

CLAIMS

What is claimed is:

1. An anti-hCCR8 monoclonal antibody or an antigen-binding portion thereof that binds specifically to human C-C Motif Chemokine Receptor 8 (hCCR8), the
5 sequence of which is set forth as SEQ ID NO: 1, expressed on the surface of an activated human regulatory T cell (Treg) with an EC₅₀ of 20 nM ± 25% or lower as measured by a binding assay as described in Example 11 and mediates antibody-dependent cellular cytotoxicity (ADCC) killing of the activated human Treg, or a modified version of said anti-hCCR8 monoclonal antibody or an
10 antigen-binding portion thereof which comprises a modified heavy chain constant region that binds with higher affinity to an Fcγ receptor and mediates enhanced ADCC compared to the unmodified anti-hCCR8 antibody, wherein the monoclonal antibody or modified monoclonal antibody or antigen-binding portion thereof comprises the following CDR domains as defined by the Kabat method:
 - 15 (a) 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
20 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 consecutively linked amino acids having the sequence set forth as SEQ ID NO: 37; and a light chain variable region CDR3 comprising consecutively
25 linked amino acids having the sequence set forth as SEQ ID NO: 38;
 - (b) 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
30 region CDR3 comprising consecutively linked amino acids having the sequence set forth as SEQ ID NO: 41; a light chain variable region CDR1 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;

5 (c) 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;

10 (d) 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;

15 (e) 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

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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; or

(f) 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.

2. The monoclonal antibody or modified monoclonal antibody or antigen-binding portion thereof of claim 1, which:

- (i) binds specifically to human CCR8-expressing Chinese Hamster Ovary cells with an EC_{50} , as measured by a binding assay as described in Example 11, of:
- (a) $10 \text{ nM} \pm 25\%$ or lower;
 - (b) $5 \text{ nM} \pm 25\%$ or lower;
 - (c) $1.7 \text{ nM} \pm 25\%$ or lower;
 - (d) $1 \text{ nM} \pm 25\%$ or lower;
 - (e) $0.5 \text{ nM} \pm 25\%$ or lower;
 - (f) $0.1 \text{ nM} \pm 25\%$ or lower;
 - (g) $0.1 \pm 25\% \text{ nM}$;
 - (h) $1.7 \pm 25\% \text{ nM}$;
 - (i) between $0.1 \text{ nM} \pm 25\%$ and $10 \text{ nM} \pm 25\%$;
 - (j) between $0.1 \text{ nM} \pm 25\%$ and $2 \text{ nM} \pm 25\%$;
 - (k) between $0.5 \text{ nM} \pm 25\%$ and $5 \text{ nM} \pm 25\%$;
 - (l) between $1 \text{ nM} \pm 25\%$ and $2 \text{ nM} \pm 25\%$; or
 - (m) between $0.5 \text{ nM} \pm 25\%$ and $1 \text{ nM} \pm 25\%$;

and/or

(ii) binds specifically to activated regulatory T cells (Tregs) with an EC_{50} , as measured by a binding assay as described in Example 11, of:

- (a) 14 nM $\pm$ 25% or lower;
- (b) 5 nM $\pm$ 25% or lower;
- (c) 2 nM $\pm$ 25% or lower;
- (d) 0.5 nM $\pm$ 25% or lower;
- (e) 0.3 nM $\pm$ 25% or lower;
- (f) 0.1 nM $\pm$ 25% or lower;
- (g) 0.03 nM $\pm$ 25% or lower;
- (h) 1.7 nM $\pm$ 25%;
- (i) between 0.03 nM $\pm$ 25% and 10 nM $\pm$ 25%;
- (j) between 0.1 nM $\pm$ 25% and 5 nM $\pm$ 25%; or
- (k) between 0.2 nM $\pm$ 25% and 2 nM $\pm$ 25%;

