

CLAIMS

1. An antibody or an antigen-binding portion thereof that specifically binds to one or more amino acids within the N-terminal extracellular domain of human CCR8, wherein the antibody or an antigen-binding portion thereof comprises a variable heavy (VH) chain, comprising a VH complementarity-determining region (CDR) 1 comprising the amino acid sequence set forth in SEQ ID NO: 45, a VH CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 46, a VH CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 47, a variable light (VL) chain comprising a VL CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 48, a VL CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 49, and a VL CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 50.
2. The antibody or an antigen-binding portion thereof of claim 1, which is capable of:
 - (a) enhancing an immune response to a tumor;
 - (b) reducing, depleting, or killing tumor infiltrating regulatory T ("Treg") cells;
 - (c) inducing internalization of CCR8 in tumor infiltrating regulatory T ("Treg") cells;
 - (d) activating NK cells,
 - (e) inducing NK cell mediated killing of tumor infiltrating regulatory T ("Treg") cells;
 - (f) binding to cynomolgus monkey ("cyno") CCR8;
 - (g) binding to human CCR8 with KD of 10 nM or less as measured by BIACORE™
 - (h) inducing antibody-dependent cellular cytotoxicity (ADCC) in a subject following administration of the anti-CCR8 antibody;
 - (i) inducing upregulation of 4-1BB, ICAM-1, or both 4-1BB and ICAM-1 on the surface of NK cells;

- (j) inducing down-regulation of CD16 on the surface of NK cells in the subject; or
 - (k) any combination thereof.
3. The antibody or antigen-binding portion thereof of claim 1 or 2, which comprises a VH chain comprising the amino acid sequence set forth in SEQ ID NO: 41 and a VL chain comprising the amino acid sequence set forth in SEQ ID NO: 43.
 4. The antibody or antigen-binding portion thereof of any one of claims 1 to 3, which is a human antibody, a humanized antibody, or a chimeric antibody.
 5. The antibody or antigen-binding portion thereof of any one of claims 1 to 4, which is an afucosylated antibody.
 6. The antibody or antigen-binding portion thereof of any one of claims 1 to 4, which comprises a single-chain variable fragment (scFv) of an antibody.
 7. The antibody or antigen-binding portion thereof of any one of claims 1 to 6, which is a bispecific antibody, a bispecific T cell engager (BiTE), a multispecific antibody, a biparatopic antibody, an immunoconjugate, an antibody drug conjugate, or any combination thereof.
 8. A bispecific antibody or a multispecific antibody comprising the antibody or antigen-binding portion thereof of any one of claims 1 to 6.
 9. A BiTe comprising the antibody or antigen-binding portion thereof of any one of claims 1 to 6.
 10. A biparatopic antibody comprising the antibody or antigen-binding portion thereof of any one of claims 1 to 6.
 11. The antibody or antigen-binding portion thereof of claim 7, wherein the bispecific antibody, the BiTE, the multispecific antibody, or the biparatopic antibody comprises a first VH domain, comprising a first VH CDR1, a first VH CDR2, and a first VH CDR3; a first VL domain, comprising a first VL CDR1, a first VL CDR2, and a first VL CDR3; a

second VH domain, comprising a second VH CDR1, a second VH CDR2, and a second VH CDR3; and a second VL domain, comprising a second VL CDR1, a second VL CDR2, and a second VL CDR3; wherein

the first VH CDR1 comprises the amino acid sequence set forth in SEQ ID NOs: 45, the first VH CDR2 comprises the amino acid sequence set forth in SEQ ID NO: 46, the first VH CDR3 comprises the amino acid sequence set forth in SEQ ID NO: 47, the first VL CDR1 comprises the amino acid sequence set forth in SEQ ID NO: 48, the first VL CDR2 comprises the amino acid sequence set forth in SEQ ID NO: 49, and the first VL CDR3 comprises the amino acid sequence set forth in SEQ ID NO: 50;

and wherein:

