO: 19).
10. The antibody or antibody fragment of claim 7 comprising a set of 6 CDRs selected from one of the following sets of 6 CDRs:

SEQ ID NO: 12, SEQ ID NO: 6, SEQ ID NO: 3, SEQ ID NO: 8, SEQ ID NO: 9, and SEQ ID NO: 10;

SEQ ID NO: 15, SEQ ID NO: 6, SEQ ID NO: 3, SEQ ID NO: 8, SEQ ID NO: 9, and SEQ ID NO: 10;

SEQ ID NO: 5, SEQ ID NO: 17, SEQ ID NO: 3, SEQ ID NO: 8, SEQ ID NO: 9, and SEQ ID NO: 10;

SEQ ID NO: 5, SEQ ID NO: 19, SEQ ID NO: 3, SEQ ID NO: 8, SEQ ID NO: 9, and SEQ ID NO: 10; and

SEQ ID NO: 22, SEQ ID NO: 6, SEQ ID NO: 3, SEQ ID NO: 8, SEQ ID NO: 9, and SEQ ID NO: 10.

11. The antibody or antibody fragment, comprising a light chain variable region and a heavy chain variable region, each said light chain variable region and each said heavy chain variable region independently having at least 80%, 85%, 90%, 95%, 98% or 99% identity to a pair of amino acid sequences selected from SEQ ID NOS: 11 and 13, SEQ ID NOS: 14 and 13, SEQ ID NOS: 16 and 13, SEQ ID NOS: 18 and 13, SEQ ID NOS: 20 and 13, and SEQ ID NOS: 21 and 13; and said antibody or antibody fragment specifically binds to human CD46 protein.

12. The antibody or antibody fragment of claim 7 comprising a light chain variable region and a heavy chain variable region having a pair of sequences selected from: SEQ ID NOS: 11 and 13, SEQ ID NOS: 14 and 13, SEQ ID NOS: 16 and 13, SEQ ID NOS: 18 and 13, SEQ ID NOS: 20 and 13, and SEQ ID NOS: 21 and 13.

13. An isolated antibody or antibody fragment, which competes with the binding to human CD46 with any of the antibodies or antibody fragments of any one of claims 7-12.

14. The antibody or antibody fragment of any one of claims 7-13, wherein the antibody or antibody fragment has a higher binding activity to CD46 protein at a value of a condition in a tumor microenvironment in comparison with a different value of a same condition that occurs in a non-tumor microenvironment.

15. The antibody or antibody fragment of claim 14, wherein the condition is pH.

16. The antibody or antibody fragment of claim 15, wherein the pH in the tumor microenvironment is in a range of from 5.0 to 6.8 and the pH in the non-tumor microenvironment is in a range of from 7.0 to 7.6.
17. The antibody or antibody fragment of any one of claims 7-16, wherein the antibody or antibody fragment has a ratio of binding activity to human CD46 protein at a value of a condition in a tumor microenvironment to a binding activity to the CD46 protein at a different value of the same condition in a non-tumor microenvironment of at least about 1.5:1, at least about 2:1, at least about 3:1, at least about 4:1, at least about 5:1, at least about 6:1, at least about 7:1, at least about 8:1, at least about 9:1, at least about 10:1, at least about 20:1, at least about 30:1, at least about 50:1, at least about 70:1, or at least about 100:1.
18. An immunoconjugate comprising the antibody or antibody fragment of any one of claims 7-17.
19. The immunoconjugate of claim 18, wherein the immunoconjugate comprises at least one agent selected from a chemotherapeutic agent, a radioactive atom, a cytostatic agent and a cytotoxic agent.
20. The immunoconjugate of claim 19, comprising at least two said agents.
21. The immunoconjugate of any one of claims 18-20, wherein the at least one agent is a radioactive agent.
22. The immunoconjugate of claim 21, wherein the radioactive agent is selected from an alpha emitter, a beta emitter and a gamma emitter.
23. The immunoconjugate of any one of claims 18-22, wherein the antibody or antibody fragment and the at least one agent are covalently bonded to a linker molecule.
24. The immunoconjugate of any one of claims 18-23, wherein the at least one agent is selected from maytansinoids, auristatins, dolastatins, calicheamicin, pyrrolobenzodiazepines, and anthracyclines.

25. A pharmaceutical composition comprising the polypeptide of any one of claims 1-6, the antibody or antibody fragment of any one of claims 7-17, or the immunoconjugate of any one of claims 18-24; and a pharmaceutically acceptable carrier.
26. The pharmaceutical composition of claim 25, further comprising a tonicity agent.
27. A single dose of the pharmaceutical composition of any one of claims 25-26, comprising an amount of the polypeptide, the antibody or antibody fragment, or the immunoconjugate of about 135 mg, 235 mg, 335 mg, 435 mg, 535 mg, 635 mg, 735 mg, 835 mg, 935 mg, 1035 mg, 1135 mg, 1235 mg, or 1387 mg.
28. A single dose of the pharmaceutical composition of any one of claims 25-26, comprising an amount of the polypeptide, the antibody or antibody fragment, or the immunoconjugate in a range of 135-235 mg, 235-335 mg, 335-435 mg, 435-535 mg, 535-635 mg, 635-735 mg, 735-835 mg, 835-935 mg, 935-1035 mg, 1035-1135 mg, 1135-1235 mg, or 1235-1387 mg.
29. The pharmaceutical composition of any one of claims 25-26, further comprising an immune checkpoint inhibitor molecule.
30. The pharmaceutical composition of claim 29, wherein the immune checkpoint inhibitor molecule is an antibody or antibody fragment against an immune checkpoint.
31. The pharmaceutical composition of claim 30, wherein the immune checkpoint is selected from CTLA4, LAG3, TIM3, TIGIT, VISTA, BTLA, OX40, CD40, 4-1BB, PD-1, PD-L1, GITR, B7-H3, B7-H4, KIR, A2aR, CD27, CD70, DR3, and ICOS.
32. The pharmaceutical composition of claim 30, wherein the immune checkpoint is CTLA4, PD-1 or PD-L1.
33. The pharmaceutical composition of any one of claims 29-32, further comprising an antibody or antibody fragment against an antigen selected from CTLA4, PD1, PD-L1, AXL, ROR2, CD3, HER2, B7-H3, ROR1, SFRP4 and a WNT protein.

34. A method of treating cancer comprising a step of administering the polypeptides of any one of claims 1-6, the antibody or antibody fragment of any one of claims 7-17, the immunoconjugate of any one of claims 18-24 or the pharmaceutical composition of any one of claims 25-33 to a patient with cancer.

35. A kit for diagnosis or treatment, said kit comprising the polypeptides of any one of claims 1-6, the antibody or antibody fragment of any one of claims 7-17, or the immunoconjugate of any one of claims 18-24 or the pharmaceutical composition of any one of claims 25-33 and instructions for using the antibody or antibody fragment, the immunoconjugate and/or the pharmaceutical composition for diagnosis or treatment.