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) 100 nM $\pm$ 25% or lower;
- (b) 50 nM $\pm$ 25% or lower;
- (c) 10 nM $\pm$ 25% or lower;
- (d) 5 nM $\pm$ 25% or lower;
- (e) 1.6 nM $\pm$ 25%;
- (f) 1.0 nM $\pm$ 25% or lower;
- (g) 0.5 nM $\pm$ 25% or lower;
- (h) 0.1 nM $\pm$ 25% or lower;
- (i) between 100 nM $\pm$ 25% and 0.1 $\pm$ 25% nM;
- (j) between 50 nM $\pm$ 25% and 0.5 $\pm$ 25% nM;
- (k) between 10 nM $\pm$ 25% and 1 nM $\pm$ 25%; or
- (l) between 2 nM $\pm$ 25% and 1 nM $\pm$ 25%;

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:

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- (a) 100 nM $\pm$ 25% or lower;
 - (b) 50 nM $\pm$ 25% or lower;
 - (c) 25 nM $\pm$ 25% or lower;
 - (d) 10 nM $\pm$ 25% or lower;
 - (e) 1.0 nM $\pm$ 25% or lower;
 - (f) 20 nM $\pm$ 25%;
 - (g) between 100 nM $\pm$ 25% and 1 nM $\pm$ 25%;
 - (h) between 50 nM $\pm$ 25% and 10 nM $\pm$ 25%; or
 - (i) between 30 nM $\pm$ 25% and 20 nM $\pm$ 25%.
- 10 3. The monoclonal antibody or modified monoclonal antibody or antigen-binding portion thereof of claim 1 or 2, 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
- 15 or uterus tissue, or peripheral blood mononuclear cells (PBMCs).
4. The monoclonal antibody or modified monoclonal antibody or antigen-binding portion thereof of any one of the preceding claims, which:
- (i) inhibits binding of C-C Motif Chemokine Ligand 1 (CCL1) to CCR8 and inhibits CCR8/CCL1 signaling as measured by inhibition of calcium flux
- 20 as described in Example 15 with an IC₅₀ of:
- (a) 10 nM $\pm$ 25% or lower;
 - (b) 5 nM $\pm$ 25% or lower;
 - (c) 1 nM $\pm$ 25% or lower;
 - (d) 0.5 nM $\pm$ 25% or lower;
 - 25 (e) 0.1 nM $\pm$ 25% or lower;
 - (f) 0.01 nM $\pm$ 25% or lower;
 - (g) between 0.01 nM $\pm$ 25% and 10 nM $\pm$ 25%;
 - (h) between 0.05 nM $\pm$ 25% and 5 nM $\pm$ 25%;
 - (i) between 0.1 nM $\pm$ 25% and 1 nM $\pm$ 25%; or
 - 30 (j) 0.46 nM $\pm$ 25%;
- and/or
- (ii) mediates depletion of the activated human Treg with an EC₅₀, as measured

by a CD16 cross-linking assay as described in Example 17, of:

- (a) 100 pM $\pm$ 25% or lower;
- (b) 30 pM $\pm$ 25% or lower;
- (c) 10 pM $\pm$ 25% or lower;
- 5 (d) 3 pM $\pm$ 25% or lower;
- (e) 1 pM $\pm$ 25% or lower;
- (f) 0.5 pM $\pm$ 25% or lower;
- (g) 0.1 pM $\pm$ 25% or lower;
- (h) 0.05 pM $\pm$ 25% or lower;
- 10 (i) 0.7 $\pm$ 25% pM;
- (j) between 0.05 pM $\pm$ 25% and 50 pM $\pm$ 25%;
- (k) between 0.1 pM $\pm$ 25% and 10 pM $\pm$ 25%;
- (l) between 0.3 pM $\pm$ 25% and 7 pM $\pm$ 25%; or
- (m) between 0.6 pM $\pm$ 25% and 3 pM $\pm$ 25%;
- 15 and/or
- (iii) mediates depletion of the activated human Treg with an EC₅₀, as measured
by an apoptosis assay as described in Example 19, of:
 - (a) 500 pM $\pm$ 25% or lower;
 - (b) 100 pM $\pm$ 25% or lower;
 - 20 (c) 30 pM $\pm$ 25% or lower;
 - (d) 15 pM $\pm$ 25% or lower;
 - (e) 5 pM $\pm$ 25% or lower;
 - (f) 1 pM $\pm$ 25% or lower;
 - (g) 13 pM $\pm$ 25%;
 - 25 (h) between 1 pM $\pm$ 25% and 500 pM $\pm$ 25%;
 - (i) between 5 pM $\pm$ 25% and 100 pM $\pm$ 25%; or
 - (j) between 10 pM $\pm$ 25% and 50 pM $\pm$ 25%.

