

CLAIMS

What is claimed is:

1. A monoclonal antibody, or an antigen-binding portion thereof, that specifically binds to C-C Motif Chemokine Receptor 8 (CCR8) expressed on the surface of a cell and mediates depletion of the CCR8-expressing cell by antibody-dependent cellular cytotoxicity (ADCC).
2. The monoclonal antibody or antigen-binding portion thereof of claim 1, which specifically binds to human CCR8 (hCCR8), the sequence of which is set forth as SEQ ID NO: 1.
3. The monoclonal antibody or antigen-binding portion thereof of claim 1 or 2, which comprises a heavy chain constant region which is of a human IgG1 or IgG3 isotype.
4. A modified anti-hCCR8 monoclonal antibody, or an antigen-binding portion thereof, which comprises a modified heavy chain constant region that binds with higher affinity to an Fc γ receptor (Fc γ R) and mediates enhanced ADCC compared to the monoclonal antibody or antigen-binding portion thereof of any one of the preceding claims, optionally which mediates at least:
 - (a) 2 times enhanced ADCC activity;
 - (a) 5 times enhanced ADCC activity; or
 - (c) 10 times enhanced ADCC activity;as measured by a reduction in the EC₅₀ for cell lysis in the NK cell lysis assay described in Example 17.
5. The modified anti-hCCR8 monoclonal antibody or antigen-binding portion thereof of claim 4, comprising a modified IgG1 heavy chain constant region which exhibits reduced fucosylation, optionally comprising a modified IgG1 heavy chain constant region which is hypofucosylated or nonfucosylated.
6. The modified anti-hCCR8 monoclonal antibody or antigen-binding portion thereof of claim 4 or 5, comprising a modified IgG1 heavy chain constant region which contains a mutation, or a multiplicity of mutations, that mediate enhanced ADCC,

optionally wherein the mutation or multiplicity of mutations is chosen from G236A; S239D; F243L; E333A; G236A/I332E; S239D/I332E; S267E/H268F; S267E/S324T; H268F/S324T; G236A/S239D/I332E; S239D/A330L/I332E; S267E/H268F/S324T; and G236A/S239D/A330L/I332E.

- 5 7. The monoclonal or modified monoclonal antibody or antigen-binding portion thereof of any one of the preceding claims, which
- (i) specifically binds to human CCR8-expressing Chinese Hamster Ovary (CHO) cells with an EC_{50} , as measured by the binding assay as described in Example 11, of:
- 10 (a) about 10 nM or lower;
(b) about 5 nM or lower;
(c) about 1.7 nM or lower;
(d) about 1 nM or lower;
(e) about 0.5 nM or lower;
15 (f) about 0.1 nM or lower;
(g) about 0.1 nM;
(h) about 1.7 nM;
(i) between about 0.1 nM and about 10 nM;
(j) between about 0.1 nM and about 2 nM;
20 (k) between about 0.5 nM and about 5 nM;
(l) between about 1 nM and about 2 nM; or
(m) between about 0.5 nM and about 1 nM;
- and/or
- (ii) specifically binds to activated regulatory T cells (Tregs) with an EC_{50} , as
- 25 measured by the binding assay as described in Example 11, of:
- (a) about 50 nM or lower;
(b) about 14 nM or lower;
(c) about 5 nM or lower;
(d) about 2 nM or lower;
30 (e) about 0.5 nM or lower;
(f) about 0.3 nM or lower;
(g) about 0.1 nM or lower;
(h) about 0.03 nM or lower;

- (i) about 1.7 nM;
- (j) between about 0.03 nM and about 10 nM;
- (k) between about 0.1 nM and about 5 nM; or
- (l) between about 0.2 nM and about 2 nM;

5 and/or

(iii) binds to a N-terminal peptide of human CCR8 comprising sulfated tyrosine-15 and tyrosine-17 residues with a K_D , as measured by surface plasmon resonance (SPR) as described in Example 11, of:

- (a) about 100 nM or lower;
- 10 (b) about 50 nM or lower;
- (c) about 10 nM or lower;
- (d) about 5 nM or lower;
- (e) about 1.6 nM;
- (f) about 1.0 nM or lower;
- 15 (g) about 0.5 nM or lower;
- (h) about 0.1 nM or lower;
- (i) between about 100 nM and about 0.1 nM;
- (j) between about 50 nM and about 0.5 nM;
- (k) between about 10 nM and about 1 nM; or
- 20 (l) between about 2 nM and about 1 nM;

and/or

(iv) binds to a N-terminal peptide of human CCR8 comprising a single sulfated residue, tyrosine-15, with a K_D , as measured by SPR as described in Example 11, of:

- 25 (a) about 100 nM or lower;
- (b) about 50 nM or lower;
- (c) about 25 nM or lower;
- (d) about 10 nM or lower;
- (f) about 1.0 nM or lower;
- 30 (e) about 20 nM;
- (i) between about 100 nM and about 1 nM;
- (j) between about 50 nM and about 10 nM; or
- (k) between about 30 nM and about 20 nM.

