

WHAT IS CLAIMED IS:

CLAIMS

1. A monoclonal antibody that binds to C-C motif chemokine receptor 8 (CCR8), wherein the antibody comprises a heavy chain variable domain (VH) comprising (a) a CDR-H1 comprising the amino acid sequence of SEQ ID NO: 29 or SEQ ID NO: 30, (b) a CDR-H2 comprising the amino acid sequence of SEQ ID NO: 31, and (c) a CDR-H3 comprising the amino acid sequence of SEQ ID NO: 32, and a light chain variable domain (VL) comprising (d) a CDR-L1 comprising the amino acid sequence of SEQ ID NO: 26, (e) a CDR-L2 comprising the amino acid sequence of SEQ ID NO: 27, and (f) a CDR-L3 comprising the amino acid sequence of SEQ ID NO: 28.
2. The antibody of claim 1, wherein:
 - (A) the antibody binds to CCR8 independent of sulfation of CCR8;
 - (B) the antibody binds to an epitope comprised of one or more of amino acid residues 2-6 of SEQ ID NO: 106; and/or
 - (C)
 - (a) the VH comprises an amino acid sequence having at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NOs: 35-47;
 - (b) the VL comprises an amino acid sequence having at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NOs: 48-52; or
 - (c) the antibody comprises the VH as defined in (a) and the VL as defined in (b).
3. The antibody of claim 1 or 2, wherein:
 - (a) the VH comprises an amino acid sequence having at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to the amino acid sequence of SEQ ID NO: 47 and the VL comprises an amino acid sequence having at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to the amino acid sequence of SEQ ID NO: 48;
 - (b) the VL comprises a V4M mutation, a P43A mutation, a F46L mutation, a C90Q mutation, or a combination thereof;
 - (c) the VH comprises a G49S mutation, a K71R mutation, a S73N mutation, or a combination thereof; and/or

(d) the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 55, 60, 111, or 113 and a light chain comprising the amino acid sequence of SEQ ID NO: 56.

4. A monoclonal antibody that binds to CCR8, wherein the antibody comprises a VH comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 35-47 and a VL comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 48-52.

5. A monoclonal antibody that binds to CCR8, wherein the antibody comprises a VH comprising the amino acid sequence of SEQ ID NO: 47 and a VL comprising the amino acid sequence of SEQ ID NO: 48.

6. A monoclonal antibody that binds to CCR8, wherein the antibody comprises a heavy chain variable domain (VH) comprising (a) a CDR-H1 comprising the amino acid sequence of SEQ ID NO: 4 or SEQ ID NO: 5, (b) a CDR-H2 comprising the amino acid sequence of SEQ ID NO: 6, and (c) a CDR-H3 comprising the amino acid sequence of SEQ ID NO: 7, and a light chain variable domain (VL) comprising (d) a CDR-L1 comprising the amino acid sequence of SEQ ID NO: 1, (e) a CDR-L2 comprising the amino acid sequence of SEQ ID NO: 2, and (f) a CDR-L3 comprising the amino acid sequence of SEQ ID NO: 3.

7. The antibody of claim 6, wherein:

(A) the antibody binds to CCR8 independent of sulfation of CCR8;

(B) the antibody binds to an epitope comprised of one or more of amino acid residues 91-104 and 172-193 of SEQ ID NO: 106; and/or

(C)

(a) the VH comprises an amino acid sequence having at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NOs: 10-21;

(b) the VL comprises an amino acid sequence having at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NOs: 22-25; or

(c) the antibody comprises the VH as defined in (a) and the VL as defined in (b).

8. The antibody of claim 6 or 7, wherein:

(a) the VH comprises an amino acid sequence having at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to an amino acid sequence of SEQ ID NO: 21 and the VL comprises an amino acid sequence having at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to an amino acid sequence of SEQ ID NO: 24;

(b) the VL comprises a Y2I mutation;

(c) the VH comprises a S73N mutation, a V78L mutation, a T76N mutation, a F91Y mutation, a P105Q mutation, or a combination thereof; and/or

(d) the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 57, 61, 112, or 114 and a light chain comprising the amino acid sequence of SEQ ID NO: 58.