5. The monoclonal antibody or modified monoclonal antibody or antigen-binding
portion thereof of any one of the preceding claims, which binds to an epitope
30 located in the N-terminal domain of human CCR8 as determined by X-ray
crystallography, wherein:
- (a) the epitope comprises at least one amino acid within a peptide having the
sequence Y₁₅Y₁₆Y₁₇P₁₈D₁₉I₂₀F₂₁ (SEQ ID NO: 2) and comprises a sulfated

- Y₁₅ or a sulfated Y₁₇ residue;
- (b) 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) and comprises a sulfated Y₁₅ or a sulfated Y₁₇ residue;
- 5 (c) the epitope comprises all 7 of the amino acids in the peptide having the sequence Y₁₅Y₁₆Y₁₇P₁₈D₁₉I₂₀F₂₁ (SEQ ID NO: 2) and comprises a sulfated Y₁₅ or a sulfated Y₁₇ residue;
- (d) the epitope consists of all 7 of the amino acids in the peptide having the sequence Y₁₅Y₁₆Y₁₇P₁₈D₁₉I₂₀F₂₁ (SEQ ID NO: 2) and comprises a sulfated Y₁₅ or a sulfated Y₁₇ residue;
- 10 (e) the epitope comprises at least one amino acid within a peptide having the sequence V₁₂T₁₃D₁₄Y₁₅Y₁₆Y₁₇P₁₈D₁₉I₂₀F₂₁S₂₂ (SEQ ID NO: 109) and comprises sulfated Y₁₅ and sulfated Y₁₇ residues;
- (f) 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) and comprises sulfated Y₁₅ and sulfated Y₁₇ residues;
- 15 (g) the epitope comprises all 11 of the amino acids in the peptide having the sequence V₁₂T₁₃D₁₄Y₁₅Y₁₆Y₁₇P₁₈D₁₉I₂₀F₂₁S₂₂ (SEQ ID NO: 109) and comprises sulfated Y₁₅ and sulfated Y₁₇ residues; or
- 20 (h) the epitope consists of all 11 of the amino acids in the peptide having the sequence V₁₂T₁₃D₁₄Y₁₅Y₁₆Y₁₇P₁₈D₁₉I₂₀F₂₁S₂₂ (SEQ ID NO: 109) and comprises sulfated Y₁₅ and sulfated Y₁₇ residues.
6. An anti-hCCR8 monoclonal antibody or an antigen-binding portion thereof, which is capable of mediating antibody-dependent cellular cytotoxicity (ADCC), or a modified version of said anti-CCR8 monoclonal antibody or an antigen-binding portion thereof comprising a modified heavy chain constant region that binds with higher affinity to an Fcγ receptor and mediates enhanced ADCC compared to the unmodified anti-hCCR8 monoclonal antibody or antigen-binding portion thereof, which binds specifically to an epitope on human C-C Motif Chemokine Receptor 8 (hCCR8) located in the N-terminal domain of human CCR8, and wherein the epitope:
- 25 (a) comprises amino acids Y₁₅Y₁₆Y₁₇P₁₈D₁₉I₂₀F₂₁ (SEQ ID NO: 2), wherein amino acid Y₁₅ or Y₁₇ is sulfated; or
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- (b) consists of amino acids Y₁₅Y₁₆Y₁₇P₁₈D₁₉I₂₀F₂₁ (SEQ ID NO: 2), wherein amino acid Y₁₅ or Y₁₇ is sulfated; or
 - (c) comprises all 11 of the amino acids in the peptide having the sequence V₁₂T₁₃D₁₄Y₁₅Y₁₆Y₁₇P₁₈D₁₉I₂₀F₂₁S₂₂ (SEQ ID NO: 109), wherein amino acids Y₁₅ and Y₁₇ are sulfated; or
 - (d) consists of all 11 of the amino acids in the peptide having the sequence V₁₂T₁₃D₁₄Y₁₅Y₁₆Y₁₇P₁₈D₁₉I₂₀F₂₁S₂₂ (SEQ ID NO: 109), wherein amino acids Y₁₅ and Y₁₇ are sulfated.