8. The monoclonal or modified monoclonal antibody or antigen-binding portion thereof of any one of the preceding claims, which binds specifically to rare and scattered immune cells in the medulla of the thymus and dermis of the skin but does not bind to human cerebrum, cerebellum, heart, liver, lung, kidney, tonsil, spleen, thymus, colon, stomach, pancreas, adrenal, pituitary, skin, peripheral nerve, testis or uterus tissue, or peripheral blood mononuclear cells (PBMCs).
9. The monoclonal or modified monoclonal antibody or antigen-binding portion thereof of any one of the preceding claims, which further inhibits binding of C-C Motif Chemokine Ligand 1 (CCL1) to CCR8 and inhibits CCR8/CCL1 signaling as measured by inhibition of calcium flux as described in Example 15.
10. The monoclonal or modified monoclonal antibody or antigen-binding portion thereof of any one of the preceding claims, which
 - (i) inhibits CCR8/CCL1 signaling with an IC₅₀ of:
 - (a) about 10 nM or lower;
 - (b) about 5 nM or lower;
 - (c) about 1 nM or lower;
 - (d) about 0.5 nM or lower;
 - (e) about 0.1 nM or lower;
 - (f) about 0.01 nM or lower;
 - (g) between about 0.01 nM and about 10 nM;
 - (h) between about 0.05 nM and about 5 nM;
 - (i) between about 0.1 nM and about 1 nM; or
 - (j) about 0.46 nM;
 - and/or
 - (ii) mediates depletion of the CCR8-expressing cell with an EC₅₀, as measured by a CD16 cross-linking assay as described in Example 17, of:
 - (a) about 100 pM or lower;
 - (b) about 30 pM or lower;
 - (c) about 10 pM or lower;
 - (d) about 3 pM or lower;
 - (e) about 1 pM or lower;
 - (e) about 0.5 pM or lower;

- (f) about 0.1 pM or lower;
- (g) about 0.05 pM or lower;
- (h) about 0.7 pM;
- (i) between about 0.05 pM and about 50 pM;
- (j) between about 0.1 pM and about 10 nM;
- (k) between about 0.3 nM and about 7 nM; or
- (l) between about 0.6 nM and about 3 nM;

and/or

- (iii) mediates depletion of activated Tregs with an EC₅₀, as measured by an apoptosis assay as described in Example 19, of:
 - (a) about 500 pM or lower;
 - (b) about 100 pM or lower;
 - (c) about 30 pM or lower;
 - (d) about 15 pM or lower;
 - (e) about 5 pM or lower;
 - (f) about 1 pM or lower;
 - (g) about 13 pM;
 - (h) between about 1 pM and about 500 pM;
 - (i) between about 5 pM and about 100 pM; or
 - (j) between about 10 pM and about 50 pM.

11. The monoclonal or modified monoclonal antibody or antigen-binding portion thereof of any one of the preceding claims, which binds to an epitope located in the N-terminal domain of human CCR8 as determined by X-ray crystallography, wherein the epitope comprises at least one amino acid within a peptide having the sequence:

(a) Y₁₅Y₁₆Y₁₇P₁₈D₁₉I₂₀F₂₁ (SEQ ID NO: 2), optionally wherein

(i) the epitope comprises 2, 3, 4, 5, 6, or all the amino acids within a peptide having the sequence of Y₁₅Y₁₆Y₁₇P₁₈D₁₉I₂₀F₂₁ (SEQ ID NO: 2); optionally wherein

(ii) the epitope comprises all 7 of the amino acids in the peptide having the sequence Y₁₅Y₁₆Y₁₇P₁₈D₁₉I₂₀F₂₁ (SEQ ID NO: 2); optionally wherein

(iii) amino acid Y₁₅ and/or Y₁₇ is sulfated; or

(b) V₁₂T₁₃D₁₄Y₁₅Y₁₆Y₁₇P₁₈D₁₉I₂₀F₂₁S₂₂ (SEQ ID NO: 109), optionally wherein

(i) the epitope comprises 2, 3, 4, 5, 6, 7, 8, 9, 10 or all the amino acids within a peptide having the sequence