- (a) the second VH CDR1 comprises the amino acid sequence set forth in SEQ ID NOs: 5, the second VH CDR2 comprises the amino acid sequence set forth in SEQ ID NO: 6, the second VH CDR3 comprises the amino acid sequence set forth in SEQ ID NO: 7, the second VL CDR1 comprises the amino acid sequence set forth in SEQ ID NO: 8, the second VL CDR2 comprises the amino acid sequence set forth in SEQ ID NO: 9, and the second VL CDR3 comprises the amino acid sequence set forth in SEQ ID NO: 10;
- (b) the second VH CDR1 comprises the amino acid sequence set forth in SEQ ID NO: 15, the second VH CDR2 comprises the amino acid sequence set forth in SEQ ID NO: 16, the second VH CDR3 comprises the amino acid sequence set forth in SEQ ID NO: 17, the second VL CDR1 comprises the amino acid sequence set forth in SEQ ID NO: 18, the second VL CDR2 comprises the amino acid sequence set forth in SEQ ID NO: 19, and the second VL CDR3 comprises the amino acid sequence set forth in SEQ ID NO: 20;
- (c) the second VH CDR1 comprises the amino acid sequence set forth in SEQ ID NO: 25, the second VH CDR2 comprises the amino acid sequence set forth in SEQ ID NO: 26, the second VH CDR3 comprises the amino acid sequence set forth in SEQ ID NO: 27, the second VL CDR1 comprises the amino acid

sequence set forth in SEQ ID NO: 28, the second VL CDR2 comprises the amino acid sequence set forth in SEQ ID NO: 29, and the second VL CDR3 comprises the amino acid sequence set forth in SEQ ID NO: 30;

- (d) the second VH CDR1 comprises the amino acid sequence set forth in SEQ ID NO: 35, the second VH CDR2 comprises the amino acid sequence set forth in SEQ ID NO: 36, the second VH CDR3 comprises the amino acid sequence set forth in SEQ ID NO: 37, the second VL CDR1 comprises the amino acid sequence set forth in SEQ ID NO: 38, the second VL CDR2 comprises the amino acid sequence set forth in SEQ ID NO: 39, and the second VL CDR3 comprises the amino acid sequence set forth in SEQ ID NO: 40;
- (e) the second VH CDR1 comprises the amino acid sequence set forth in SEQ ID NO: 55, the second VH CDR2 comprises the amino acid sequence set forth in SEQ ID NO: 56, the second VH CDR3 comprises the amino acid sequence set forth in SEQ ID NO: 57, the second VL CDR1 comprises the amino acid sequence set forth in SEQ ID NO: 58, the second VL CDR2 comprises the amino acid sequence set forth in SEQ ID NO: 59, and the second VL CDR3 comprises the amino acid sequence set forth in SEQ ID NO: 60;
- (f) the second VH CDR1 comprises the amino acid sequence set forth in SEQ ID NO: 65, the second VH CDR2 comprises the amino acid sequence set forth in SEQ ID NO: 66, the second VH CDR3 comprises the amino acid sequence set forth in SEQ ID NO: 67, the second VL CDR1 comprises the amino acid sequence set forth in SEQ ID NO: 68, the second VL CDR2 comprises the amino acid sequence set forth in SEQ ID NO: 69, and the second VL CDR3 comprises the amino acid sequence set forth in SEQ ID NO: 70;
- (g) the second VH CDR1 comprises the amino acid sequence set forth in SEQ ID NO: 75, the second VH CDR2 comprises the amino acid sequence set forth in SEQ ID NO: 76, the second VH CDR3 comprises the amino acid sequence set forth in SEQ ID NO: 77, the second VL CDR1 comprises the amino acid sequence set forth in SEQ ID NO: 78, the second VL CDR2 comprises the amino

acid sequence set forth in SEQ ID NO: 79, and the second VL CDR3 comprises the amino acid sequence set forth in SEQ ID NO: 80;

