Example 90. The forgoing method of Example 89, wherein the mouse comprises a xenograft.

Example 91. The forgoing antibody of Example 63, wherein the proportion of afucosylation is between about 80% to about 95%.

Example 92. The forgoing antibody of any one of Examples 1-15 and 46-48, 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.

In one aspect, the present disclosure refers to 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.

In one aspect, the present disclosure refers to 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.

In one aspect, the present disclosure refers to 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.

In one aspect, the present disclosure refers to an isolated nucleic acid encoding the antibody disclosed herein.

In one aspect, the present disclosure refers to a host cell comprising the nucleic acid disclosed herein.

In one aspect, the present disclosure refers to a method of producing an antibody that binds to CCR8, wherein the method comprises culturing the host cell disclosed herein under conditions suitable for the expression of the antibody, optionally wherein the method further comprises recovering the antibody from the host cell.

In one aspect, the present disclosure refers to a pharmaceutical composition comprising the antibody disclosed herein and a pharmaceutically acceptable carrier, optionally wherein the pharmaceutical composition further comprises an additional therapeutic agent.

In one aspect, the present disclosure refers to the antibody disclosed herein or the pharmaceutical composition disclosed herein for use as a medicament.

In one aspect, the present disclosure refers to the antibody disclosed herein or the pharmaceutical composition disclosed herein for use in treating cancer.

In one aspect, the present disclosure refers to use of the antibody disclosed herein or the pharmaceutical composition disclosed herein in the manufacture of a medicament for treating cancer.

In one aspect, the present disclosure refers to the antibody disclosed herein or the pharmaceutical composition disclosed herein for use in depleting regulatory T cells.

In one aspect, the present disclosure refers to use of the antibody disclosed herein or the pharmaceutical composition disclosed herein in the manufacture of a medicament for depleting regulatory T cells.

In one aspect, the present disclosure refers to the antibody disclosed herein or the pharmaceutical composition disclosed herein for use in depleting regulatory T cells in the tumor microenvironment in a subject having cancer.

In one aspect, the present disclosure refers to use of the antibody disclosed herein or the pharmaceutical composition disclosed herein in the manufacture of a medicament for depleting regulatory T cells in the tumor microenvironment in a subject having cancer.

In one aspect, the present disclosure refers to the antibody disclosed herein or the pharmaceutical composition disclosed herein for use in depleting regulatory T cells outside of the tumor microenvironment in a subject having cancer.

In one aspect, the present disclosure refers to use of the antibody disclosed herein or the pharmaceutical composition disclosed herein in the manufacture of a medicament for depleting regulatory T cells outside of the tumor microenvironment in a subject having cancer.

In one aspect, the present disclosure refers to 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 disclosed herein or the pharmaceutical composition disclosed herein in an amount sufficient to deplete the regulatory T cells from the cell population.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 depicts the results of a screening of anti-CCR8 monoclonal antibodies (mAbs) selectively binding to Treg cells (Tregs) from human colorectal cancer dissociated tumor cells (DTC) (obtained from Discovery Life Sciences). Shown are mean fluorescent intensity (MFI) values for CD8 T cells (defined as CD45+ CD14- CD3+ CD8+ CD4-) (circles,), conventional CD4 T cells (defined as CD45+ CD14- CD3+ CD8- CD4+ FOXP3-) (squares, □), and Treg cells (defined as CD45+ CD14- CD3+ CD8- CD4+ FOXP3+) (triangles, ▲). Three of the five anti-CCR8 mAb clones Ab1-Ab5 specifically stained intratumoral Treg cells and not conventional CD4 or CD8 T cells, and were ranked based on CCR8 MFI: **hu.Ab4.H1L1 > hu.Ab5.H1L1 > hu.Ab3.H1L1**.

FIGS. 2A-2B depicts the proposed mechanism of action of natural killer (NK) cell-mediated antibody-dependent cellular cytotoxicity (ADCC), resulting in depletion of tumor-infiltrating CCR8-expressing Tregs (**FIG. 2A**) and the ADCC activities of human/cyno cross-reactive anti-CCR8 mAbs brought forward for further study (**FIG. 2B**). EC_{50} values were determined as 0.02 nM, 0.02 nM, and 0.08 nM for anti-CCR8 mAbs **hu.Ab3.H1L1**, **hu.Ab5.H1L1**, and **hu.Ab4.H1L1**, respectively.