V₁₂T₁₃D₁₄Y₁₅Y₁₆Y₁₇P₁₈D₁₉I₂₀F₂₁S₂₂ (SEQ ID NO: 109); optionally wherein

(ii) the epitope comprises all 11 of the amino acids in the peptide having the sequence V₁₂T₁₃D₁₄Y₁₅Y₁₆Y₁₇P₁₈D₁₉I₂₀F₂₁S₂₂ (SEQ ID NO: 109); optionally wherein

(iii) the epitope consists of all 11 of the amino acids in the peptide having the sequence V₁₂T₁₃D₁₄Y₁₅Y₁₆Y₁₇P₁₈D₁₉I₂₀F₂₁S₂₂ (SEQ ID NO: 109); optionally wherein

~~(iii)~~(iv) both amino acids Y₁₅ and Y₁₇ are sulfated.

12. A monoclonal antibody, or an antigen-binding portion thereof, which is capable of mediating ADCC and which specifically binds to an epitope on human C-C Motif Chemokine Receptor 8 (hCCR8) expressed on the surface of a cell, the sequence of which is set forth as SEQ ID NO: 1, wherein the epitope is located in the N-terminal domain of hCCR8 as determined by X-ray crystallography within a peptide spanning approximately amino acid residues:

(a) 15-21 (Y₁₅Y₁₆Y₁₇P₁₈D₁₉I₂₀F₂₁; SEQ ID NO: 2), optionally wherein

(i) the epitope comprises at least one amino acid within a peptide having the sequence Y₁₅Y₁₆Y₁₇P₁₈D₁₉I₂₀F₂₁ (SEQ ID NO: 2);

(ii) the epitope comprises 2, 3, 4, 5, 6, or all the amino acids within a peptide having the sequence of Y₁₅Y₁₆Y₁₇P₁₈D₁₉I₂₀F₂₁ (SEQ ID NO: 2); or

(iii) the epitope comprises all 7 of the amino acids in the peptide having the sequence Y₁₅Y₁₆Y₁₇P₁₈D₁₉I₂₀F₂₁ (SEQ ID NO: 2); optionally wherein

(iv) amino acid Y₁₅ and/or Y₁₇ is sulfated; or

(b) 12 to 22 (V₁₂T₁₃D₁₄Y₁₅Y₁₆Y₁₇P₁₈D₁₉I₂₀F₂₁S₂₂; SEQ ID NO: 109)-as determined by X-ray crystallography, optionally wherein :

(i) the epitope comprises at least one amino acid within a peptide

having the sequence V₁₂T₁₃D₁₄Y₁₅Y₁₆Y₁₇P₁₈D₁₉I₂₀F₂₁S₂₂ (SEQ ID NO: 109);

(ii) the epitope comprises 2, 3, 4, 5, 6, 7, 8, 9, 10 or all the amino acids within a peptide having the sequence V₁₂T₁₃D₁₄Y₁₅Y₁₆Y₁₇P₁₈D₁₉I₂₀F₂₁S₂₂ (SEQ ID NO: 109);

(iii) the epitope comprises all 11 of the amino acids in the peptide having the sequence V₁₂T₁₃D₁₄Y₁₅Y₁₆Y₁₇P₁₈D₁₉I₂₀F₂₁S₂₂ (SEQ ID NO: 109); or

(iv) the epitope consists of all 11 of the amino acids in the peptide having the sequence V₁₂T₁₃D₁₄Y₁₅Y₁₆Y₁₇P₁₈D₁₉I₂₀F₂₁S₂₂ (SEQ ID NO: 109), optionally wherein

(v) amino acids Y₁₅ and Y₁₇ are sulfated.

13. The monoclonal antibody or antigen-binding portion thereof of any one of the preceding claims, wherein

(i) the antibody or portion thereof, when bound to CCR8 on the surface of a cell, does not cause internalization of CCR8 either in the presence or absence of a cross-linking antibody; and/or

(ii) the antibody or portion thereof promotes depletion of human tumor-associated Tregs *in vitro*; and/or

(iii) the antibody or portion thereof specifically induces depletion of tumor Tregs without depleting CCR8⁺ T cells in non-tumor tissue, optionally wherein the non-tumor tissue is the skin, thymus, spleen or blood; and/or

(iv) the antibody or portion thereof is capable of inhibiting growth of tumor cells in a subject, wherein the antibody or portion thereof is to be ~~when~~ administered as monotherapy to the subject; and/or

(v) the antibody or portion thereof is capable of inhibiting growth of tumor cells in a subject, wherein the antibody or portion thereof is to be ~~when~~ administered to the subject in combination with an additional therapeutic agent for treating a cancer.