 7. The monoclonal antibody or modified monoclonal antibody or antigen-binding portion thereof of claim 5 or 6, which binds to an epitope located in the N-terminal domain of human CCR8 with a K_D of 10 nM ± 25% or lower, wherein the epitope comprises a peptide having the sequence:
 - (a) Y₁₅Y₁₆Y₁₇P₁₈D₁₉I₂₀F₂₁ (SEQ ID NO: 2) and comprises sulfated Y₁₅ or Y₁₇ residues; or
 - (b) V₁₂T₁₃D₁₄Y₁₅Y₁₆Y₁₇P₁₈D₁₉I₂₀F₂₁S₂₂ (SEQ ID NO: 109) and comprises sulfated Y₁₅ and Y₁₇ residues.
 8. The modified monoclonal antibody or antigen-binding portion thereof of any one of the preceding claims, which mediates at least 2, 5 or 10 times enhanced ADCC activity compared to the unmodified monoclonal antibody or antigen-binding portion thereof as measured by a reduction in the EC₅₀ for cell lysis in an NK cell lysis assay as described in Example 17.
 9. The monoclonal antibody or modified monoclonal antibody or antigen-binding portion thereof of any one of the preceding claims, which:
 - (a) promotes depletion of human tumor-associated Tregs *in vitro*; and/or
 - (b) specifically induces depletion of tumor Tregs without depleting CCR8⁺ T cells in non-tumor tissue; and/or
 - (c) inhibits growth of tumor cells in a subject when administered as monotherapy to the subject; and/or
 - (d) inhibits growth of tumor cells in a subject when administered to the subject in combination with an additional therapeutic agent for treating a cancer.
 10. The monoclonal antibody or modified 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 or exhibits all of the following properties:

- 5 (a) binds specifically to CCR8 expressed on the surface of a cell with an EC_{50} , as measured by an antibody-binding assay as described in Example 11, of $2 \text{ nM} \pm 25\%$ 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
10 uterus tissue, or peripheral blood mononuclear cells (PBMCs);
 - (c) inhibits binding of CCL1 to CCR8 and inhibits CCR8/CCL1 signaling with an IC_{50} of $5 \text{ nM} \pm 25\%$ or lower;
 - (d) when bound to CCR8 on the surface of a cell mediates depletion of the cell with an EC_{50} of $10 \text{ pM} \pm 25\%$ or lower;
 - 15 (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*;
 - (g) promotes depletion of human tumor-associated Tregs in *ex-vivo* human
20 tumor slice samples;
 - (h) mediates depletion of tumor Tregs specifically while sparing CCR8⁺ T cells in non-tumor tissues;
 - (i) inhibits growth of tumor cells in a subject when administered as monotherapy to the subject; and
 - 25 (j) inhibits growth of tumor cells in a subject when administered to the subject in combination with an additional therapeutic agent for treating a cancer.
11. The monoclonal antibody or modified monoclonal antibody or antigen-binding portion thereof of any one of the preceding claims, which binds to the same hCCR8 epitope as does a reference antibody, and/or which cross-competes for
30 binding to hCCR8 with the reference antibody, wherein the reference antibody comprises 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.