9. A monoclonal antibody that binds to CCR8, wherein the antibody comprises a VH comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 10-21 and a VL comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 22-25.

10. A monoclonal antibody that binds to CCR8, wherein the antibody comprises a VH comprising the amino acid sequence of SEQ ID NO: 21 and a VL comprising the amino acid sequence of SEQ ID NO: 24.

11. A monoclonal antibody that binds to CCR8, wherein the antibody comprises a heavy chain variable domain (VH) comprising (a) a CDR-H1 comprising the amino acid sequence of SEQ ID NO: 82 or SEQ ID NO: 83, (b) a CDR-H2 comprising the amino acid sequence of SEQ ID NO: 84, and (c) a CDR-H3 comprising the amino acid sequence of SEQ ID NO: 85, and a light chain variable domain (VL) comprising (d) a CDR-L1 comprising the amino acid sequence of SEQ ID NO: 73, (e) a CDR-L2 comprising the amino acid sequence of SEQ ID NO: 74, and (f) a CDR-L3 comprising the amino acid sequence of SEQ ID NO: 75.

12. The antibody of claim 11, wherein:

(A)

(a) the VH comprises an amino acid sequence having at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to an amino acid sequence of SEQ ID NO: 95;

(b) the VL comprises an amino acid sequence having at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to an amino acid sequence of SEQ ID NO: 94; or

(c) the antibody comprises the VH as defined in (a) and the VL as defined in (b); and/or

(B) the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 101 or 115 and a light chain comprising the amino acid sequence of SEQ ID NO: 100.

13. A monoclonal antibody that binds to CCR8, wherein the antibody comprises a heavy chain variable domain (VH) comprising (a) a CDR-H1 comprising the amino acid sequence of SEQ ID NO: 86 or SEQ ID NO: 87, (b) a CDR-H2 comprising the amino acid sequence of SEQ ID NO: 88, and (c) a CDR-H3 comprising the amino acid sequence of SEQ ID NO: 89, and a light chain variable domain (VL) comprising (d) a CDR-L1 comprising the amino acid sequence of SEQ ID NO: 76, (e) a CDR-L2 comprising the amino acid sequence of SEQ ID NO: 77, and (f) a CDR-L3 comprising the amino acid sequence of SEQ ID NO: 78.

14. The antibody of claim 13, wherein:

(A)

(a) the VH comprises an amino acid sequence having at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to an amino acid sequence of SEQ ID NO: 97;

(b) the VL comprises an amino acid sequence having at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to an amino acid sequence of SEQ ID NO: 96; or

(c) the antibody comprises the VH as defined in (a) and the VL as defined in (b); and/or

(B) the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 103 or 116 and a light chain comprising the amino acid sequence of SEQ ID NO: 102.

15. A monoclonal antibody that binds to CCR8, wherein the antibody comprises a heavy chain variable domain (VH) comprising (a) a CDR-H1 comprising the amino acid sequence of SEQ ID NO: 90 or SEQ ID NO: 91, (b) a CDR-H2 comprising the amino acid sequence of SEQ ID NO: 92, and (c) a CDR-H3 comprising the amino acid sequence of SEQ ID NO: 93, and a light chain variable domain (VL) comprising (d) a CDR-L1 comprising the amino acid sequence of SEQ ID NO: 79, (e) a CDR-L2 comprising the amino acid sequence of SEQ ID NO: 80, and (f) a CDR-L3 comprising the amino acid sequence of SEQ ID NO: 81.