14. The monoclonal antibody or antigen-binding portion thereof of any one of the preceding claims, which exhibits at least one, two, three, four, five or six of the following properties:

- (a) specifically binds to CCR8 expressed on the surface of a cell with an EC₅₀ of about 2 nM or lower;
- (b) binds specifically to rare and scattered immune cells in the medulla of the thymus and dermis of the skin but does not bind to human cerebrum, cerebellum, heart, liver, lung, kidney, tonsil, spleen, thymus, colon, stomach, pancreas, adrenal, pituitary, skin, peripheral nerve, testis or uterus tissue, or peripheral blood mononuclear cells (PBMCs);
- (c) inhibits binding of CCL1 to CCR8 and inhibits CCR8/CCL1 signaling with an IC₅₀ of about 5 nM or lower;
- (d) when bound to CCR8 on the surface of a cell mediates depletion of the cell with an EC₅₀ of about 10 pM or lower;
- (e) when bound to CCR8 on the surface of a cell does not cause internalization of CCR8 either in the presence or absence of a cross-linking antibody;
- (f) promotes depletion of human tumor-associated Tregs *in vitro* using the assay described in Example 22;
- (g) promotes depletion of human tumor-associated Tregs in *ex-vivo* human tumor slice samples using the assay described in Example 20;
- (h) mediates depletion of tumor Tregs specifically while sparing CCR8⁺ T cells in non-tumor tissues;
- (i) capable of inhibiting growth of tumor cells in a subject, wherein the monoclonal antibody or antigen-binding portion thereof is to be ~~when~~ administered as monotherapy to the subject; and
- (j) capable of inhibiting growth of tumor cells in a subject, wherein the monoclonal antibody or antigen-binding portion thereof is to be ~~when~~ administered to the subject in combination with an additional therapeutic agent for treating a cancer; optionally wherein the monoclonal antibody or antigen-binding portion thereof exhibits all of those properties.;
15. The monoclonal antibody or antigen-binding portion thereof of claim ~~34 or 35~~ 13 or 14, which further binds to an epitope located in the N-terminal domain of human CCR8 with a K_D of about 10 nM or lower, wherein the epitope comprises a peptide having the sequence V₁₂T₁₃D₁₄Y₁₅Y₁₆Y₁₇P₁₈D₁₉I₂₀F₂₁S₂₂ (SEQ ID NO: 109) and sulfated tyrosine-15 and tyrosine-17 residues.

16. A modified anti-hCCR8 monoclonal antibody, or an antigen-binding portion thereof, which comprises a modified heavy chain constant region that binds with higher affinity to an Fcγ receptor (FcγR) and mediates at least 2, 5 or 10 times enhanced ADCC compared to the monoclonal antibody or antigen-binding portion thereof of claim 14 or 15.
17. The monoclonal antibody or antigen-binding portion thereof of any one of the preceding claims, which binds to the same epitope as does a reference antibody, wherein the reference antibody comprises:
 - (a) a V_H comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 3 and a V_L comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 15;
 - (b) a V_H comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 4 and a V_L comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 16;
 - (c) a V_H comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 5 and a V_L comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 17;
 - (d) a V_H comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 6 and a V_L comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 18;
 - (e) a V_H comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 7 and a V_L comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 19;
 - (f) a V_H comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 8 and a V_L comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 20;
 - (g) a V_H comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 9 and a V_L comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 21;
 - (h) a V_H comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 10 and a V_L comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 22;
 - (i) a V_H comprising consecutively linked amino acids having the sequence set

- forth as SEQ ID NO: 11 and a V_L comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 23;
- (j) a V_H comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 12 and a V_L comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 24;
- (k) a V_H comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 13 and a V_L comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 25;
- (l) a V_H comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 14 and a V_L comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 26; or
- (m) a V_H comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 115 and a V_L comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 116.
18. The monoclonal antibody or antigen-binding portion thereof of any one of the preceding claims, which cross-competes for binding to hCCR8 with a reference antibody, wherein the reference antibody comprises:
- (a) a V_H comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 3 and a V_L comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 15;
- (b) a V_H comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 4 and a V_L comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 16;
- (c) a V_H comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 5 and a V_L comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 17;
- (d) a V_H comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 6 and a V_L comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 18;
- (e) a V_H comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 7 and a V_L comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 19;
- (f) a V_H comprising consecutively linked amino acids having the sequence set