12. The monoclonal antibody or modified 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:
- 5 (a) 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;
- (b) 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;
- 10 (c) 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;
- (d) 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;
- 15 (e) 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; or
- (f) 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.
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13. The monoclonal antibody or modified monoclonal antibody or an antigen-binding portion thereof of any one of the preceding claims, wherein 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.
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14. The monoclonal antibody or modified monoclonal antibody or antigen-binding portion thereof of any one of the preceding claims, which comprises the following CDR domains as defined by the Kabat method: 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
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- 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.
15. The monoclonal antibody or modified monoclonal antibody or antigen-binding portion thereof of claim 14, which ~~or~~ comprises a V_H comprising consecutively linked amino acids having a sequence that is at least 80% identical to the sequence set forth as SEQ ID NO: 6 and a V_L comprising consecutively linked amino acids having a sequence that is at least 80% identical to the sequence set forth as SEQ ID NO: 18, and retains the functional properties of an antibody comprising V_H and V_L regions having the sequences set forth as SEQ ID NO: 6 and SEQ ID NO: 18, respectively;
- or comprises 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;
- or comprises 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.
16. The monoclonal antibody or modified monoclonal antibody or antigen-binding portion thereof of any one of the preceding claims, which comprises:
- (a) 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;
 - (b) 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;
 - (c) 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;

- (d) 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;
- (e) 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; or
- (f) 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;
- or comprises:
- (g) 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;
- (h) 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;
- (i) 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; or
- (j) 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.
17. The monoclonal anti-hCCR8 antibody or modified 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, a human IgG1 isotype, a human IgG3 isotype, or comprises a modified IgG1 heavy chain constant region which mediates enhanced ADCC, or an ADCC-mediating fragment of any of said antibodies.

18. The modified monoclonal antibody or antigen-binding portion thereof of claim 17 comprising a modified IgG1 heavy chain constant region, which:
 - (i) is hypofucosylated or nonfucosylated; and/or
 - (ii) contains a mutation or a multiplicity of mutations that mediates enhanced ADCC.
19. The modified anti-hCCR8 monoclonal antibody or antigen-binding portion thereof of claim 18, wherein the mutation or multiplicity of IgG1 mutations is chosen from G236A; S239D; F243L; E333A; G236A/I332E; S239D/I332E; S267E/H268F; S267E/S324T; H268F/S324T; and G236A/S239D/I332E according to the EU numbering convention.
20. A modified monoclonal antibody comprising a heavy chain constant region which is hypofucosylated or nonfucosylated, which binds specifically to human C-C Motif Chemokine Receptor 8 (hCCR8), the sequence of which is set forth as SEQ ID NO: 1, expressed on the surface of a cell and mediates depletion of the CCR8-expressing cell by antibody-dependent cellular cytotoxicity (ADCC), wherein said monoclonal antibody comprises 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.
21. An immunoconjugate comprising the monoclonal antibody or modified monoclonal antibody or antigen-binding portion thereof of any one of the preceding claims, linked to a cytolytic agent.
22. The immunoconjugate of claim 21, wherein the cytolytic agent is a cytotoxin or a radioactive isotope.
23. A bispecific molecule comprising the monoclonal antibody or modified monoclonal antibody or antigen-binding portion thereof of any one of claims 1-20, linked to a binding domain that has a different binding specificity than the monoclonal antibody or modified monoclonal antibody or antigen binding portion thereof.
24. A composition comprising:

- (a) the monoclonal antibody or modified monoclonal antibody or antigen-binding portion thereof of any one of claims 1-20; or
 - (b) the immunoconjugate of claim 21 or 22; or
 - (c) the bispecific molecule of claim 23;
- 5 and a pharmaceutically acceptable carrier.
25. An isolated nucleic acid encoding the monoclonal antibody or modified monoclonal antibody or antigen-binding portion thereof of any one of claims 1-20.
26. An expression vector comprising the nucleic acid of claim 25.
27. A host cell comprising the expression vector of claim 26.
- 10 28. The host cell of claim 27, which comprises an altered glycosylation machinery.
29. The host cell of claim 28, wherein the altered glycosylation machinery is an absence of an α -(1,6) fucosyltransferase (FUT8) enzyme, and antibodies produced in the cell are hypofucosylated or nonfucosylated.
30. The host cell of any one of claims 27-29, which is a eukaryotic cell.
- 15 31. The host cell of claim 30, wherein the eukaryotic cell is a mammalian cell.
32. A method for preparing an anti-CCR8 monoclonal antibody or a modified monoclonal antibody or an antigen-binding portion thereof which comprises expressing the antibody or antigen-binding portion thereof in the host cell of any one of claims 27-31 and isolating the antibody or antigen-binding portion thereof
- 20 from the host cell.
33. Use of the composition of claim 24 in the preparation of a medicament for treating a cancer in a subject afflicted with the cancer.
34. Use of the composition of claim 24 in the preparation of a medicament for inhibiting growth of tumor cells in a subject.
- 25 35. The use of claim 33 or 34, wherein the medicament further comprises a therapeutically effective amount of an additional therapeutic agent for treating a cancer or for inhibiting growth of tumor cells in the subject.

36. The use of claim 35, wherein the additional therapeutic agent is a compound that reduces inhibition, or increases stimulation, of the immune system; an immune checkpoint inhibitor; a chemotherapeutic agent; radiation therapy; a small-molecule compound; a macrocyclic peptide; a fusion protein; and/or an antibody.
- 5 37. The use of any one of claims 33-36, wherein the additional therapeutic agent is an antagonistic agent or an agonistic agent.
38. The use of claim 37, wherein:
- 10 (a) the antagonistic agent is an antagonistic monoclonal antibody 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
- 15 (b) the agonistic agent is an agonistic monoclonal antibody 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).
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39. The use of claim 38, wherein:
- (a) the antagonistic agent is an antagonistic antibody or an antigen-binding portion thereof that binds specifically to PD-1; or
- 25 (b) the antibody that binds specifically to PD-1 is chosen from nivolumab, pembrolizumab, cemiplimab, spartalizumab, camrelizumab, sintilimab, tislelizumab, toripalimab, dostarlimab, retifanlimab, and pimivalimab; or
- (c) the antagonistic agent is an antagonistic antibody or an antigen-binding portion thereof that binds specifically to PD-L1; or
- 30 (d) the antibody 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

- (e) the antagonistic agent is an antagonistic antibody or an antigen-binding portion thereof that binds specifically to CTLA-4; or
- (f) the antibody that binds specifically to CTLA-4 is ipilimumab or tremelimumab.

5 40. The use of any one of claims 33-39, wherein the cancer is a solid tumor or a hematological malignancy, or the tumor cells are cells of a solid tumor or of a hematological malignancy.

41. The use of claim 40, wherein the solid tumor is:

- 10 (a) 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
- 25 (b) a cancer chosen from non-small cell lung cancer (NSCLC), squamous cell
- 30

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

- 5 (c) 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
- 10 (d) 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
- 15 (e) a cancer chosen from colon adenocarcinoma, bladder carcinoma, mammary carcinoma, and fibrosarcoma.