- (h) the second VH CDR1 comprises the amino acid sequence set forth in SEQ ID NO: 85, the second VH CDR2 comprises the amino acid sequence set forth in SEQ ID NO: 86, the second VH CDR3 comprises the amino acid sequence set forth in SEQ ID NO: 87, the second VL CDR1 comprises the amino acid sequence set forth in SEQ ID NO: 88, the second VL CDR2 comprises the amino acid sequence set forth in SEQ ID NO: 89, and the second VL CDR3 comprises the amino acid sequence set forth in SEQ ID NO: 90;
- (i) the second VH CDR1 comprises the amino acid sequence set forth in SEQ ID NO: 95, the second VH CDR2 comprises the amino acid sequence set forth in SEQ ID NO: 96, the second VH CDR3 comprises the amino acid sequence set forth in SEQ ID NO: 97, the second VL CDR1 comprises the amino acid sequence set forth in SEQ ID NO: 98, the second VL CDR2 comprises the amino acid sequence set forth in SEQ ID NO: 99, and the second VL CDR3 comprises the amino acid sequence set forth in SEQ ID NO: 100;
- (j) the second VH CDR1 comprises the amino acid sequence set forth in SEQ ID NO: 125, the second VH CDR2 comprises the amino acid sequence set forth in SEQ ID NO: 126, the second VH CDR3 comprises the amino acid sequence set forth in SEQ ID NO: 127, the second VL CDR1 comprises the amino acid sequence set forth in SEQ ID NO: 128, the second VL CDR2 comprises the amino acid sequence set forth in SEQ ID NO: 129, and the second VL CDR3 comprises the amino acid sequence set forth in SEQ ID NO: 130;
- (k) the second VH CDR1 comprises the amino acid sequence set forth in SEQ ID NO: 155, the second VH CDR2 comprises the amino acid sequence set forth in SEQ ID NO: 156, the second VH CDR3 comprises the amino acid sequence set forth in SEQ ID NO: 157, the second VL CDR1 comprises the amino acid sequence set forth in SEQ ID NO: 158, the second VL CDR2 comprises the

amino acid sequence set forth in SEQ ID NO: 159, and the second VL CDR3 comprises the amino acid sequence set forth in SEQ ID NO: 160; or

- (l) the second VH CDR1 comprises the amino acid sequence set forth in SEQ ID NO: 165, the second VH CDR2 comprises the amino acid sequence set forth in SEQ ID NO: 166, the second VH CDR3 comprises the amino acid sequence set forth in SEQ ID NO: 167, the second VL CDR1 comprises the amino acid sequence set forth in SEQ ID NO: 168, the second VL CDR2 comprises the amino acid sequence set forth in SEQ ID NO: 169, and the second VL CDR3 comprises the amino acid sequence set forth in SEQ ID NO: 170.
12. An immunoconjugate comprising the antibody or antigen-binding portion thereof of any one of claims 1 to 6.
 13. The immunoconjugate of claim 12, which is an antibody-drug conjugate.
 14. A chimeric antigen receptor (CAR) comprising the antibody or antigen-binding portion thereof of any of any one of claims 1 to 6.
 15. A T cell receptor (TCR) comprising the antibody or antigen-binding portion thereof of any of any one of claims 1 to 6.
 16. A nucleic acid molecule or a set of nucleic acid molecules encoding the antibody or antigen-binding portion thereof of any one of claims 1 to 7 or 11, the bispecific or multispecific antibody of claim 8, the BiTE of claim 9, the biparatopic antibody of claim 10, the CAR of claim 14, or the TCR of claim 15.
 17. A vector or a set of vectors comprising the nucleic acid molecule or the set of nucleic acid molecules of claim 16.
 18. A cell comprising the CAR of claim 14, the TCR of claim 15, the nucleic acid molecule or the set of nucleic acid molecules of claim 16, or the vector or the set of vectors of claim 17.
 19. The cell of claim 18, which is a host cell.