- forth as SEQ ID NO: 8 and a V_L comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 20;
- (g) a V_H comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 9 and a V_L comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 21;
- (h) a V_H comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 10 and a V_L comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 22;
- (i) a V_H comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 11 and a V_L comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 23;
- (j) a V_H comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 12 and a V_L comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 24;
- (k) a V_H comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 13 and a V_L comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 25;
- (l) a V_H comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 14 and a V_L comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 26; or
- (m) a V_H comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 115 and a V_L comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 116.
19. The monoclonal antibody or antigen-binding portion thereof of any one of the preceding claims, which comprises the CDR1, CDR2 and CDR3 domains in each of:
- (a) a V_H comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 3 and a V_L comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 15;
- (b) a V_H comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 4 and a V_L comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 16;
- (c) a V_H comprising consecutively linked amino acids having the sequence set

- forth as SEQ ID NO: 5 and a V_L comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 17;
- 5 (d) a V_H comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 6 and a V_L comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 18;
- (e) a V_H comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 7 and a V_L comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 19;
- 10 (f) a V_H comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 8 and a V_L comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 20;
- (g) a V_H comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 9 and a V_L comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 21;
- 15 (h) a V_H comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 10 and a V_L comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 22;
- (i) a V_H comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 11 and a V_L comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 23;
- 20 (j) a V_H comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 12 and a V_L comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 24;
- (k) a V_H comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 13 and a V_L comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 25;
- 25 (l) a V_H comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 14 and a V_L comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 26; or
- 30 (m) a V_H comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 115 and a V_L comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 116.

20. The monoclonal antibody or antigen-binding portion thereof of claim 19, which

comprises the following CDR domains as defined by the Kabat method:

- 5 (a) a heavy chain variable region CDR1 comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 27; a heavy chain variable region CDR2 comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 28; a heavy chain variable region CDR3 comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 29; a light chain variable region CDR1 comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 30; a light chain variable region CDR2 comprising
- 10 consecutively linked amino acids having the sequence set forth as SEQ ID NO: 31; and a light chain variable region CDR3 comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 32;
- 15 (b) a heavy chain variable region CDR1 comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 33; a heavy chain variable region CDR2 comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 34; a heavy chain variable region CDR3 comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 35; a light chain variable region CDR1 comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 36; a light chain variable region CDR2 comprising
- 20 consecutively linked amino acids having the sequence set forth as SEQ ID NO: 37; and a light chain variable region CDR3 comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 38;
- 25 (c) a heavy chain variable region CDR1 comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 39; a heavy chain variable region CDR2 comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 40; a heavy chain variable region CDR3 comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 41; a light chain variable region CDR1
- 30 comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 42; a light chain variable region CDR2 comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 43; and a light chain variable region CDR3 comprising consecutively

- linked amino acids having the sequence set forth as SEQ ID NO: 44;
- (d) a heavy chain variable region CDR1 comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 45; a heavy chain variable region CDR2 comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 46; a heavy chain variable region CDR3 comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 47; a light chain variable region CDR1 comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 48; a light chain variable region CDR2 comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 49; and a light chain variable region CDR3 comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 50;
- (e) a heavy chain variable region CDR1 comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 51; a heavy chain variable region CDR2 comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 52; a heavy chain variable region CDR3 comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 53; a light chain variable region CDR1 comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 54; a light chain variable region CDR2 comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 55; and a light chain variable region CDR3 comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 56;
- (f) a heavy chain variable region CDR1 comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 57; a heavy chain variable region CDR2 comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 58; a heavy chain variable region CDR3 comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 59; a light chain variable region CDR1 comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 60; a light chain variable region CDR2 comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 61; and a light chain variable region CDR3 comprising consecutively

- linked amino acids having the sequence set forth as SEQ ID NO: 62;
- (g) a heavy chain variable region CDR1 comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 63; a heavy chain variable region CDR2 comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 64; a heavy chain variable region CDR3 comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 65; a light chain variable region CDR1 comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 66; a light chain variable region CDR2 comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 67; and a light chain variable region CDR3 comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 68;
- (h) a heavy chain variable region CDR1 comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 69; a heavy chain variable region CDR2 comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 70; a heavy chain variable region CDR3 comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 71; a light chain variable region CDR1 comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 72; a light chain variable region CDR2 comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 73; and a light chain variable region CDR3 comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 74;
- (i) a heavy chain variable region CDR1 comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 75; a heavy chain variable region CDR2 comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 76; a heavy chain variable region CDR3 comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 77; a light chain variable region CDR1 comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 78; a light chain variable region CDR2 comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 79; and a light chain variable region CDR3 comprising consecutively