42. The use of claim 40, wherein the hematological malignancy is:

- 20 (a) 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;
- 25 or
- (b) an acute, chronic, lymphocytic (lymphoblastic) and/or myelogenous leukemia; a lymphoma, Hodgkin's lymphoma; non-Hodgkin's lymphomas, B cell lymphomas, diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), chronic lymphocytic leukemia (CLL)/small
- 30 lymphocytic lymphoma (SLL), mantle cell lymphoma, marginal zone B-cell lymphomas (mucosa-associated lymphoid tissue (MALT) lymphoma, nodal marginal zone B-cell lymphoma, and splenic marginal zone B-cell lymphoma), Burkitt lymphoma, lymphoplasmacytoid lymphoma (LPL;

also known as Waldenström's macroglobulinemia (WM)), hairy cell lymphoma, and primary central nervous system (CNS) lymphoma; NHLs that are T cell lymphomas, precursor T-lymphoblastic lymphoma/leukemia, T-lymphoblastic lymphoma/leukemia (T-Lbly/T-ALL); peripheral T-cell lymphomas, cutaneous T-cell lymphoma (CTLC), mycosis fungoides, Sezary syndrome); adult T-cell lymphoma/leukemia, angioimmunoblastic T-cell lymphoma, extranodal natural killer/T-cell lymphoma nasal type, enteropathy-associated intestinal T-cell lymphoma (EATL), anaplastic large-cell lymphoma (ALCL), and peripheral T-cell lymphoma unspecified, acute myeloid lymphoma, lymphoplasmacytoid lymphoma, monocytoid B cell lymphoma, angiocentric lymphoma, intestinal T-cell lymphoma, primary mediastinal B-cell lymphoma, post-transplantation lymphoproliferative disorder, true histiocytic lymphoma, primary effusion lymphoma, diffuse histiocytic lymphoma (DHL), immunoblastic large cell lymphoma, and precursor B-lymphoblastic lymphoma; myelomas, multiple myeloma, smoldering myeloma (indolent myeloma), monoclonal gammopathy of undetermined significance (MGUS), solitary plasmacytoma, IgG myeloma, light chain myeloma, nonsecretory myeloma, and amyloidosis; and any combinations of said hematological malignancies.

43. Use of the composition of claim 24 in the preparation of a medicament for potentiating an anti-tumor immune response elicited by a therapeutic agent in a subject afflicted with a cancer.
44. The use of claim 43, wherein the therapeutic agent is an immune checkpoint inhibitor, a chemotherapeutic agent, or radiotherapy.
45. The use of claim 44, wherein the immune checkpoint inhibitor is an anti-PD-1, anti-PD-L1 or anti-CTLA-4 antibody.
46. Use of the modified monoclonal antibody of claim 20 in the preparation of a medicament for treating a cancer in a subject.
47. The use of claim 46, wherein the medicament further comprises nivolumab.

48. The use of any one of claims 33-47, wherein the subject is a human.
49. A kit for treating a cancer or for inhibiting growth of tumor cells in a subject afflicted with the cancer, the kit comprising:
- 5 (a) one or more dosages ranging from $0.01 \pm 25\%$ to $20 \pm 25\%$ mg/kg body weight of the anti-CCR8 monoclonal antibody or the modified monoclonal antibody or the antigen-binding portion thereof of any one claims 1-20; and
- (b) instructions for treating the cancer or for inhibiting growth of the tumor cells in the subject.
- 10 50. The kit of claim 49, further comprising one or more dosages ranging from $0.1 \pm 25\%$ to $20 \pm 25\%$ mg/kg body weight, or $200 \pm 25\%$ to $1600 \text{ mg} \pm 25\%$ fixed dose of a monoclonal antibody or an antigen-binding portion thereof that binds specifically to PD-1, PD-L1 or CTLA-4, and instructions for treating the cancer or for inhibiting growth of the tumor cells with the monoclonal antibody or portion thereof that binds specifically to PD-1, PD-L1 or CTLA-4 in combination with the
- 15 anti-CCR8 monoclonal antibody or modified monoclonal antibody or the antigen-binding portion thereof.