16. The antibody of claim 15, wherein:

(A)

(a) the VH comprises an amino acid sequence having at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to an amino acid sequence of SEQ ID NO: 99;

(b) the VL comprises an amino acid sequence having at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to an amino acid sequence of SEQ ID NO: 98; or

(c) the antibody comprises the VH as defined in (a) and the VL as defined in (b); and/or

(B) the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 105 or 117 and a light chain comprising the amino acid sequence of SEQ ID NO: 104.

17. A monoclonal antibody that binds to CCR8, wherein the antibody binds to CCR8 independent of sulfation of CCR8.

18. The antibody of claim 17, wherein the antibody binds to an epitope comprised of:

(a) one or more of amino acid residues 2-6 of SEQ ID NO: 106; or

(b) one or more of amino acid residues 91-104 and 172-193 of SEQ ID NO: 106.

19. A monoclonal antibody that binds to mouse CCR8, wherein the antibody comprises a heavy chain variable domain (VH) comprising (a) a CDR-H1 comprising the amino acid sequence of SEQ ID NO: 65 or SEQ ID NO: 66, (b) a CDR-H2 comprising the amino acid sequence of SEQ ID NO: 67 and (c) a CDR-H3 comprising the amino acid sequence of SEQ ID NO: 68, and a light chain variable domain (VL) comprising (d) a CDR-L1 comprising the amino acid sequence of SEQ ID NO: 62, (e) a CDR-L2 comprising the amino acid sequence of SEQ ID NO: 63, and (f) a CDR-L3 comprising the amino acid sequence of SEQ ID NO: 64.

20. The antibody of claim 19, wherein:

(A)

(a) the VH comprises an amino acid sequence having at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to an amino acid sequence of SEQ ID NO: 70;

- (b) the VL comprises an amino acid sequence having at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to an amino acid sequence of SEQ ID NO: 69; or
- (c) the antibody comprises the VH as defined in (a) and the VL as defined in (b); and/or
- (B) the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 72 and a light chain comprising the amino acid sequence of SEQ ID NO: 71.
21. The antibody of any one of claims 1 to 18, wherein:
- (a) the antibody is a human antibody or a humanized antibody; or
- (b) the CCR8 is a human CCR8.
22. The antibody of any one of claims 1 to 20, which is a chimeric antibody.
23. The antibody of any one of claims 1 to 22, wherein:
- (a) the antibody is an antibody fragment that binds to CCR8 or a full-length antibody, optionally wherein the antibody is a full-length IgG1 antibody;
- (b) the antibody comprises an IgG1 constant domain comprising the amino acid sequence of SEQ ID NO: 53 or SEQ ID NO: 59;
- (c) the antibody comprises a kappa constant domain comprising the amino acid sequence of SEQ ID NO: 54;
- (d) the antibody binds to CCR8 with a binding affinity (K_d) of from about 1×10^{-12} M to about 1×10^{-11} M; and/or
- (e) the antibody is afucosylated, optionally wherein the proportion of afucosylation is between about 80% to about 95%.
24. An isolated nucleic acid encoding the antibody of any one of claims 1 to 23.
25. A host cell comprising the nucleic acid of claim 24.
26. A method of producing an antibody that binds to CCR8, wherein the method comprises culturing the host cell of claim 25 under conditions suitable for the expression of the antibody, optionally wherein the method further comprises recovering the antibody from the host cell.
27. An antibody produced by the method of claim 26.