- linked amino acids having the sequence set forth as SEQ ID NO: 80;
- (j) a heavy chain variable region CDR1 comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 81; a heavy chain variable region CDR2 comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 82; a heavy chain variable region CDR3 comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 83; a light chain variable region CDR1 comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 84; a light chain variable region CDR2 comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 85; and a light chain variable region CDR3 comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 86;
- (k) a heavy chain variable region CDR1 comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 87; a heavy chain variable region CDR2 comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 88; a heavy chain variable region CDR3 comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 89; a light chain variable region CDR1 comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 90; a light chain variable region CDR2 comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 91; and a light chain variable region CDR3 comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 92;
- (l) a heavy chain variable region CDR1 comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 93; a heavy chain variable region CDR2 comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 94; a heavy chain variable region CDR3 comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 95; a light chain variable region CDR1 comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 96; a light chain variable region CDR2 comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 97; and a light chain variable region CDR3 comprising consecutively

- linked amino acids having the sequence set forth as SEQ ID NO: 98; or
- (m) a heavy chain variable region CDR1 comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 103; a heavy chain variable region CDR2 comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 104; a heavy chain variable region CDR3 comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 105; a light chain variable region CDR1 comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 106; a light chain variable region CDR2 comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 107; and a light chain variable region CDR3 comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 108.
21. The monoclonal antibody or antigen-binding portion thereof of claim 19 or 20, which comprises:
- (a) a V_H comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 3 and a V_L comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 15;
- (b) a V_H comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 4 and a V_L comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 16;
- (c) a V_H comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 5 and a V_L comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 17;
- (d) a V_H comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 6 and a V_L comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 18;
- (e) a V_H comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 7 and a V_L comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 19;
- (f) a V_H comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 8 and a V_L comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 20;

- (g) a V_H comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 9 and a V_L comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 21;
- 5 (h) a V_H comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 10 and a V_L comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 22;
- (i) a V_H comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 11 and a V_L comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 23;
- 10 (j) a V_H comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 12 and a V_L comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 24;
- (k) a V_H comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 13 and a V_L comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 25;
- 15 (l) a V_H comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 14 and a V_L comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 26; or
- (m) a V_H comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 115 and a V_L comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 116.
- 20
22. The monoclonal antibody or antigen-binding portion thereof of claim 20 or 21, which comprises:
- 25 (a) a heavy chain comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 99 and a light chain comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 111;
- (b) a heavy chain comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 100 and a light chain comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 112;
- 30 (c) a heavy chain comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 101 and a light chain comprising

- consecutively linked amino acids having the sequence set forth as SEQ ID NO: 113;
- 5 (d) a heavy chain comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 102 and a light chain comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 114;
- 10 (e) a heavy chain comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 117 and a light chain comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 118; or
- (f) a heavy chain comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 110 and a light chain comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 119.
- 15 23. The monoclonal antibody or antigen-binding portion thereof of any one of the preceding claims, which is a chimeric antibody, a humanized antibody, a human antibody, or a fragment thereof.
- 20 24. An immunoconjugate comprising the monoclonal antibody or antigen-binding portion thereof of any one of the preceding claims, linked to a cytolytic agent, optionally wherein the cytolytic agent is a cytotoxin or a radioactive isotope.
- 25 25. A bispecific molecule comprising the monoclonal antibody or antigen-binding portion thereof of any one of claims 1-23, linked to a binding domain that has a different binding specificity than the monoclonal antibody or antigen binding portion thereof.
- 30 26. A composition comprising:
- (a) the monoclonal antibody or antigen-binding portion thereof of any one of claims 1-23;
- (b) the immunoconjugate of claim 24; or
- (c) the bispecific molecule of claim 25,
- and a pharmaceutically acceptable carrier.

27. An isolated nucleic acid encoding the monoclonal antibody or antigen-binding portion thereof of any one of claims 1-23.

28. An expression vector comprising the nucleic acid of claim 27.

29. A host cell comprising the expression vector of claim 28.

5 30. A method for preparing an anti-CCR8 antibody or antigen-binding portion thereof which comprises expressing the antibody or antigen-binding portion thereof in the host cell of claim 29 and isolating the antibody or antigen-binding portion thereof from the host cell.

10 31. ~~A method for treating a subject afflicted with a cancer, comprising administering to the subject a therapeutically effective amount of~~ Use of the monoclonal or modified monoclonal antibody or antigen-binding portion thereof of any one of claims 1-23, the immunoconjugate of claim 24, the bispecific molecule of claim 25, or the pharmaceutical composition of claim 26 in the manufacture of a medicament for treating a subject afflicted with a cancer, wherein a
15 therapeutically effective amount of the monoclonal or modified monoclonal antibody or antigen-binding portion thereof, the immunoconjugate, the bispecific molecule, or the pharmaceutical composition is to be administered to the subject, such that for the subject is to be treated.