20. A pharmaceutical composition comprising the antibody or antigen-binding portion thereof of any one of claims 1 to 7 or 11, the bispecific or multispecific antibody of claim 8, the BiTE of claim 9, the biparatopic antibody of claim 10, the immunoconjugate of claim 12 or 13, the CAR of claim 14, the TCR of claim 15, the nucleic acid molecule or the set of nucleic acid molecules of claim 16, the vector or the set of vectors of claim 17, or the cell of claim 18 or 19, and a pharmaceutically acceptable carrier.
21. Use of the antibody or an antigen-binding portion thereof of any one of claims 1 to 7 or 11, the bispecific or multispecific antibody of claim 8, the BiTE of claim 9, the biparatopic antibody of claim 10, the immunoconjugate of claim 12 or 13, the CAR of claim 14, the TCR of claim 15, or the pharmaceutical composition of claim 20 for the manufacture of a medicament in:
 - (a) treating a tumor in a subject in need thereof; and/or
 - (b) reducing, depleting, or killing tumor infiltrating regulatory T ("Treg") cells; and/or
 - (c) activating NK cells or inducing NK cell mediated killing of tumor infiltrating regulatory T ("Treg") cells.
22. The use of claim 21, wherein the antibody or antigen-binding portion thereof:
 - (a) induces activation of NK cells;
 - (b) induces upregulation of 4-1BB, ICAM-1, or both 4-1BB and ICAM-1 on the surface of NK cells;
 - (c) induces down-regulation of CD16 on the surface of NK cells;
 - (d) induces NK cell mediated killing of tumor infiltrating Treg cells;
 - (e) induces NK cell mediated killing of tumor infiltrating Treg cells;

- (f) depletes the number of tumor infiltrating Treg cells relative to the number of tumor infiltrating Treg cells in the absence of the antibody or antigen binding portion thereof;
 - (g) depletes the number of tumor infiltrating Treg cells by at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, or at least 50% relative to the number of tumor infiltrating Treg cells in the absence of the antibody or antigen binding portion thereof; and/or
 - (h) induces internalization of CCR8 by tumor infiltrating Treg cells.
23. The use of claim 21 or 22, wherein the tumor is selected from the group consisting of Kaposi's sarcoma, leukemia, acute lymphocytic leukemia, acute myelocytic leukemia, myeloblasts promyelocyte myelomonocytic monocytic erythroleukemia, chronic leukemia, chronic myelocytic (granulocytic) leukemia, chronic lymphocytic leukemia, mantle cell lymphoma, primary central nervous system lymphoma, Burkitt's lymphoma and marginal zone B cell lymphoma, Polycythemia vera Lymphoma, Hodgkin's disease, non-Hodgkin's disease, multiple myeloma, Waldenstrom's macroglobulinemia, heavy chain disease, solid tumors, sarcomas, and carcinomas, fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, osteosarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon sarcoma, colorectal carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatocellular carcinoma (HCC), hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilm's tumor, cervical cancer, uterine cancer, testicular tumor, lung carcinoma, small cell lung carcinoma, non-small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, menangioma, melanoma, neuroblastoma,

retinoblastoma, nasopharyngeal carcinoma, esophageal carcinoma, basal cell carcinoma, biliary tract cancer, bladder cancer, bone cancer, brain and central nervous system (CNS) cancer, cervical cancer, choriocarcinoma, colorectal cancers, connective tissue cancer, cancer of the digestive system, endometrial cancer, esophageal cancer, eye cancer, head and neck cancer, gastric cancer, intraepithelial neoplasm, kidney cancer, larynx cancer, liver cancer, lung cancer (small cell, large cell), melanoma, neuroblastoma; oral cavity cancer (for example lip, tongue, mouth and pharynx), ovarian cancer, pancreatic cancer, retinoblastoma, rhabdomyosarcoma, rectal cancer; cancer of the respiratory system, sarcoma, skin cancer, stomach cancer, testicular cancer, thyroid cancer, uterine cancer, and cancer of the urinary system, or any combination thereof.