28. A pharmaceutical composition comprising the antibody of any one of claims 1 to 23 and a pharmaceutically acceptable carrier, optionally wherein the pharmaceutical composition further comprises an additional therapeutic agent.
29. The antibody of any one of claims 1 to 23 or the pharmaceutical composition of claim 28 for use as a medicament.
30. The antibody of any one of claims 1 to 23 or the pharmaceutical composition of claim 28 for use in treating cancer.
31. Use of the antibody of any one of claims 1 to 23 or the pharmaceutical composition of claim 28 in the manufacture of a medicament for treating cancer.
32. The antibody of any one of claims 1 to 23 or the pharmaceutical composition of claim 28 for use in depleting regulatory T cells.
33. Use of the antibody of any one of claims 1 to 23 or the pharmaceutical composition of claim 28 in the manufacture of a medicament for depleting regulatory T cells.
34. The antibody of any one of claims 1 to 23 or the pharmaceutical composition of claim 28 for use in depleting regulatory T cells in the tumor microenvironment in a subject having cancer.
35. Use of the antibody of any one of claims 1 to 23 or the pharmaceutical composition of claim 28 in the manufacture of a medicament for depleting regulatory T cells in the tumor microenvironment in a subject having cancer.
36. The antibody of any one of claims 1 to 23 or the pharmaceutical composition of claim 28 for use in depleting regulatory T cells outside of the tumor microenvironment in a subject having cancer.
37. Use of the antibody of any one of claims 1 to 23 or the pharmaceutical composition of claim 28 in the manufacture of a medicament for depleting regulatory T cells outside of the tumor microenvironment in a subject having cancer.

38. An *in vitro* method of depleting regulatory T cells from a cancer cell population, wherein the method comprises contacting the cell population with the antibody of any one of claims 1 to 23 or the pharmaceutical composition of claim 28 in an amount sufficient to deplete the regulatory T cells from the cell population.
39. The antibody for use, use, or method of any one of claims 32-35 and 38, wherein the regulatory T cells present in the tumor microenvironment of the cancer are depleted.
40. The antibody for use, use, or method of any one of claims 32, 33, and 36-38, wherein the regulatory T cells outside of the tumor microenvironment of the cancer are depleted.
41. The antibody for use, use, or method of any one of claims 30-40, wherein:
- (a) the cancer is selected from the group consisting of bladder cancer, blastoma, blood cancer, bone cancer, brain cancer, breast cancer, cervical cancer, colorectal cancer, endometrial cancer, esophageal cancer, gastric cancer, head and neck cancer, kidney cancer, liver cancer, lung cancer, ovarian cancer, pancreatic cancer, prostate cancer, sarcoma, skin cancer, testicular cancer, and uterine cancer; and/or
 - (b) an additional therapeutic agent is to be administered.
42. The antibody for use, use, or method of claim 41, wherein the additional therapeutic agent is an anti-cancer agent.
43. The antibody for use, use, or method of claim 42, wherein the anti-cancer agent is selected from the group consisting of a microtubule disruptor, an antimetabolite, a topoisomerase inhibitor, a DNA intercalator, an alkylating agent, a hormonal therapy, a kinase inhibitor, a receptor antagonist, an activator of tumor cell apoptosis, antiangiogenic agent, an immunomodulatory agent, an inhibitor of cell adhesion, a cytotoxic or cytostatic agent, an activator of cell apoptosis, an agent that increases the sensitivity of cells to apoptotic inducers, a cytokine, an anti-cancer vaccine or oncolytic virus, a toll-like receptor (TLR) agent, a bispecific antibody, a cellular therapy, and immune cell engager.
44. The antibody for use, use, or method of claim 42 or 43, wherein the anti-cancer agent is a PD-L1 binding antagonist.

45. The antibody for use, use, or method of claim 44, wherein the PD-L1 binding antagonist is atezolizumab.
46. The antibody for use or use of any one of claims 34-37, wherein the subject is a human.
47. The antibody for use or use of any one of claims 34-37, wherein the subject is a mouse.
48. The monoclonal antibody of claim 19 or 20 for use in treating a disease in a mouse, optionally wherein the mouse comprises a xenograft.
49. Use of the monoclonal antibody of claim 19 or 20 in the manufacture of a medicament for treating a disease in a mouse, optionally wherein the mouse comprises a xenograft.
50. The antibody of any one of claims 1-5, 17, and 18, wherein the mean clearance after a single 10 mg/kg dose administered intravenously on day 1 is between about 3 to about 5 mL/day/kg over a 35-day period.