20 32. ~~A method for inhibiting growth of tumor cells in a subject, comprising administering to the subject a therapeutically effective amount of~~ Use of the monoclonal or modified monoclonal antibody or antigen-binding portion thereof of any one of claims 1-23, the immunoconjugate of claim 24, the bispecific molecule of claim 25, or the pharmaceutical composition of claim 26 in the
25 manufacture of a medicament for inhibiting growth of tumor cells in a subject, wherein a therapeutically effective amount of the monoclonal or modified monoclonal antibody or antigen-binding portion thereof, the immunoconjugate, the bispecific molecule, or the pharmaceutical composition is to be administered to the subject, such that for growth of tumor cells in the subject is to be inhibited.

30 33. The ~~method~~ use of claim 31 or 32, wherein ~~the method further comprises administering to the subject a therapeutically effective amount of an additional~~

therapeutic agent for treating a cancer is to be further administered to the subject,
optionally wherein the additional therapeutic agent is a chemotherapeutic agent,
radiation therapy, or a compound that reduces inhibition, or increases stimulation,
of the immune system.

5

34. The ~~method~~use of any one of claims 31-33, wherein the subject is a human.

35. The ~~method~~use of any one of claims 31-34, wherein:

(a) the cancer is a solid tumor, optionally wherein the solid tumor is:

(i) a cancer chosen from squamous cell carcinoma, small cell lung
cancer (SCLC), non-small cell lung cancer (NSCLC), squamous NSCLC,
non-squamous NSCLC, head and neck cancer, breast cancer, cancer of the
esophagus, gastric cancer, gastrointestinal cancer, cancer of the small
intestine, liver cancer, hepatocellular carcinoma (HCC), pancreatic cancer
(PAC), kidney cancer, renal cell carcinoma (RCC), bladder cancer, cancer
of the urethra, cancer of the ureter, colorectal cancer (CRC), colon cancer,
colon carcinoma, cancer of the anal region, endometrial cancer, prostate
cancer, a fibrosarcoma, neuroblastoma, glioma, glioblastoma, germ cell
tumor, pediatric sarcoma, sinonasal natural killer, melanoma, skin cancer,
bone cancer, cervical cancer, uterine cancer, carcinoma of the
endometrium, carcinoma of the fallopian tubes, ovarian cancer, carcinoma
of the cervix, carcinoma of the vagina, carcinoma of the vulva, testicular
cancer, cancer of the endocrine system, thyroid cancer, cancer of the
parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue,
cancer of the penis, carcinoma of the renal pelvis, neoplasm of the central
nervous system (CNS), primary CNS lymphoma, tumor angiogenesis,
spinal axis tumor, brain cancer, brain stem glioma, pituitary adenoma,
Kaposi's sarcoma, epidermoid cancer, squamous cell cancer, solid tumors
of childhood, environmentally-induced cancers, virus-related cancers,
cancers of viral origin, advanced cancer, unresectable cancer, metastatic
cancer, refractory cancer, recurrent cancer, and any combination thereof;
or

(ii) a cancer chosen from non-small cell lung cancer (NSCLC),

squamous cell carcinoma of the head and neck (SCCHN), colorectal cancer (CRC), gastric cancer, gastroesophageal (GE) junction cancer, and cervical cancer; or

(iii) a cancer chosen from head and neck squamous cell carcinoma (HNSC), lung adenocarcinoma (LUAD), stomach adenocarcinoma (STAD), lung squamous cell carcinoma (LUSC), pancreatic adenocarcinoma (PAAD), rectum adenocarcinoma (READ), esophageal carcinoma (ESCA), breast invasive carcinoma (BRCA), colon adenocarcinoma (COAD) and cervical squamous cell carcinoma and endocervical adenocarcinoma (CESC); or

(iv) a cancer chosen from squamous cell carcinoma of the head and neck (SCCHN), cervical cancer, colorectal cancer (CRC), non-small cell lung cancer-squamous cell carcinoma (NSCLC-SCC), NSCLC-adenocarcinoma (NSCLC-ADC), pancreatic cancer, gastric cancer, bladder cancer and breast cancer; or

(v) a cancer chosen from colon adenocarcinoma, bladder carcinoma, mammary carcinoma, and fibrosarcoma; or

(b) the cancer is a hematological malignancy or the tumor cells are cells of a hematological malignancy, optionally wherein the hematological malignancy is selected from acute lymphoblastic leukemia (ALL), acute myelogenous leukemia (AML), chronic lymphocytic leukemia (CLL), chronic myelogenous leukemia (CML), a T cell lymphoma, Hodgkin's lymphoma (HL), non-Hodgkin's lymphomas (NHLs), multiple myeloma, smoldering myeloma, monoclonal gammopathy of undetermined significance (MGUS), advanced, metastatic, refractory and/or recurrent hematological malignancies, and any combinations of said hematological malignancies.