24. The use of any one of claims 21 to 23, further comprising administering an additional anticancer agent, a radiation therapy, a surgery, or a combination thereof.
25. The use of claim 24, wherein the additional anticancer agent is selected from a small molecule, a polypeptide, and a combination thereof.
26. The use of claim 24 or 25, wherein:
 - (a) the additional anticancer agent comprises a chemotherapy, wherein the chemotherapy comprises a platinum based chemotherapy;
 - (b) the additional anticancer agent comprises a PD-1 antagonist, wherein the PD-1 antagonist is selected from the group consisting of PDR001, nivolumab, pembrolizumab, pidilizumab, MEDI0680, REGN2810, TSR-042, PF-06801591, and AMP-224;
 - (c) the additional anticancer agent comprises a PD-L1 inhibitor, wherein the PD-L1 inhibitor is selected from the group consisting of FAZ053, Atezolizumab, Avelumab, Durvalumab, and BMS-936559;
 - (d) the additional anticancer agent comprises an anticancer agent selected from the group consisting of Sunitinib (SUTENT®), Cabozantinib (CABOMETYX®), Axitinib (INLYTA®), Lenvatinib (LENVIMA®), Everolimus (AFINITOR®),

Bevacizumab (AVASTIN®), epacadostat, NKTR-214 (CD-122-biased agonist), Tivozanib (FOTIVDA®), abexinostat, Ipilimumab (YERVOY®), tremelimumab, Pazopanib (VOTRIENT®), Sorafenib (NEXAVAR®), Temsirolimus (TORISEL®), Ramucirumab (CYRAMZA®), niraparib, savolitinib, vorolanib (X-82), Regorafenib (STIVARGO®), Donafenib (multikinase inhibitor), Camrelizumab (SHR-1210), pexastimogene devacirepvec (JX-594), Ramucirumab (CYRAMZA®), apatinib (YN968D1), encapsulated doxorubicin (THERMODOX®), Tivantinib (ARQ197), ADI-PEG 20, binimetinib, apatinib mesylate, nintedanib, lirilumab, Nivolumab (OPDIVO®), Pembrolizumab (KEYTRUDA®), Atezolizumab (TECENTRIQ®), Avelumab (BAVENCIO®), Durvalumab (IMFIMZI®), Cemiplimab-rwlc (LIBTAYO®), tislelizumab, spartalizumab, and any combination thereof;

- (e) the additional anticancer agent comprises a TIM-3 inhibitor, wherein the TIM-3 inhibitor is MGB453 or TSR-022;
- (f) the additional anticancer agent comprises a LAG-3 inhibitor, wherein the LAG-3 inhibitor is selected from the group consisting of LAG525, BMS-986016, and TSR-033;
- (g) the additional anticancer agent comprises a TIGIT inhibitor, wherein the additional anticancer agent comprises a CD112R inhibitor;
- (h) the additional anticancer agent comprises a TAM (Axl, Mer, Tyro) inhibitor;
- (i) the additional anticancer agent comprises a 4-1BB agonist;
- (j) the additional anticancer agent comprises a Tyrosine Kinase Inhibitor (TKI);
- (k) the additional anticancer agent comprises a CCL2 inhibitor; and/or
- (l) the additional anticancer agent comprises an agent that induces NK cell activation.

27. The use of any one of claims 24 to 26, wherein:

- (a) the antibody or antigen-binding portion thereof is administered prior to the additional anticancer agent;
 - (b) the antibody or antigen-binding portion thereof is administered after the additional anticancer agent; or
 - (c) the antibody or antigen-binding portion thereof and the additional anticancer agent are co-administered.
28. A method of making an antibody or an antigen-binding portion thereof, comprising culturing the cell of claim 18 or 19 under suitable conditions.