FIGS. 3A-3D depict the agonist and antagonist activities of the human/cyno cross-reactive anti-CCR8 mAbs **hu.Ab4.H1L1, hu.Ab5.H1L1,** and **hu.Ab3.H1L1**, as well as comparator anti-CCR8 mAbs (the humanized anti-human Yoshida anti-CCR8 antibody, murine anti-human CCR8 mAb 433H (BD Biosciences), and murine anti-human CCR8 mAb L263G8 (Biolegend)). As shown in **FIG. 3A**, CCL1, a known ligand for CCR8, shows agonist activity, but none of the anti-CCR8 test mAbs show agonistic effects. The data in **FIG. 3B** shows anti-CCR8 mAb **hu.Ab4.H1L1** demonstrates antagonistic (neutralizing) activity against the CCR8 ligand CCL1 (20 nM of ligand), whereas anti-CCR8 mAbs **hu.Ab5.H1L1** and **hu.Ab3.H1L1** demonstrate no ligand blocking (non-neutralizing) activity at the concentration studied. The data in **FIG. 3C** shows that comparator anti-CCR8 mAbs (the humanized anti-human Yoshida anti-CCR8 antibody, murine anti-human CCR8 mAb 433H (BD Biosciences), and murine anti-human CCR8 mAb L263G8 (Biolegend)) do not show agonistic effects, whereas the CCR8 ligand CCL1 does. The data in **FIG. 3D** shows comparator anti-CCR8 mAbs (the humanized anti-human Yoshida anti-CCR8 antibody, murine anti-human CCR8 mAb 433H (BD Biosciences), and murine anti-human Biolegend L263G8 (Biolegend)) demonstrate

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 95%, at least 96%, at least 97%, at least 98%, or at least 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 95%, at least 96%, at least 97%, at least 98%, or at least 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 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to the amino acid sequence of SEQ ID NO: 47 and the VL comprises an amino acid sequence having at least 95%, at least 96%, at least 97%, at least 98%, or at least 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. The antibody of any one of claims 1 to 5, wherein:

(a) the antibody is a humanized antibody; or

(b) the CCR8 is a human CCR8.

7. The antibody of any one of claims 1 to 5, which is a chimeric antibody.

8. The antibody of any one of claims 1 to 7, 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; and/or

(d) the antibody is afucosylated, optionally wherein the proportion of afucosylation is between 80% to 95%.

9. An isolated nucleic acid encoding the antibody of any one of claims 1 to 8.

10. A host cell comprising the nucleic acid of claim 9.

11. A method of producing an antibody that binds to CCR8, wherein the method comprises culturing the host cell of claim 10 under conditions suitable for the expression of the antibody, optionally wherein the method further comprises recovering the antibody from the host cell.

12. A pharmaceutical composition comprising the antibody of any one of claims 1 to 8 and a pharmaceutically acceptable carrier, optionally wherein the pharmaceutical composition further comprises an additional therapeutic agent.

13. The antibody of any one of claims 1 to 8 or the pharmaceutical composition of claim 12 for use as a medicament.

14. The antibody of any one of claims 1 to 8 or the pharmaceutical composition of claim 12 for use in treating cancer.

15. Use of the antibody of any one of claims 1 to 8 or the pharmaceutical composition of claim 12 in the manufacture of a medicament for treating cancer.

16. The antibody of any one of claims 1 to 8 or the pharmaceutical composition of claim 12 for use in depleting regulatory T cells.

17. Use of the antibody of any one of claims 1 to 8 or the pharmaceutical composition of claim 12 in the manufacture of a medicament for depleting regulatory T cells.

18. The antibody of any one of claims 1 to 8 or the pharmaceutical composition of claim 12 for use in depleting regulatory T cells in the tumor microenvironment in a subject having cancer.

19. Use of the antibody of any one of claims 1 to 8 or the pharmaceutical composition of claim 12 in the manufacture of a medicament for depleting regulatory T cells in the tumor microenvironment in a subject having cancer.

20. The antibody of any one of claims 1 to 8 or the pharmaceutical composition of claim 12 for use in depleting regulatory T cells outside of the tumor microenvironment in a subject having cancer.

21. Use of the antibody of any one of claims 1 to 8 or the pharmaceutical composition of claim 12 in the manufacture of a medicament for depleting regulatory T cells outside of the tumor microenvironment in a subject having cancer.

22. 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 8 or the pharmaceutical composition of claim 12 in an amount sufficient to deplete the regulatory T cells from the cell population.

23. The use or method of claim 19 or 22, wherein the regulatory T cells present in the tumor microenvironment of the cancer are depleted.

24. The use or method of claim 21 or 22, wherein the regulatory T cells outside of the tumor microenvironment of the cancer are depleted.

25. The use or method of any one of claims 15, 19, and 21 to 24, 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.

26. The use or method of claim 25, wherein the additional therapeutic agent is an anti-cancer agent.

27. The use or method of claim 26, 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.

28. The use or method of claim 26 or 27, wherein the anti-cancer agent is a PD-L1 binding antagonist.

29. The use or method of claim 28, wherein the PD-L1 binding antagonist is atezolizumab.

30. The use of claim 19 or 21, wherein the subject is a human.

31. The use of claim 19 or 21, wherein the subject is a mouse.

32. The antibody of any one of claims 1 to 5, wherein the mean clearance after a single 10 mg/kg dose administered intravenously on day 1 is between 3 to 5 mL/day/kg over a 35-day period.