36. The ~~method~~ use of claim 31, wherein the additional therapeutic agent is:

(a) an antagonistic agent that binds specifically to Programmed Death-1 (PD-1), Programmed Death Ligand-1 (PD-L1), Cytotoxic T-Lymphocyte Antigen-4 (CTLA-4), Lymphocyte Activation Gene-3 (LAG-3), B and T lymphocyte Attenuator (BTLA), T cell Immunoglobulin and Mucin domain-3 (TIM-3), Killer Immunoglobulin-like Receptor (KIR), Killer cell

Lectin-like Receptor G1 (KLRG-1), Adenosine A2a Receptor (A2aR), T Cell Immunoreceptor with Ig and ITIM Domains (TIGIT), V-domain Ig Suppressor of T cell activation (VISTA), proto-oncogene tyrosine-protein kinase MER (MerTK), Natural Killer Cell Receptor 2B4 (CD244), or CD160; or

(b) an agonistic agent that binds specifically to Inducible T cell Co-Stimulator (ICOS), CD137 (4-1BB), CD134 (OX40), CD27, Glucocorticoid-Induced TNFR-Related protein (GITR), or HerpesVirus Entry Mediator (HVEM); and optionally wherein:

(i) the antagonistic agent that binds specifically to PD-1 is chosen from nivolumab, pembrolizumab, cemiplimab, spartalizumab, camrelizumab, sintilimab, tislelizumab and toripalimab; or

(ii) the antagonistic agent that binds specifically to PD-L1 is chosen from atezolizumab, durvalumab, avelumab, envafolimab, BMS-936559, CK-301, CS-1001, SHR-1316, CBT-502, and BGB-A333; or

(iii) the antagonistic agent that binds specifically to CTLA-4 is ipilimumab or tremelimumab.

37. ~~A method for potentiating an anti-tumor immune response elicited by a therapeutic agent in a subject afflicted with a cancer, comprising administering to the subject a therapeutically effective amount of~~ Use of the monoclonal or modified monoclonal antibody or antigen-binding portion thereof of any one of claims 1-23, the immunoconjugate of claim 24, the bispecific molecule of claim 25, or the pharmaceutical composition of claim 26 in the manufacture of a medicament for, ~~potentiating an anti-tumor immune response elicited by a therapeutic agent in a subject afflicted with a cancer, wherein a therapeutically effective amount of the monoclonal or modified monoclonal antibody or antigen-binding portion thereof, the immunoconjugate, the bispecific molecule, or the pharmaceutical composition is to be administered to the subject, such that the subject experiences a stronger immune response against the cancer compared to the immune response elicited by the therapeutic agent alone.~~

38. The ~~method~~ use of claim 37, wherein the therapeutic agent is a chemotherapeutic agent, an immune checkpoint inhibitor or radiotherapy, optionally wherein the

checkpoint inhibitor is an anti-PD-1, anti-PD-L1 or anti-CTLA-4 antibody.

39. A kit for use in treating a subject afflicted with a cancer, the kit comprising:
- (a) one or more dosages ranging from about 0.01 to about 20 mg/kg body weight of a monoclonal or modified monoclonal antibody or an antigen-binding portion thereof that binds specifically to C-C Motif Chemokine Receptor 8 (CCR8) and mediates depletion of the CCR8-expressing cell by ADCC;
 - (b) optionally one or more dosages ranging from about 200 to about 1600 mg of a monoclonal antibody or an antigen-binding portion thereof that binds specifically to PD-1, PD-L1 or CTLA-4; and
 - (c) instructions for using the monoclonal or modified monoclonal antibody or portion thereof that binds specifically to CCR8, and optionally the monoclonal antibody or portion thereof that binds specifically to PD-1, PD-L1 or CTLA-4, in the ~~method~~use of any one of claims 31-36.

40. The monoclonal or modified monoclonal antibody or antigen-binding portion thereof of any one of claims 1-23, the immunoconjugate of claim 24, the bispecific molecule of claim 25, or the pharmaceutical composition of claim 26 for use in therapy.